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Hearing Loss

From Multidisciplinary Teamwork to Public Health

Edited by Tang-Chuan Wang

Hearing Loss - From Multidisciplinary Teamwork to Public Health

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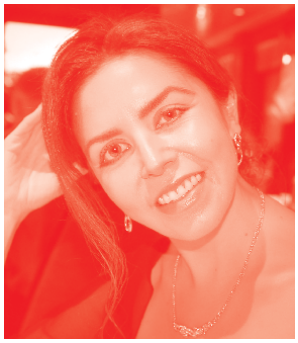

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Hearing Loss - From Multidisciplinary Teamwork to Public Health
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Edited by Tang-Chuan Wang

Contributors
Rajesh Paluru, Devender Singh Negi, Alejandra Itzel Contreras Rivas, Gaston Eduardo Estudillo Jimenez, Alejandro Brice, Alberto Behar, Apoorva Dwivedi, Prateek Asthana, Gargi Khanna, Tarun Chaudhary, Penelope Rachel Brock, Kaukab Rajput, Lindsey Edwards, Annelot Meijer, Alex Hoetink, Philippa Simpkin, Marry Van Den Heuvel-Eibrink, Mariana Kruger, Michael Sullivan, Sampson Antwi, Mohammed Issahalq, Francis Msume Banda, Britt Nakstad, Jiho Lee, Joong-Keun Kwon, Reza Hashemian, Edgar Flores Molina, Patricio Guerra Ulloa

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Meet the editor

Dr. Tang-Chuan Wang is an excellent otolaryngologist-head and neck surgeon in Taiwan. He is also a research scholar of Harvard Medical School and University of Iowa Hospitals. During his profound experience, he has worked in the Hospital of the University of Pennsylvania, Boston Children's Hospital, and Massachusetts Eye and Ear. Besides, he is not only working hard on clinical and basic medicine but also launching out into public health in Taiwan. In recent years, he has devoted himself to medical innovations and telemedicine. He always says that "in theoretical or practical aspects, no innovation is a step backward." Due to his contribution to bio-design, he was invited into the executive committee of HIWIN-CMU Joint R&D Center in Taiwan.

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Preface

The auditory system is one of the finest structures in the human body. Although the auditory anatomical structure is so small compared to other organs, without it, it would greatly affect a person's basic life. Hearing loss, also known as hearing impairment, is a partial or total inability to hear. When people communicate with others, listening is always the first step. That is why Helen Keller once said, "Blindness separates people from things; deafness separates people from people."

Noise-induced hearing loss, a common cause of hearing loss, is a kind of hearing impairment resulting from exposure to loud sound. There is continuous and endless noise in many workplaces, which may cause chronic and cumulative damage. Some young people often work hard, but they easily neglect or forget to protect themselves. This type of hearing loss is avoidable and preventable. In the section "Teamwork Approach to Noise-Induced Hearing Loss, Dr. Alberto Behar talks about noise exposure. The question to answer is how to determine the risk of a person performing in an environment where the noise levels, duration, and frequency content change with time. Dr. Joong-Keun Kwon and Dr. Jiho Lee introduce the scientific basis of noise-induced hearing loss, the impacts of ototraumatic substance, and the co-existing impact on hearing loss. In addition, Dr. Alejandro Brice provides a case study from a speech-language pathologist's perspective and discusses the occurrences that affected comprehension along with the compensatory strategies that assisted listening and comprehension.

Hearing loss in children is a problem worthy of attention. Around 7% of the people with disabling hearing loss are children, and it is very worrisome to note that 5 out of every 1000 infants are born with or develop disabling hearing loss in early childhood. Hearing loss can affect a child's ability to develop speech, language, and social skills. I have managed children with hearing loss for many years, and the most touching sight is the light that blooms on a child's face when hearing his or her mother's voice for the first time. Then the scene of "happy tears" impressed me so much. To hear the voice that has not been heard is so pleasant, as if this ordinary listening experience is a supreme listening enjoyment. In the section "Teamwork Approach to Hearing Loss in Children," Dr. Alejandra Itzel Contreras Rivas et al. present neonatal hearing screening. It is very important to screen all newborns in order to establish the appropriate diagnosis and the necessary treatment to avoid delays in development. Dr. Penelope Brock et al. discuss cisplatin ototoxicity in children. They focus on cisplatin-induced hearing loss, its mechanisms, its health impact on the young person, and ways to mitigate or reduce the severity of ototoxicity.

Hearing loss comorbidities is a term that means that a person's hearing health is affected by other medical conditions and vice versa. In the section "Teamwork Approach to Hearing Loss Comorbidities," Dr. Sampson Antwi and Dr. Mohammed Duah Issahalq share the topic of hearing loss in chronic kidney disease. Hearing loss is not uncommonly associated with chronic kidney disease and this comorbidity is often overlooked by health caregivers. Dr. Rajesh Paluru and Dr. Devendra Singh Negi investigate brainstem auditory evoked potentials in type 2 diabetes mellitus. When brainstem auditory evoked potentials were carried out in diabetic patients

early, then impairment of the entire auditory pathway might be detected even before the onset of any clinical signs and symptoms.

Hearing aids innovations have proceeded all around the world for decades, and the latest innovations make hearing aids better than ever. In the section "Teamwork Approach to Hearing Aids Innovations," Dr. Apoorva Dwivedi et al. seek to improve a highly sensitive microelectromechanical systems (MEMS) capacitive accelerometer as a probable completely implantable hearing aid microphone. Besides, Dr. Reza Hashemian offers a simple and cost-effective method for the design and implementation of stand-alone analog amplifiers or preamplifiers for hearing aids.

Public health has been defined as "the science and art of preventing disease," improving quality of life through organized efforts. We must develop comprehensive, multifaceted strategies to address public health needs. In the section "Implementation Strategies in Public Health," Dr. Francis Msume Banda and Dr. Britt Nakstad highlight the problem of childhood hearing loss in developing countries. Hearing loss should be considered a public health priority in developing countries for which concerted efforts must be made to prevent it by all means. Children who have hearing loss should be identified as early as possible and be enrolled in appropriate intervention services so that they can enjoy equal opportunities in life.

Hearing loss is very common in the United States. It is the third most chronic health condition in the United States. To avoid the "epidemic" of hearing loss in the near future, it is necessary to promote early screening, change public attitudes toward noise, and wear hearing aids appropriately. Based on the contributions of many authors, whom I sincerely respect, this book incorporates updated developments as well as future perspectives in the ever-expanding field of hearing loss. Besides, it is also a great reference for audiologists, speech pathologists, otolaryngologists, pediatricians, neurologists, researchers in clinical and basic medicine, experts in science and technology, as well as specialists in occupational, environmental, and public health.

I have appreciated everyone who has contributed to the editorial process of this book, including the author service manager, the publishing process manager, the commissioning editor, and the technical editor. They have made great efforts toward this project, and their wonderful assistance resulted in the success of academic work. At last, I am always full of gratitude toward my family, teachers, and colleagues who made me mature.

Tang-Chuan Wang (Vincent Wang)
Chairman of Otolaryngology-Head and Neck Surgery,
China Medical University Hsinchu Hospital,
Taiwan

School of Medicine,
College of Medicine,
China Medical University,
Taiwan

Department of Public Health,
College of Public Health,
China Medical University,
Taiwan

Research Scholar of Harvard Medical School,
MA, USA

Research Scholar of University of Iowa Hospitals and Clinics,
IA, USA

Member of American Academy of Otolaryngology-Head and Neck Surgery
Fellow of the American College of Surgeons

Section 1

Teamwork Approach to Noise-Induced Hearing Loss

Chapter 1

Noise Exposure

Alberto Behar

Abstract

Noise exposure is a basic concept used to assess the risk of noise induced hearing loss in the workplace. It is very important, since loud noise is omnipresent in almost all human activity, especially in industry, construction, mining and transportation. The question to answer is how to determine the risk of a person performing in an environment where the noise levels, duration and frequency content change with time. The answer is obtained by measuring his noise exposure. Although the measurement itself is not complex or difficult, a proper knowledge of what exactly is the noise exposure and how to deal with the measurement result in fundamental to avoid getting wrong conclusions.

Keywords: loud noise, noise induced hearing loss, risk assessment, noise exposure, hearing loss prevention

1. Introduction

Occupational noise is the most common health hazard that is predominant in most workplaces. In a recent survey of working adults in Canada, 42% reported being exposed to hazardous noise levels in the workplace [1]. Exposure to excessive occupational noise can cause permanent hearing loss through sensory-neural damage in the cochlea. In general, hearing is first affected in a specific range of audible frequencies (3000 to 6000 Hz) and then spreads to higher and lower frequencies. Hearing loss is often accompanied by other long-term auditory effects, such as tinnitus (ringing in the ears); increased sensitivity to loud noise; and poorer frequency selectivity (i.e., decreased ability to hear sounds in background noise) compared to individuals with normal hearing. It can also cause other, non-auditory adverse effects, the most common been the cardiovascular (e.g., changes in heart rate, increasing blood pressure). Being a stressor, noise causes also important psychological effects [2].

Noise levels in the workplace vary in level, duration and frequency content. In general, they are of high levels and are persistent for most of the work shift. They can be continuous, impulsive or interrupted. From the frequency point of view, most are of the wide band type, although they can be rich in high or low frequencies, especially if vibrations are also present in the workplace.

Reduction of the sound levels and, consequently the risk of noise induced hearing loss is the objective of every hearing conservation program in the industrial world [3].

The approach to the reduction of the risk follows several steps. The first is finding and recognizing potentially hazardous areas in the workplace. This tends to be done as a result of personal, subjective observations, the principal been difficulties in understanding speech: people ask frequently questions and answers to

be repeated. Complaints of excessive noise are also important indications that the noise may be so loud as to create a health risk. This first step is usually performed through a walk-through survey. Sometimes, spot noise level measurements are also done using a sound level meter.

Once the areas with high noise levels have been found, the next step is to quantify the risk. This is done by measuring the noise exposure of individuals or groups of workers working in those areas. This procedure is known as the exposure survey.

Also, the extent of the exposed population (number of exposed persons) is also quantified to find out the magnitud of the problem.

2. Why noise exposure

Noise exposure is a fundamental concept in assessing the risk from high noise levels.

It is universally accepted that hearing loss occurs as a consequence of long duration exposures to high noise levels. What is usually not too clear is how long the "long duration" is and how high are the "high noise levels". There is no, however discussion regarding that the effect is caused by a combination of both: duration and level. The concept of noise exposure combines both causes and that makes it so important. As mentioned above, in determining the risk of occupational hearing loss, measuring workers' noise exposure is an essential part of any hearing conservation program.

It all derives from an ISO standard [4] that estimates the probability of acquiring noise induced hearing loss after being exposed to a given noise exposure level for different periods of time. As an example, after 40 years of been exposed to 85 dBA for 8 hs a day, 50% of the population will acquire an average of extra 5 dB hearing loss between 500 Hz and 6 KHz, on top of the hearing loss due to age.

On the basis of the above statement, the limit of 85 dBA has been adopted almost internationally for a workday of 8 hs.

3. Standards and definitions

Reference [5] lists important standards from different institutions, related to noise exposure.

Noise exposure is a complex combination of sound levels a person has been exposed to and the duration of each one of those sound levels [5–8]. The closer analogy is to think in terms of noise energy that enters the persons' ears and damage the delicate organ of hearing. So, two variables are involved there: sound levels and time duration [9].

There are several concepts involved that need to be explained and defined. Their understanding is essential when dealing with this issue.

Equivalent sound level, Leq, t in dBA is the first of them. The easier way to understand it is as follows: In real life, sound levels constantly vary with time. They rise when the worker is using a power tool and diminish between operations, while changing continuously. Leq, t is a kind of an "average", constant sound level for the entire period of exposure (working) time, encompassing all "quiet" and "noisy" periods, with the same energy of the real one. It is defined as the value of a noise of constant sou**n**d level that contains the same total A-weighted acoustical energy as the sound of interest. In other words, while the real noise is of a varying sound level, the equivalent has a constant level of the same energy.

Now is the time to clarify the meaning of the letter "t" at the end of the Leq, t. It is there to signify that the Leq in question is for the period of time the worker has been exposed to.

Here we arrive at another important point that needs to be stated: whenever Leq is mentioned, the duration of the exposure (t), should also be stated. Otherwise the Leq has no meaning. This is not too difficult to understand as per the following example: suppose we have two workers. One of them is exposed every day to 90 dBA for 4 hs. The other one is exposed also to 90 dBA, but for 8 hs. It is obvious that the effect to the hearing of the second worker will be larger. In other words even though Leq,4 of the first is equal to the Leq,8 of the second, their effects are not the same.

The numerical definition of Leq, t is as follows: ten times the logarithm (base 10) of the time integral over a stated time, t hours, of the squared A-weighted sound pressure relative to 20 μPa, divided by that time.

Noise exposure level, Lex, T, in dBA, is another important measure. This is the one used to predict noise-induced hearing loss as per [4]. It is derived from the measured Leq,t by a simple adjustment to account for the longer or shorter duration of the workday on the workers' hearing. In other words, it answers the following question: what will be the value of Leq,t if the energy that entered the worker's ear during t hs would enter during 8 hs. By calculating Lex,T (with capital T), Leq,t for working days of different durations can be compared directly.

The following formula converts Leq,t into Lex,T:

$$Lex,\mathrm{T} = Leq,\mathrm{t} + 10\log\left(\mathrm{t}/\mathrm{T}\right) \tag{1}$$

Where: t is the duration of the actual exposure, in hr. and

T is the normalized duration, usually = 8 hr.

As an example, if a worker is exposed to 85 dBA for four hours a day (Leq,4), his exposure for a normalized 8 hs duration will be:

$$Lex,8 = Leq,4 + 10\log\left(\mathrm{t}/\mathrm{T}\right) = 85 + 10\log\left(4/8\right) = 82\,dBA. \tag{2}$$

If, on the contrary, he is exposed to 85 dBA for 12 hs (Leq,12), his exposure for a normalized 8 hs duration will be:

$$Lex,8 = Leq,12 + 10\log\left(\mathrm{t}/\mathrm{T}\right) = 85 + 10\log\left(12/8\right) = 87\,dBA. \tag{3}$$

The above example shows again how two workers with the same Leq,t, have different Leq,T and, consequently, different risk of hearing loss.

Mathematically, Lex,T is defined **as** ten times the logarithm (base 10) of the time integral of the squared A-weighted sound pressure relative to 20 μPa for the time actually worked, divided by T hours (usually the standardized shift duration of 8 h).

Finally, it has to be stated that while Leq,t is essentially measured, Leq,T is calculated from the Leq,t value. As it will be described further, the actual measuring instrument, the dosimeter, performs both the measurement and the calculation. Both values, Leq,t and Leq,T can be read on the same device. This greatly simplifies the task of the person performing the noise exposure survey. On the other hand, it can create misunderstandings if the operator does not has clear knowledge of the difference between Leq,t and Leq,T. As mentioned above, the one that is to be used when assessing the risk of hearing loss is the noise exposure level, Leq,T.

Noise dose in % is another important measure. Although the use of the noise dose is declining lately, many instruments still allow its measurement. The concept is familiar mainly to Occupational Hygienists and commonly used when dealing with hazardous substances. The idea is quite simple: it defines the relation between the amount of a substance absorbed by a person in a given period of time (usually 8 hs) and the maximum allowed by a local jurisdiction. For example, if this limit is set to 85 dBA for an exposure of 8 hs and the actual exposure for the same period of time has been 88 dBA, then his dose will be 200%[1].

The following equation allows for the calculation of Leq,t from a given dose[2]:

$$Leq,\mathrm{t} = 10\log\left(\mathrm{D}/100\times 8/\mathrm{T}\right) + Lc \qquad (4)$$

where D = dose in % for 8 h.

T = duration of the daily exposure in hours.

Lc = criterion sound level in dBA[3].

For example, a dose of 100% acquired during 4 hs (using Lc = 85 dBA) will result in

$$Leq,\mathrm{t} = 10\log\left(100/100\ \mathrm{x}\ 8/4\right) + 85 = 88\,dBA. \qquad (5)$$

Criterion level (LC) in dBA is a constant sound level which, if it continues for the criterion duration (usually 8 hs), will result in the worker's allowable noise exposure. ISO (the International Organization for Standardization), as well as most Canadian provinces [10] and NIOSH (the USA National Institute for Occupational Safety and Health) [11] has adopted LC = 85 dBA for 8 hs.

Exchange rate is the increase (decrease) in sound level for which permissible exposure time is halved (doubled)[4]. ISO, most Canadian provinces and NIOSH has adopted 3 dB exchange rate. So, for instance, if a person is allowed to have Lex(8) = 85 dBA for 8 hs, he is also allowed to Lex(4) = 88 dBA for 4 hs.

4. Noise exposure measurements

There are two issues involved in the measurement of Leq,t: one is related to the instrumentation involved and the other deals with the measurement technique and procedures. Although managing the instrument itself is a relatively simple task, the measurement procedure requires basic knowledge of noise as well as practical knowledge regarding where to put the dosimeter, for how long to measure, etc. Measuring noise exposure of groups is more complex and requires some knowledge on statistics to be able to decide how many individuals to sample and for how long.

---

[1] For this calculation it is assumed that every time the noise exposure increases 3 dB, the exposure is multiplied by two. This is known as "exchange rate" (in this case = 3)

[2] As a matter of fact, this calculation is also performed by the dosimeter. Therefore the operator can read the result of the measurement as a Dose as well as Leq,t or Lex,T.

[3] Lc is the maximum Lex,T, a person is allowed to be exposed for 8 hs, daily.

[4] The two common exchange rates used are 3 dB and 5 dB. Even where the 5 dB exchange rate is required in a Regulation, it is recommended that the 3 dB exchange rate be used as well since it provides a higher degree of protection (for exposure of 8 h) or less).

4.1 Instruments

Noise exposure can be measured using regular sound level meters and integrating sound level meters. However, there is a device specifically designed to measure Leq,t. It is the **noise dosimeter**. In its basic version it consists of an ¼" diameter microphone connected through a long cord to a container with the battery and the electronic components of the instrument. It also includs a readout device that allows for reading of the measured Leq,t. The microphone is to be attached close to the ear of the person whose exposure will be measured. The rest of the instrument is usually worn on the belt or in the shirt pocket (see photographs in **Figure 1a** and **b).**

Figure 1.
Dosimeters with separate microphones.

Recently, manufactures have opted for compact, small size dosimeters called Noise Badges that contain both the microphone and the microprocessor of the instrument. By having the entire instrument in a single body, they eliminate the cord that is a nuisance and also can be a workplace hazard. Measurement results can still be read on the dosimeter itself. Thay can also be transmitted via Bluetooth technology to another device with facilities for recording for future use. This is especially handy when a noise exposure survey is carried out on several workers simultaneously, while each is carrying his own dosimeter. In some models, the receiver is also a charger for the batteries of all instruments. **Figure 2a** and **b** shows Noise Badges from two manufacturers.

There is a wide variety or instruments in the market, able to perform different measurements and calculations. They all belong to the following two basic types of dosimeters: **measuring** and logging.

Measuring dosimeters allow for the straight measurement of Leq,t and, eventually calculate Lex,T. Although most allow for reading the results on the instruments themselves, some others relay on a separate measurement device. This is done to keep the results visible to the operators only.

Dosimeters measure sound levels at predetermined intervals of time. **Measuring** dosimeters do not allow for extracting individual readings, just the final results at the end of the measurement period. **Logging** dosimeters, on the contrary, allow for the extraction of individual Leq,t. In such a way one can obtain the entire history of the sound levels at predetermined time intervals. The results can then be downloaded into a computing device and shown as a graph, spreadsheet, etc. By analyzing the partial data, one can follow their variation with time. Then, by knowing where the person was located at different times of the day or what kind of operation he was involved in, one can pinpoint the important noise sources or operations. Noise history is a powerful tool used for the design of noise controls in the workplace.

Another advantage of the logging dosimeters is that by studying the noise history one can determine if there have been abnormal events and then "clean" false results caused from malingering or noises not normal in the particular workplace.

4.2 Measurement techniques

4.2.1 Individuals

Measuring Leq,t of individuals using a dosimeter is a relatively simple exercise, generally explained in the manual supplied with the instrument[5]. Manuals contain also information on how to care and the main precautions that have to be taken to obtain proper results.

A most important task, often overlooked, is to inform the person(s) under test the reason for testing and how it will be done. In many instances not knowing the "why" and "how" lead to malingering and falls results. Often workers suspect that the instrument will in fact transmit their conversations to the supervisor. In other instances, some individuals created artificially loud noises to show levels that do not exist in reality.

After calibrating the instrument and ensuring that the batteries have enough charge to last during the testing period, the microphone of the dosimeter is attached close to the wearer's ear (generally on the shoulder or close by, and switched on.

[5] Instructions in this Section are absolutely basics. More detailed instructions are needed to perform correctly a noise exposure survey.

A. DC112 by CESVA

b) PRO DLX by Quest Technologies

Figure 2.
Dosimeters with incorporated microphones (noise badges).

Then the individual is sent to perform his tasks as usual. If the task is repetitive, then the measurement is done during a couple of repetitions, only. However, when the sound levels vary during the shift or if the worker works in different places, the measurement should last for the entire shift.

As mentioned above, if the measurement has been performed for the entire shift, then Lex,T is equal to Lex,t. In other words, the daily reading is his daily noise exposure, Lex,T. If that is not the case, then the Eq. [1] (page YYY) should be used to convert the measured Leq,t in Lex,T.

4.2.2 Groups

In many instances, there is a need to assess a group of workers that perform identical tasks or are located in the same environment. Providing each one of them with a dosimeter is not necessary or practical. There are procedures to be followed that reduce considerably the number of instruments needed and still obtain reliable, statistically significant results[6].

5. Lex,T for T different of 8 hs

Noise induced occupational hearing loss is the effect on a person being exposed to high noise levels for extended periods of time. Epidemiological data, used as bases for our present knowledge of hearing loss, were derived from populations working for many years in such high noise environments [12]. This is also the origin of the equal energy theory and the 3 dB exchange rate [13].

As explained above, when the measurement period t is different from T = 8 hs, Eq. 1 is to be used,. The formula is meant for 8 hs long work day where acoustical conditions repeat day after day, month after month, for the assumed 40 active years of a person.

Presently, in many occupations, the duration of the workday is 12 hs a day with several days off to equal to 40 hs a week or 80 hs every two weeks. The question is, shall we still use Eq. 1 with T = 8 hs? No official document exists for such a situation. However, common sense indicate that since the average duration of the workday is still T = 8 hs, (the average over the 2 or the 4 weeks), Eq. 1 is still valid and shall be used.

As an example [14], the total of hs worked by the musicians at the National Ballet of Canada is 350 hs. Therefore, the average Leq,t during their rehearsals/ performances was corrected using Eq. 1 as follows:

$$Lex,\mathrm{T} = Leq,\mathrm{t} + 20\log \mathrm{t}/\mathrm{T} = Leq,\mathrm{t} + 10\log 350/2000 = Leq,\mathrm{t} - 7.56\,dBA \qquad (6)$$

Where t = 350 are the actual annual number of hours worked and.

T = 2000 the number of work hours in a year.

We do not really know what happens to ears exposed to 12 hs a day, for a 40 hs week. Nor we know about yearly exposures of less than 2000 hs, that is the average exposure resulting of 8 hs a day, 40 hs a week. We can only assume that the equal energy principle can be extended to cover exposures of different durations.

Using the equal energy principle, one can calculate exposures of different workday duration too. For example, if a worker whose workday is 8 hs and whose exposure measured for 5 hs was Leq,5 = 85 will be.

$$Lex,\mathrm{T} = Leq,\mathrm{t} + 20\log(\mathrm{t}/8) = 85 + 20\log(5/8) = 83\,dBA. \qquad (7)$$

[6] See Appendix B in Ref. [9]

However, if his workday is t = 12 hs, then

$$Lex,\mathrm{T} = 85 + 20\log\left(12/8\right) = 87\ dBA \tag{8}$$

In the case of temporary worker, that performs 350 hs a year, it will be t = 350 hs, T = 2000 hs and Eq. 1 will be

$$Lex.\mathrm{T} = 85 + 20\log\left(350/2000\right) = 77.4\ dB \tag{9}$$

Author details

Alberto Behar
Ryerson University, Toronto, Canada

*Address all correspondence to: albehar31@gmail.com

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Chapter 2

Occupational Hearing Loss

Joong-Keun Kwon and Jiho Lee

Abstract

Occupational hearing loss received attention after the Industrial Revolution and through World Wars I and II. It currently accounts for the largest portion of occupational diseases, and a third of all hearing loss is due to noise. Occupational hearing losses include noise-induced hearing loss (NIHL), hearing loss caused by ototoxic substances and hearing loss caused by their complex interactions. In the case of NIHL, even when exposed to the same noise, the degree of hearing damage and recovery may vary from person to person, and also be affected by other noise in daily life. Various organic solvents and some heavy metals exposed in workplace are important causes of ototoxic hearing loss, and they are known to have additive or synergistic effects when accompanied by noise. In Korea, NIHL is the most common occupational disease and has been increasing continuously since the 1990s. The number of claims for compensation has also been increasing steadily. However, the developed country including Korea almost never considered the effects of chemicals on the diagnosis and compensation for hearing loss workers. Occupational hearing loss can be prevented through hearing conservation programs. In this chapter, we will introduce the scientific basis of noise induced hearing loss, the impacts of ototoxic substance and co-existence impact on hearing loss.

Keywords: occupational hearing loss, noised-induced hearing loss, noise, solvents, ototoxicity, co-exposure

1. Introduction

1.1 Noise-induced hearing loss

Occupational noise exposure is very common around the world. Up to 25% of workers are exposed to workplace noise above 85 dB(A) (weighted decibel relative to human ear) [1]. Noise-induced hearing loss (NIHL) is the second most common cause of hearing loss after age-related hearing loss (ARHL) and 16% of adult hearing loss is estimated to be caused by workplace noise [2]. In addition, one-third of workers exposed to noise showed audiometric evidence of NIHL, with 16% experiencing material hearing loss [3, 4].

The prevalence of NIHL is increasing worldwide. Prevalence in Korea is also increasing, especially over the past 20 years. Cases of accepted compensation for NIHL are more rapidly rising from 2016 than the cases for audiometric diagnosis (**Figure 1**).

Hearing loss is associated with cognitive decline and depression, and now accepted as a risk factor for dementia [5]. Noise from by daily life (subways, electric tools) or hobby (music concerts, sports viewing, hunting, etc.) can also contribute to hearing loss.

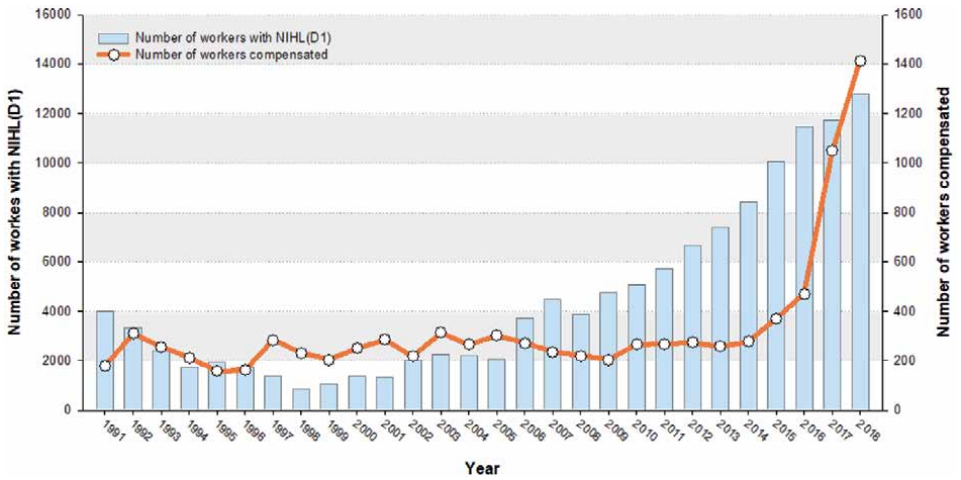

Figure 1.
Prevalence of noise-induced hearing loss (D1) and compensated cases in Korea by year (1991 to 2018). Prevalence of noise-induced hearing loss (D1) (in blue bars) and cases for compensation (in red line) have increased from 1991 to 2018. Diagnostic criteria of NIHL in Korea requires hearing loss more than 30 dB on average threshold across 0.5 kHz, 1 kHz, and 2 kHz and more than 50 dB at 4 kHz. If the average threshold exceeds 40 dB, decision for compensation could be made. The compensated cases for NIHL were increasing more sharply since 2016, whereas the diagnosed cases were increasing more steadily. http://www.kosha.or.kr/kosha/data/healthExamination.do. http://www.moel.go.kr/policy/policydata/view.do?bbs_seq=20200401401.

There are jobs where hearing is very important due to the nature of work itself or safety concerns. Hearing loss reduces speech recognition ability in the noisy environment and hearing protection devices (HPDs) also hampers speech recognition in noise. When hearing impaired workers wear a HDPs, their difficulty increases in hearing warning signals. There was association between the severity of hearing loss and the risk of work-related injury requiring hospitalization [6]. Even in the workplace where hearing is less important, hearing loss is a major cause of stress-related sick leave [7]. Economic impact of NIHL on social burden includes lost productivity, absenteeism, reduced income and tax revenues, welfare payment and compensation, special education, vocational rehabilitation programs, and health care [8].

The purpose of this review is to have a comprehensive overview of NIHL including pathophysiology, diagnosis, prevention, and to understand the recently emerging topics on noise-induced cochlear synaptopathy.

1.2 Pathophysiology

Noise-induced hearing loss is a complex disease caused by the interaction of genetic and environmental factors. It is usually caused by chronic loud noise exposure but also could be caused by transient or repetitive acoustic trauma of very high intensity, resulting in greater damage [9]. The total energy level of noise causing NIHL is determined by the intensity of the noise and the total exposure time. The noise at the same total energy level will cause the same amount of cochlear damage [10].

The inner ear damage caused by noise is divided into temporary threshold shift (TTS) and permanent threshold shift (PTS) depending on the duration of the hearing loss. Hearing loss recovers within 24–48 hours in TTS, while it is irreversible in PTS. Mechanisms of TTS and PTS are considered to be different. Animal study showed that TTS in early life can accelerates age-related hearing loss (ARHL) [11]. However, long-term impact of TTS in human ear is lacking. Pathology of

noise induced damage is the loss of outer hair cells leading to threshold elevations and poorer frequency discrimination. Main threshold shift occurs at an half octave higher than the frequency of loud noise, with the largest damage at 4 kHz and the smallest at 0.5 kHz [12]. Susceptibility around 4 kHz is associated with the mechanical properties of the middle ear and resonance frequency of external auditory canal [13].

Mechanism of cochlear pathology can be categorized into mechanical and metabolic [12]. Metabolic damage is a major mechanism of NIHL from chronic exposure to noise. Characteristic finding is loss of hair cells as a result of increased free radicals such as reactive oxygen species (ROS) and reactive nitrogen species within cochlear hair cells [14]. Damage starts in outer hair cells in row 2 and 3 of most vulnerable area to noise, possibly as a result of necrosis [15]. Noise releases ROS from mitochondria into cytoplasm of hair cells via release of Ca^{2+}. Cytoplasmic ROS leads to production of pro-inflammatory cytokines and pro-apoptotic factors, finally to apoptosis of hair cells. Free radicals can persist for 7–10 days after cessation of noise exposure, which could induce progressive cochlear damage [16]. Noise-induced ischemia and reperfusion also increase the generation of ROS [14]. Lipid peroxidation induced by ROS acts as a toxic substance, causing apoptosis [15].

When the noise is extremely loud over 130 dB SPL, mechanical damage could occur via excessive vibrations of the delicate cochlear structures. Breaking or fusion of stererocilia of hair cells are most specific morphopathology. Noise could damage other cochlear structures; damage to cochlear vasculature, loss of fibrocytes, rupture of attachments of stereocilia tips to the tectorial membrane, distension or rupture of tip links, damage to pillar cells, and rupture of dendrites [14]. Noise could crumple pillar cell, decreasing length of the OHC, and detaching stereocilia from tectorial membrane in reversible way, which is understood as a mechanism of TTS [17].

Recent hot topic on noise-induced damage on auditory system is cochlear synaptopathy. Until recently, noise that does not cause threshold shift was considered safe. However, recent animal experiments have shown that noise exposure that does not cause hair cell loss may damage ribbon synapse between inner hair cell and spiral ganglion neuron [11]. Cochlear inner hair cells (IHCs) are important as mechano-electrical transducer of auditory information. Receptor potential generated by IHCs releases the neurotransmitter at the synaptic end, while outer hair cells work as cochlear amplifier via process of electromotility which increases the vibration of basilar membrane. Synaptic ribbon is specialized electron-dense structure, which is anchored to pre-synaptic membrane only nanometers apart. It contains large pool of "readily releasable" vesicles to finely vary synaptic output continuously in sensory organ of hearing and vision [18]. Thus, damage of ribbon synapse between IHCs and spiral neurons results in improper conveyance of neural information to auditory nerve fiber. Noise causes damage of presynaptic ribbons and postsynaptic nerve terminals showing various degree of swelling. The mechanism of damage for postsynaptic terminal is glutamate-mediated excitotoxicity, while mechanism of ribbon loss is unclear [19]. In cochlear synaptopathy, hearing threshold is normal because OHC is undamaged, but the amplitude of auditory nerve activity decreases as a result of silenced auditory nerve fibers [20].

Auditory nerve fibers (ANFs) could be functionally categorized by their spontaneous rate (SR). High-SR ANFs respond to sound at threshold level, whereas low-SR ANFs react to loud sound, follow rapid amplitude changes of acoustic signal, and are considered to have an important role in the hearing in noisy environment due to their larger dynamic range. Low-SR ANF appears to be damaged selectively after noise exposure [20]. Because it causes functional hearing loss without threshold change, it is also called "noise-induced hidden hearing loss".

Cochlear synaptopathy could be permanent and lead to a degenerative death of the spiral ganglion neuron [21]. The results of human studies on cochlear synaptopathy are controversial. If the cochlear synaptopathy is confirmed in human subjects, the conventional belief that noise would be safe if it does not cause a threshold shift should be changed [19].

1.3 Individual susceptibility

Severity of cochlear damage after noise exposure varies among individuals. Genetic factors would account for the different susceptibility up to 50% [22]. In animal study, genetic deficits leading to ARHL predispose the inner ear to NIHL [23]. Single Nucleotide Polymorphism (SNP) is the most common site of genomic mutations. It is estimated that the SNP of K^+ recycling gene and heat shock protein (HSP) gene in the inner ear is associated with the sensitivity of NIHL [24, 25].

ISO 1999:2013 model assesses the risk of NIHL with age, gender in addition to intensity of exposed noise and exposure time in years [26]. The prevalence of NIHL is higher in male than in female and racial difference exists with lower prevalence in darker pigmentation [27]. Increasing age, smoking, poor diet, lack of exercise, comorbidity such as diabetes, cardiovascular disease may increase risk of NIHL [28]. Sufficient nutrition helps to preserve high frequency hearing [29].

1.4 Noise exposure levels by occupational group

The prevalence of hearing loss among noise-exposed workers is various across industries and occupations. Noise exposure is common in industries of mining, construction, manufacturing, forestry, utilities, repair and maintenance, and transportation sectors [2]. Sixty-one percent of the mining workers, 51% of the construction workers, and 47% of the manufacturing workers are exposed to noise [1]. Among workers of the above industry sectors, 20 ~ 25% have a material hearing impairment [30]. In Korea, NIHL was most common in the workers of manufacturing sector, followed by construction sector (**Figure 2**).

1.5 Diagnosis

Audiometric evidence of NIHL is characteristic notch or bulge between 3 kHz and 6 kHz, mostly worst at 4 kHz, with preserved hearing at 8 kHz and lower frequencies [31]. Notch deepens and widens with continued noise exposure, eventually involving lower frequencies. Hearing aggravates in the first 10–15 years of noise exposure, and then process slows down [17]. The maximum hearing loss from NIHL has been accepted not to exceed 75 dB at higher frequencies and 40 dB at lower frequencies [32]. However, it could reach 80 dB or worse in 2.6% of construction industry engineers [33]. Notch could be observed in 19.9% of persons without history of loud noise exposure, so audiometric notch does not necessarily mean NIHL [3].

Unlike NIHL, the ARHL accelerates over time. Hearing loss in ARHL starts at 8 kHz or higher frequencies and expands to lower frequencies. When NIHL and ARHL coexist, the notch widens and looks like a bulge [34]. As the combined ARHL progresses with advanced age, noise notch may be rarely observed [35]. Sometimes medicolegal opinion is sought about which factor contributes more on the etiology of hearing loss between noise and age. It is impossible to distinguish the allocation of each factor in aged persons.

Hearing in noise may be compromised probably due to cochlear synaptopathy. To quantify damage from noise exposure, speech recognition in quiet and noise is

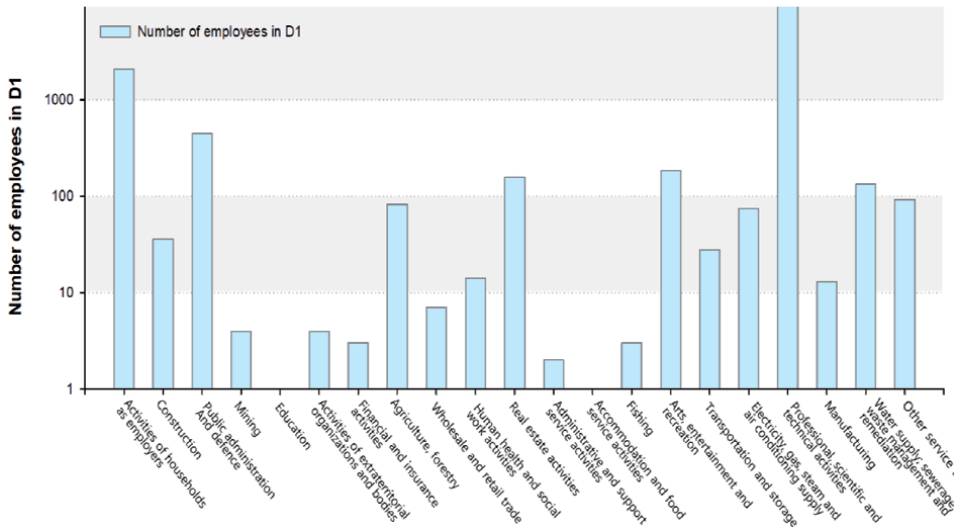

Figure 2.
Prevalence of noise-induced hearing loss (D1) according to Korean standard industrial classification. A total of 12,822 cases were diagnosed as NIHL in 2018 in Korea. Among them, NIHL was most commonly reported in manufacturing sector with 9,455 cases, followed by construction, mining, transportation, and business facility management and business support services sectors. http://www.kosha.or.kr/kosha/data/healthExamination.do.

also recommended [21]. Otoacoustic emission (OAE) can be used as an earlier test before PTA deficit is evident [36]. But recent studies showed that OAE was not more sensitive than PTA in assessing hearing loss caused by long-term exposure to noise [37]. Possibility of middle ear acoustic reflex as a diagnosis of cochlear synaptopathy was also suggested [38].

1.6 Asymmetric NIHL

Noise-induced hearing loss is typically bilateral because noise affects both ears symmetrically. However, it could be asymmetric. Prevalence of asymmetric hearing gap larger than 15 dB in general population is 1% while those of NIHL were reported as 4.7–36% [35]. Left ear was more affected, especially in male [39, 40]. Lateral difference was most prominent in 3–6 kHz [41]. The firefighters and public safety workers may no longer be able to carry their duties because asymmetric hearing disturbs to distinguish sound direction and causes work-related risk [42].

There are two theories about mechanism of lateral asymmetry. One is head shadowing effect that makes noise level affecting each ear unequal [43]. Another is that left ear is more susceptible to noise damage for physiological reasons. It involves a less sensitive acoustic reflex in left side and a stronger protective auditory efferent system of the right olivocochlear bundle [44, 45].

MRI scan should be performed to rule out vestibular schwannoma in asymmetric hearing loss. Medicolegal decision of asymmetric NIHL is quite unconvincing. According to Robinson's criteria, if there is no evidence of NIHL in the better ear, patients can be declined compensation [45]. Whereas, Fernandes et al. insisted that comment should be made on the causation as being noise-induced, if there is no other cause to explain the asymmetry [46].

1.7 Tinnitus and hyperacusis

The prevalence of tinnitus among noise-exposed workers is 24%, which is much higher than that of the general population [47]. Tinnitus is bilateral in majority of

workers exposed to noise, however, some of them complains of unilateral symptom, more commonly in left ear [48]. Tinnitus degrades quality of life in workers and distracts military personnel during military operation [49]. Although association of noise and hyperacusis have rarely been studied, pop and rock musicians were at high risk for the development of hyperacusis [50].

1.8 Noise and dizziness

Besides hearing loss, noise can induce vestibular dysfunction through the damage to sacculocolic reflex pathway or damage to vestibular hair cell [51, 52]. The relationship between NIHL and abnormal vestibular evoked myogenic potentials (VEMPs) was reported in human study [53]. Noise exposure reduced the stereocilia bundle density of the vestibular end organ and reduces the firing rate of the anterior semicircular canal (ASCC) without significant change of the vestibular-ocular reflex, suggesting possibility of "hidden vestibular loss" [52]. Abnormal electronystagmography (ENoG) was more common in the asymmetrical NIHL group than in symmetrical NIHL [54].

1.9 Prevention

Noise regulation is the best option to prevent NIHL. Current noise regulations are based on the intensity of chronic continuous noise rather than impulsive acoustic trauma. Degree of exposure is calculated as registered in individual reporting or hearing protection programs [30]. Noise of intensity below 80 dB (A) (weighted decibel relative to human ear) reduces the risk of NIHL [55]. Daily permissible exposure limit (PEL) and exchange rate should be set to run hearing conservation program. Many countries legislate PEL at 85 dB(A) for an 8-hour workday. Some countries loosely permit up to 90 dB(A). Exchange rate defines the 3–5 dB increase in noise intensity with which exposure time should be halved to protect hearing. Exchange rate of 5 dB appears to be more accurate than 3 dB [56]. For example, 4 hours of exposure to 90 dB(A) is as hazardous as 8 hours of exposure to 85 dB(A). Number of workplaces of which noise exceeds PEL of 85 dB(A) for an 8-hour workday has been decreasing in Korea. It reduced from 20.2% of total workplaces in 2014 to 15.3% in 2018 (**Figure 3**). For impulse noise, 140 dB is generally set as the upper limit [57].

Hearing protection devices (HPDs), including earmuffs and earplug, are secondary level personal protection. Most workplace noise can be attenuated to a safe level by reducing noise by 5–10 dB, and this goal can be achieved when if HPDs are worn properly and continuously [30]. However, many workers do not wear HPDs for enough time and the effect is cut in half if workers remove HPDs for only 30 minutes of an 8-hour workday [58]. Therefore, it is efficient, when selecting HPDs, to focus on consistency of use than noise reduction rate of HPDs [59]. Individual fit-test system for earplugs is more feasible for field use and could effectively prevent hearing deterioration [60]. Earmuffs can reduce noise more consistently than earplug, and 3D print earmuffs made from light materials such as acrylonitrile butadiene styrene/clay nanocomposites was helpful in reducing weight of earmuffs and would probably increase comfort [61]. Hearing conservation program in elementary school are potentially effective way to know the risks of noise exposure early in life, leading to behavioral changes such as noise reduction and HPDs [62].

It is important to reduce the "know-do" gap between knowledge accumulated to prevent NIHL and actual implementation at workplace. This requires frequent

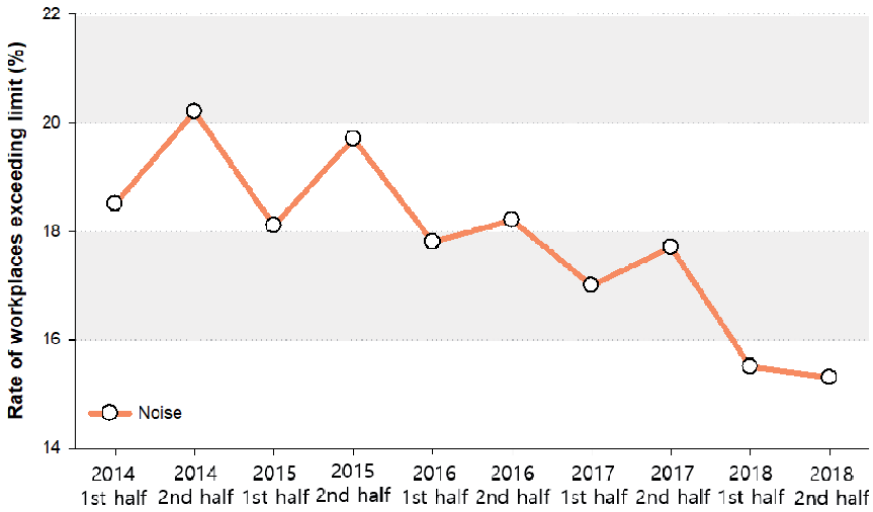

Figure 3.
Korean workplaces of which noise exceeded permissible exposure limit (2014 to 2018). Percentage of Korean workplaces of which noise exceeded permissible exposure limit was 21% until 2010 but is gradually decreasing. In the second half of 2018, it was 15.3% showing the lowest rate for the past 5 years. https://www.moel.go.kr/info/publict/publictDataView.do;jsessionid=adRh47EovBcKL142q0R3sKQStfieMxcEVFYSD2NXqjie0s2D438avLaPebxaainR.moel_was_outside_servlet_www1?bbs_seq=20200200123.

communication meetings for noise control, assigning staff to provide daily program support, noise hazard identification, selection of HPDs, and providing inexpensive sound level meters or sound measuring apps [30].

We suggest that hearing conservation program should include administrative or engineering controls to reduce sound levels. Workplace noise should be monitored using either a wearable sound level meter or a dosimeter to determine if noise exposure level is at or above 85 dB(A). If the workplace noise exceeds an 85 dB(A) for an 8-hour workday, exposed employees should be enrolled in a hearing conservation program (HCP) and audiometric test should be conducted annually by audiologist to check if the standard threshold shift occurs. Employees enrolled in HCP should be offered HPDs and take mandatory training program annually about effects of noise on hearing, purpose and value of HPDs and hearing test. Managers or supervisors must attend training sessions and should keep the record of all hearing tests, noise surveys, and training records.

1.10 Pharmacotherapy

There is no practical medication to prevent NIHL from chronic noise exposure. Most drugs have been studied either on an experimental level or on an animal study basis.

The noise exposure increases the immune and inflammatory factors in the cochlea. Steroids are the only approved medicine in treating sudden hearing loss. Animal study showed that steroids before and after the exposure to acoustic trauma were effective through control of the inflammatory response [63, 64]. It is estimated that intratympanic steroid injection would be effective in protecting outer hair cell efferent terminal synapse, and intraperitoneal steroid injection would be effective in protecting organ of Corti and stria vascularis [65]. In human studies, combined systemic & intratympanic steroid administration was more effective than systemic steroid only [66]. Long-term administration of steroid is inadequate due to its possible side effects.

Free oxygen radicals and oxidant stress are important pathological mechanisms of NIHL. N-acetylcysteine (NAC) is an antioxidant and is known to reduce noise-induced ototoxicity in animal study. There was no significant differences of overall hearing loss in military population between NAC group and placebo group [67].

Neurotropin-3 (NT3) and Brain derived neurotrophic factor (BDNF) are known to be important factors in the generation and maintenance of cochlear hair cell ribbon synapse [68, 69]. Animal study demonstrated a reduction in synaptopathy and a restoration of hearing immediately after strong noise exposure [70] but human data is lacking.

1.11 Conclusion

Noise-induced hearing loss is drawing more attention than ever before. Besides hearing loss, noise can also compromise the vestibular function. Recently, evidence on noise-induced cochlear synaptopathy is accumulating. Exposure to noise in short duration or less intense noise may result in functional hearing loss without threshold change on audiogram. So far, prevention is the best option, but we expect that continuous research on NIHL will open up the possibility for treating drug ototoxicity and ARHL as well.

2. Chemical induced hearing loss

2.1 Introduction

Chemicals such as organic solvents, metals and asphyxiants are known for their neurotoxic effects on both the central and peripheral nervous systems. These agents could injure the sensory cells and peripheral nerve endings of the cochlea [71].

Over the past 3 decades, several studies investigated the relationship between occupational exposure to chemical substances and hearing loss for humans [72]. According to the score combining human and animal data, lead (and its inorganic salts) as an only inorganic substance and the organic chemicals including toluene, styrene, and trichloroethylene were ranked as "ototoxic". Other candidate substances classified as "possibly ototoxic" are nitriles (acrylonitrile, 3-butenenitrile), carbohydrates (n-hexane, p-xylene, and ethylbenzene), hydrogen cyanide, carbon monoxide, carbon disulfide, and mercury, germanium, and tin. Recently, a classification criteria on ototoxic substances was delivered by the Nordic Expert Group (NEG). The NEG chose a quantitative approach, meticulously comparing the "no observed" or "lowest observed" effect levels with occupational exposure limits from various countries. This information can be useful for the management of toxic substances and prevention of hearing loss (**Table 1**) [73].

Until now, regarding regulatory problem, the interaction with noise has not been investigated in a satisfactory way. Although it is very difficult to combine all of the data to arrive at solid conclusions, this does not exclude the possibility of other chemical substances can worsen hearing losses due to noise.

2.2 Organic solvents induced hearing loss

In workplace, one of the most common kinds of exposure is solvents mixture. The most prevalent exposures seem to happen in industries where workers have contacts with paints, thinners, lacquers and printing inks [74]. In Korea, organic solvents have the second highest excess rate among harmful factors in workplaces.

Classification	Criteria	Ototoxic substances
Category 1	Human data indicate auditory effects below or near the existing OELs. There are also robust animal data supporting an effect on hearing resulting from exposure	toluene, styrene, carbon monoxide, carbon disulfide, lead and mercury
Category 2	Human data are lacking, whereas animal data indicate an auditory effect below or near the existing OELs.	p-xylene, ethylbenzene, and hydrogen cyanide
Category 3	Human data are poor or lacking. Animal data indicate an auditory effect well above the existing OELs.	Other substance

OEL: occupational exposure limits.

Table 1.
Classification and the criteria of ototoxic substances based on occupational exposure limits.

The exceeded rate of the occupational exposure limit maintained a similar level of 0.4 to 0.7% for the last five years from 2014 to 2018 (**Figure 4**). Although the ototoxic effects of organic solvents have been widely studied, there is no consensus about the correlation between the solvents exposure level and the resultant hearing loss.

In occupational condition, the ototoxicity of organic solvents is more difficult to prove. Because the workplace concentration of chemicals is much lower than that used in animal studies, and the workers are usually exposed to a mixture of solvents with widely varying compositions and concentrations, it is difficult to assess the effect of a single substance. Furthermore, in industrial settings, exposure to chemicals often coexists with an elevated level of noise, which makes it difficult to distinguish the solvent effect from the noise-induced hearing loss [22].

Recently, Hormozi et al. reported dose–response relationship between organic solvents mixture exposure and risk of hearing loss from a meta-analysis [72]. The results showed a statistically significant dose–response relationship between the occupational exposure level (Exposure Index, EI), duration of exposure or number of solvents and the risk of developing hearing loss (**Table 2**).

2.3 Mechanism of organic solvent ototoxicity

Long-term exposure to organic solvents has been shown to cause irreversible hearing impairment damaging the cochlear hair cells as the first target [75]. The mechanism of acute injury would be the direct action of solvents on the cells of the organ of Corti, resulting in disorganization of their membranous structures, whereas chronic ototoxic effects may be explained by the formation of chemically and biologically reactive intermediates [76].

The ototoxicity mechanisms with strong evidence were described in **Table 3**. These solvents adversely affect both peripheral and central auditory system. For example, toluene may enhance inhibitory synaptic responses as CNS depressants, also can inhibit the middle-ear acoustic reflex (cholinergic efferent system). This would make inner ear more susceptible to co-exposure even to a noise intensity below permissible limit value [77].

Śliwinska-Kowalska (2007) summarized a risk/odds ratio of organic solvent-induced hearing loss, compared to non-exposed population, as followings. 1) No excess risk was found for workers exposed to solvent mixture when: the exposure history was short (up to 4 years), or the exposure level was very low (current exposure ranged from few to 18 ppm for toluene, to few ppm for xylene and other

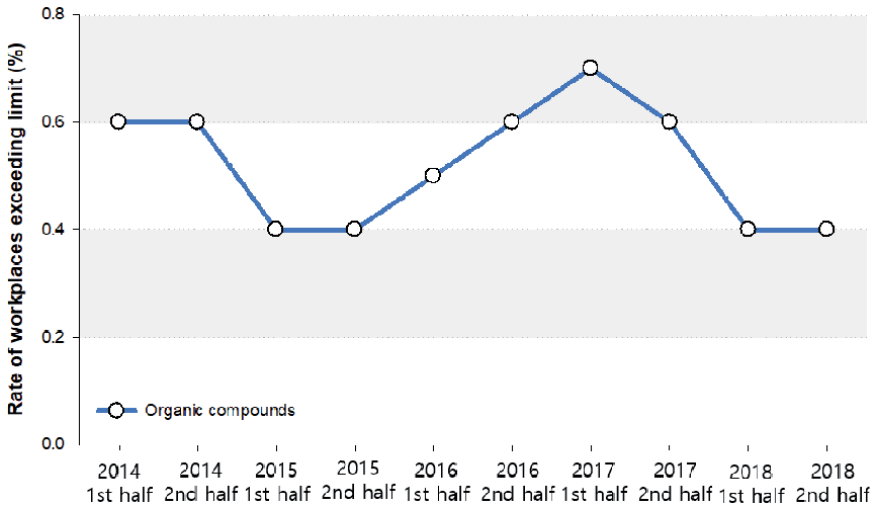

Figure 4.
Korean workplaces of which organic solvents exceeded permissible exposure limit (2014 to 2018). https://www.moel.go.kr/info/publict/publictDataView.do;jsessionid=adRh47EovBcKL142q0R3sKQStfieMxcEVFYSD2NXqjie0s2D438avLaPebxaainR.moel_was_outside_servlet_www1?bbs_seq=20200200123.

Variable	Reports (n)	OR (95% CI)†	p
Duration of exposure			0.001
< 5 years	4	1.01 (0.92–1.10)	
5–10 years	3	1.57 (1.27–1.93)	
> 10 years	7	3.36 (2.36–4.79)	
Exposure index (EI)‡			0.049
< 0.5	3	1.37 (0.75–2.48)	
0.5–0.99	3	3.25 (1.88–5.62)	
≥ 1	7	4.51 (3.46–5.90)	
Solvents			0.045
2–5	7	1.62 (1.07–2.44)	
6–8	4	4.22 (2.72–6.56)	

**Hearing loss: average hearing threshold greater than 25 dB in at least one ear (250–8000 Hz).*
†Reference group: not exposed to either noise or solvents mixture.
‡EI: the sum of the mean time-weighted exposures to each solvent was divided by its occupational exposure limit (American Conference of Governmental Industrial Hygienists threshold limit value, ACGIH TLV).
Cited from THE RISK OF HEARING LOSS ASSOCIATED WITH OCCUPATIONAL EXPOSURE TO ORGANIC SOLVENTS MIXTURE WITH AND WITHOUT CONCURRENT NOISE EXPOSURE: A SYSTEMATIC REVIEW AND META-ANALYSIS. International Journal of Occupational Medicine and Environmental Health 2017;30(4):521–535 https://doi.org/10.13075/ijomeh.1896.01024.

Table 2.
Dose–response relationship between organic solvents mixture exposure and risk of hearing loss.*

solvents, and the exposure index was <1). 2) Excess risk was found for workers exposed to solvent mixture when: the exposure level was moderate (toluene exposure ranged from 25 to 70 ppm, xylene exposure 25–40 ppm, and exposure index from 0.3–1.53), or the workers were exposed to high solvent concentrations and noise (the mean lifetime exposure to xylene was 696 ppm, to toluene 203 ppm, and the mean exposure index was 6.3) [72]. Risk/odds ratios of hearing loss due

Chemicals	Targets and impacts	Mechanism	Points to consider
Aromatic solvents	Target: Central nervous system, cochlear hair cell Impact: Enhancement in inhibitory synaptic responses, affecting middle-ear acoustic reflex.	1. In case of acute effect, direct action on the cells of the organ of Corti. 2. In case of chronic effect, formation of intermediates such as reactive oxygen species. 3. Cause K^+ flow dysfunction. 4. Outer hair cell toxicity due to K^+ massive efflux and tunnel accumulation.	1. Prolonged exposure causes irreversible hearing impairment. 2. Affect the middle-ear acoustic reflex, which partially explain the synergistic effects of co-exposure to noise and aromatic solvents.
Nitriles	Target: cochlear hair cell, spiral ganglion cells Impact: Reduces high-frequency hearing sensitivity and enhances noise-induced hearing impairment.	1. Induce loss of inner ear hair cells and spiral ganglion cells. 2. In the case of acrylonitrile, the risk of oxidative damage to the inner ear is increased due to damage to the cellular antioxidant defense mechanisms.	Permanent hearing damage may occur due to combined exposure with noise.
Halogenated hydrocarbons	Target: Outer hair cell	In the case of polychlorinated biphenyls (PCB), it is assumed to have a direct effect on outer hair cells.	Presumed to be a sequelae of thyroid disease caused by halogenated hydrocarbons.
Trichloroethylene	Target: Cochlear sensory hair cell, spiral ganglion cells, auditory nerve pathways	Unknown, but dose dependent hearing loss	Hearing loss tends to occur only at high level of exposure.

Table 3.
Summary for impacts and mechanisms of ototoxic chemicals in workplace exposure.

to exposure to organic solvent mixture were ranged 1.4 to 5.0, while the ratio of populations co-exposed to noise and solvents were 1.7 to 8.25 [78].

2.4 Interactive effects of organic solvents and noise

Previous experiments on ototraumatic substances in animals have confirmed the synergistic adverse effects of combined exposure to noise and solvents on hearing [79, 80]. In the case of combined exposure to noise and organic solvents, depending on the parameters and characteristics associated to the noise (such as intensity and impulsiveness) and solvent (such as concentration), they might interactively affect each other.

From the animal studies, the increase in auditory brainstem response (ABR) latencies after exposure by inhalation of more than two solvents observed an additive effect rather than a synergistic or antagonistic interaction. Results of these studies imply that the mechanism of ototoxicity for these solvents may be similar.

However, rats simultaneously exposed to both toluene and noise induced a more severe hearing loss than the summated hearing loss obtained from an equivalent exposure level to each agent alone [77].

From the human studies, exposure to a mixture of solvents may damage the inner ear to a much greater extent than noise exposure. The relative risk for hearing loss in workers exposed to solvents was greater (RR = 9.6) in comparison to workers exposed only to noise (RR = 4.2). Hearing loss associated with styrene significantly increased in high frequency (8–16 kHz) and mid-audiometric frequency of 2 kHz [22]. Sliwinska-Kowalska et al. (2003) found a positive linear relationship between average working life exposure to styrene concentrations and hearing thresholds at 6 and 8 kHz. The possible synergism of combined exposure to solvents and noise on hearing has not been consistently identified in human studies. Some researchers have failed to find a synergistic effect between these agents on hearing [22].

Although it is difficult to derive a dose–response relationship between the solvent concentration and the hearing outcome, the risk of hearing loss increase with the longer duration of employment and accompanying noise in workers exposed to organic solvent [72].

2.5 Diagnostic tool for ototoxic substances

Although there is no consensus on the lowest OELs for solvents in relation to their effect on the auditory organ, the current standards for solvent-exposed populations seem to be inadequate. Since organic solvents have detrimental effects both on the peripheral and central parts of the auditory pathway, pure-tone audiogram might be insufficient to monitor their ototoxicity [78].

From previous studies, researchers have found some useful tests for the evidence of adverse effects on the central auditory system in workers exposed to mixture of solvents: 1) dichotic listening: useful tool in the assessment of solvent-exposed workers, particularly in those who have had intermediate levels of exposure; 2) electrophysiological techniques (ABR): increase of the absolute latencies and inter-peak latencies (IPL) between waves of the ABR (I-III IPL; I-V IPL; III-V IPL) or prolonged P300 (a long latency auditory evoked potential); 3) otoacoustic emissions (OAEs): gradual deterioration of hearing threshold before audiometric change; 4) comprehensive battery of behavioral central auditory function assessment procedures: solvent-exposed participants presented with poorer results adjusted for age and hearing thresholds in comparison to non-exposed subjects [77]. These tests can be conjugated to evaluate possible adverse effects of solvents on the auditory system.

2.6 Recommendations

So far, the robust evidence confirms that the effects of ototoxic substances on auditory function can be aggravated by noise, which is supported by data from epidemiologic studies on human workers.

In real world, the exposure to solvent mixtures is various in terms of levels and composition. Numerous study groups reported an association between low to moderate exposure to solvent mixtures and hearing disorders. However, occupational legislation does not take environmental chemicals hazardous to hearing into consideration. Thus, there may be numerous workers with unmet needs concerning hearing conservation.

Here we are going to make some necessary suggestions for occupational health professionals and the workforce. Health care provider should be aware of the risks related to ototoxic substances. Employers and workers should be advised

accordingly. Risk management measures aimed at reducing exposure to noise and ototoxic substances, especially co-existence of them, should be encouraged. In occupational health-screening activities, ototoxicity should be included. Appropriate diagnostic tools should be developed for early detections of chemically induced hearing impairment. Suitable scientific investigations into ototoxic properties of substance and combined effects with noise should be encouraged by well-designed studies.

Occupational noise exposure has been well-known as the most deleterious factor to hearing loss, however, the impact of chemical-induced hearing loss on workers should not be underestimated [81]. Industry-based initiatives should include the identification of populations at risk and the delivery of tailored hearing conservation program accordingly to noise and chemical-exposed workers regarding their exposure levels.

Conflict of interest

The authors declare no conflict of interest.

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Author details

Joong-Keun Kwon[1] and Jiho Lee[2*]

1 Department of Otolaryngology, Ulsan University Hospital, Ulsan University, College of Medicine, Ulsan, Republic of Korea

2 Department of Occupational and Environmental Medicine, Ulsan University Hospital, Ulsan University, College of Medicine, Ulsan, Republic of Korea

*Address all correspondence to: leejh@uuh.ulsan.kr

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Chapter 3

Noise Induced Hearing Loss: A Case Study from a Speech-Language Pathologist's Perspective

Alejandro Brice

Abstract

Hearing loss is very common in the United States and the most widespread disability in the U.S. Hearing loss is the third most chronic health condition in the U.S. Noise induced hearing loss (NIHL) results from damaging external noise. This injury leads to temporarily or permanently affecting sensitive inner ear structures (e.g., cochlea, organ of Corti, and hair cells). NIHL can result from a single high-level noise exposure or repeated exposures to excessively loud noises [i.e., typically 85 dBA or greater, (A weighted decibel)]. Damage to the inner ear can also result from aging (i.e., presbycusis). This case study documents the hearing loss of an otherwise healthy 21-year-old, male individual and his progressive moderate-to-severe sensorineural hearing loss over a period of 41 years. His history will be reported along with his perspective as a speech-language pathologist and speech scientist. The individual with hearing loss has adapted to wearing hearing aids over the last five years. Issues that have occurred affecting comprehension along with compensatory strategies that assisted listening and comprehension will be discussed.

Keywords: Noise induced hearing loss, presbycusis, sensorineural hearing loss, compensatory strategies

1. Introduction

Hearing loss is very common in the United States. It is the third most chronic health condition in the U.S. [1]. A common cause of hearing loss is noise induced hearing loss (NIHL). NIHL results from damaging external noise, typically short high intensity noise. Loud sounds overstimulate delicate cells, leading to the permanent injury or death of cochlear hair cells. The hair cells cannot regenerate and there is no current cure for cochlear hair cell restoration. Therefore, once the hair cells die, the hearing loss become permanent.

NIHL injury leads to temporarily or permanently affecting sensitive inner ear structures (e.g., cochlea, organ of Corti, and hair cells). NIHL can result from a single high-level noise exposure or repeated exposures to excessively loud noises [i.e., typically 85 dBA or greater, (A weighted decibel)]. Noise induced hearing loss (NIHL) is one of the primary causes for chronic hearing loss. In the United States, NIHL from occupational noise ranges from 16–24% [2]. Up to 7% of noise induced loss in Australia has

been found to arise from occupational noise [3]. Zhou, Shi, Zhou, Hu, and Zhang [4] reported that the prevalence of NIHL in Hungary was 21.3%, with 30.2% was related to high frequency NIHL. Thus, NIHL occurs with regularity in many world societies.

NIHL can result from occupational noises and/or non-occupational noise (e.g., gun blast or loud music). A characteristic of NIHL is the classic V notch occurring around 4,000 Hz. The surrounding frequencies must be at minimum 10 Hz or less than the hearing level at 4,000 Hz [5]. Noise exposure hearing loss is likely to become permanent six months after noise exposure has ceased [4].

Cutietta, Klich, Royse, and Rainbolt [5] found that high school band teachers displayed greater degrees of hearing loss than non-music teachers. Hearing loss incidence among professional musicians has been found to be very high, i.e., musicians had 3.51 fold increase rate of NIHL than non-musicians [6]. Other high-risk professions included aviation related professionals, i.e., incidence among aviators was found to be higher for certain U.S. military branches than others. Sensorineural hearing loss (SNHL) was greater for those in the U.S. Army and Air Force than the Navy or Marines [7].

1.1 Other causes of hearing loss

Nishad, Gangadhara, Mithun, and Sequeira [8] found that 30.7% of newborn babies screened for otoacoustic emission (OAE) and brain stem-evoked response audiometry (BERA) were high risk for hearing loss. Of the babies tested for high risk, 3.6% showed left ear hearing loss; 5.2% showed right ear hearing loss; while, 6.8% showed bilateral hearing loss. Consequently, congenital hearing loss and noise induced hearing loss (NIHL) are both contributors to hearing loss world-wide. Other etiological causes of hearing loss may include head injuries. Sports accidents, work related traumas, and road accidents are among the leading causes of head trauma.

1.2 Head trauma and hearing loss

Since, the case study participant (AB) experienced repeated chronic traumatic encephalopathies (CTEs) via karate for a period of years, TBI and CTEs will be reviewed. Other types of injuries may result from sports injuries (i.e., traumatic brain injuries, repeated chronic traumatic encephalopathies). Many contact sports involve CTEs with its participants (e.g., karate, football, wrestling, basketball, etc.). Some non-contact sports may also involve head traumas, such as cycling.

It has been noted that auditory issues following mild traumatic brain injury (TBI) are common [9]. Hoover et al., [9] examined speech in noise comprehension following mild traumatic brain injury (MTBI). Measures included monaural word (WIN) tasks, sentence (QuickSIN) tasks, and binaural spatial release task. The MTBI and non-MTBI participants were matched on pure-tone thresholds, thus, measuring speech in background noise. Results indicated that a high number of individuals with MTBI experienced difficulties with speech-in-noise. Speech-in- noise difficulties were related to auditory and non-auditory factors. Spatial separation was found to be related to working memory and peripheral auditory factors.

Traumatic brain injuries and head traumas arising from concussions or repeated sub-concussive impacts have been shown to be intertwined much deeper than what was previously thought [10]. While, NIHL affects the cochlea, sub-concussive impacts affect how the brain perceives sound [9] and affects the brain's ability to comprehend speech and sustain one's auditory attention to task [10, 11]. AB's sub-concussive impacts over the period of six years may have had a more lasting impact on auditory processing [10], difficulties with speech in noise [9], and/or sustaining listening abilities over time [11] than the noise induced hearing loss.

Concussions can result in auditory processing deficits without noted hearing loss [11]. Children and adolescents who have sustained a concussion were compared to a control group (non-concussive orthopedic injuries). Thompson et al. [11] found that the children with concussion had difficulties with speech in noise and with sustaining attention on cognitively taxing auditory tasks. These auditory difficulties are compounded with the existing MTBIs.

Fluctuating hearing loss is most likely to occur within the first year of the trauma [3]. Reports of head trauma and SNHL have been minimal [10]. Studies investigating trauma and hearing loss have mostly looked at immediate and short-term effects and have not investigated long term and chronic effects. There is no consensus regarding the endpoint for sensorineural hearing loss, cognitive and language difficulties after head trauma [10]. However, it appears that 90% of individuals who suffered a TBI do not experience further deterioration of hearing following the trauma [10]. Further research into auditory processing, attention, speech-in-noise processing, and other cognitive and language difficulties following a TBI are still warranted.

1.3 Hearing loss and cognitive loss

The most common cognitive loss disorder that affects memory and disruption of executive functioning (planning, organizing, sequencing, abstracting) that also interferes with activities of daily living (ADLs) is Alzheimer's dementia (AD) [12]. According to Livingston et al. and the 2017 Lancet Commission on Dementia Prevention [13], hearing impairment is one of nine modifiable risk factors associated with dementia. The other eight factors include hypertension, smoking, obesity, depression, physical inactivity, diabetes, low social contact (i.e., limiting conversation and mental processing of sounds), and less education. The National Institutes of Health (NIH) identifies social isolation (which can be perpetuated by a hearing loss) and hearing loss as a potentially modified dementia risk factor [14]. According to the 2017 Lancet Commission model [15] and their "new model of life-course risk factors"; hearing loss contributes the highest risk factor associated with dementia.

Hearing loss may contribute to dementia via social isolation and reduced opportunities for communication. However, hearing loss has been directly associated with neurodegeneration and cortical thinning in otherwise cognitively normal adults. Ha et al. [15]. They found that right ear hearing loss was associated with right superior temporal and left dorsolateral frontal areas. Neurodegeneration precedes dementia. Griffiths et al. [16] propose an important interaction occurs between auditory and cognitive processing in the medial temporal lobe and later dementia pathology.

Nadhimi and Llano [17] have found that hearing loss in animals produced cognitive decline. Specifically, Nadhimi and Llano stated that, "The data suggest that noise-exposure produces a toxic milieu in the hippocampus consisting of a spike in glucocorticoid levels, elevations of mediators of oxidative stress and excitotoxicity, which as a consequence induce cessation of neurogenesis, synaptic loss and tau hyper-phosphorylation" (p. 1). Acute noise exposure has also been shown to have detrimental effects on hippocampal physiology, particularly neurogenesis. Individuals with hearing loss may consequently experience dementia in later life. Further study in this area is needed.

1.4 Age related hearing loss

Age related hearing loss (ARHL, presbycusis) is a progressive and chronic impairment, that is often bilateral [17]. The prevalence of ARHL increases with age. ARHL, in and of itself, can lead to decreased health care. In addition, noise induced

hearing loss (NIHL) and age-related hearing loss (ARHL) increase hearing thresholds over time [18]. Noise exposure creates a higher, combined burden on hearing loss. Grobler et al. [19] suggest that this combined hearing burden increases even if exposure to the excessive noise has stopped.

ARHL, in and of itself, leads to mild hearing loss in individuals over 60 years of age and moderate hearing loss in individuals over 72 years of age [20]. ARHL is a prevalent and chronic condition for individuals over 65 years of age. No international classification system takes into account frequencies above 4 kHz for ARHL [20]. ARHL accounts for 42% of hearing impairment for individuals from 60–69 years of age. This progressively increases until 85–90 years of age, at which time ARHL accounts for 100% of hearing loss issues [20].

2. Case study (AB)

This is a case study of a cognitively normal, male adult (AB) with a noise induced hearing loss (NIHL) from a young age (documented at 21 years of age). AB is a fluent Spanish-English speaker. Initial diagnoses pointed to two possible etiologies leading to sensorineural hearing loss: (a) a singular incident of shooting a loud firearm without ear protection; and/or (b) repeated sub-concussive impacts from karate over a period of six years (1973–1979) (diagnostic conversation with audiologist after an evaluation, Dr. Barbara Packer-Muti, 1992). Initial diagnosis at 21 years of age indicated a NIHL, bilateral, V notch hearing loss beginning at 1 K and progressing through 8 K. See **Table 1** which illustrates the hearing loss with audiograms obtained for following ages of 21, 34, 42, 49, 45, and 57 years of age.

AB's hearing has deteriorated over time. It is difficult to ascertain his loss over 4 kHz completely to ARHL [19]. However, his losses over time are most likely due to the combined factors of ARHL and NIHL [19]. Consistently, his worse frequencies are in the 4 KHz to 8 KHz. His bilateral loss is more severe in his right ear; however, the left ear also shows significant loss in these same frequencies and with severity. AB at the time of the last evaluation was 57 years of age. Evidence of age related hearing loss is apparent across frequencies from 25o Hz to 4 kHz. AB's hearing loss has progressed due to NIHL and age related hearing loss (ARHL) as illustrated by **Figure 1**. **Figure 1** shows contrasting audiograms obtained at 21 and 57 years of age.

2.1 Career as a speech-language pathologist

AB had been a practicing speech-language pathologist for 32 years when the last audiogram was obtained. He started as a school-based speech-language pathologist, worked later in private practice, and then as a university faculty. AB's research for the past 20 years has been in the area of speech perception, phonetics, and phonology. AB is a native Spanish speaker and has spoken English since 5 years of age and for over 52 years at the time of the last hearing evaluation in 2015.

AB has worked in a university environment (university faculty) for 30 years in speech-language pathology. His research after 10 years shifted towards phonology, phonetics, speech perception, and word identification among bilingual populations with and without disabilities/disorders. AB has been a member of his professional organization for over 30 years (i.e., the American Speech-Language-Hearing Association, ASHA). AB's research has focused on issues of transference or interference between two languages in the areas of phonetics (study of sounds), phonology (study of how sounds form words), semantics (words and word relationships), syntax (sentence structure) and pragmatics (how language is used in social

Age	Unmasked Air			Unmasked Bone		
	Freq. (Hz)	Threshold		Freq. (Hz)	Threshold	
		R	L		R	L
21	250	15	10	250	10	
	500	10	10	500	10	
	1,000	5	5	1,000	0	
	2,000	0	0	2,000	0	
	4,000	40	0	4,000	10	
	8,000	25	25	8,000		
34	250	10	15	250	20	
	500	20	20	500	20	
	1,000	0	10	1,000	5	
	2,000	5	10	2,000	5	
	4,000	40	40	4,000	40	
	8,000	20	50	8,000		
42	250	40	40	250		
	500	35	40	500		
	1,000	25	35	1,000		
	2,000	25	35	2,000		
	4,000	80	60	4,000		
	8,000	55	65	8,000		
49	250	25	20	250		
	500	25	20	500		
	1,000	25	20	1,000		
	2,000	20	35	2,000		
	4,000	65	65	4,000		
	8,000	45	55	8,000		
54	250	20	20	250		20
	500	20	20	500		20
	1,000	25	20	1,000		20
	2,000	15	50	2,000		40
	4,000	70	65	4,000		
	8,000	65	60	8,000		
57	250	25	15	250		
	500	20	20	500		
	1,000	25	25	1,000		
	2,000	30	60	2,000		
	4,000	75	65	4,000		
	8,000	50	60	8,000		

Table 1.
Patient's audiograms over time.

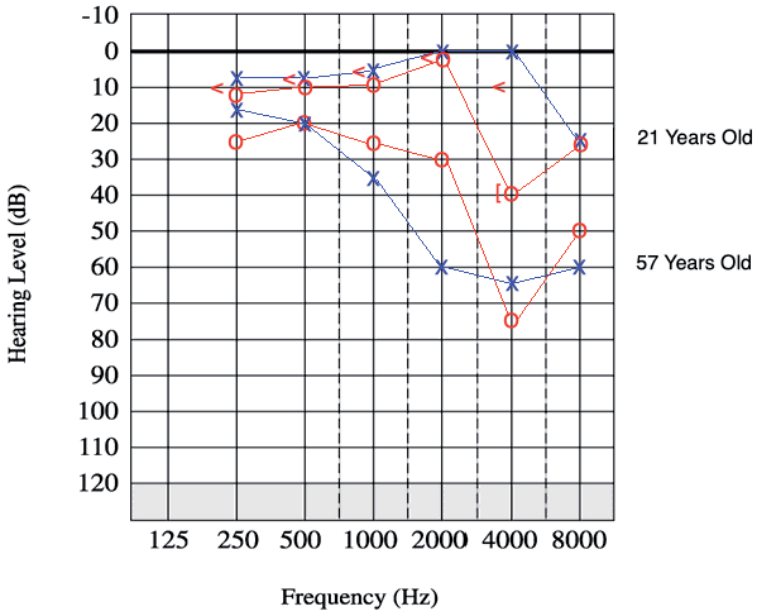

Figure 1.
Contrasting Audiograms Obtained at 21 and 57 Years of Age.

interaction) related to speech-language pathology and cognition. His clinical expertise relates to the appropriate assessment and treatment of Spanish-English speaking students and clients in the United States. Clinically, AB has worked with toddler, pre-school age children, school age children and adolescents, adults in acute care, adults in rehabilitation care, children and adults in home health care settings, and children and adults in out-patient care. AB has supervised graduate students in clinical settings. AB has worked with other professionals including audiologists, medical doctors, physical and occupational therapists, teachers, psychologists, counselors, parents, and family members. This clinical knowledge has facilitated AB's own self-care hearing rehabilitation.

2.2 Speech intelligibility

Hearing deficits impacted AB's hearing, perception, and identification of certain sounds in both Spanish and English. Sounds that have been affected have included high frequency sounds such as /p, t, k, g, h, f, s, ʃ, tʃ, θ, ð/. These sounds range from 500 Hz to 8 kHz and more specifically in the 2 to 4 kHz range.

Factors influencing speech intelligibility include loudness, distance from the speaker, pitch, unique features of consonants and vowels, and noise in the environment [21]. Sound levels (loudness) vary according to the speaker's intensity as measured in decibels (dB). The difference between speaking and shouting may vary only by 20 dB [21]. The distance from the speaker will also affect the sound's intensity. Hence, a speaker at 1 meter may produce an utterance at 55 dB, however, at 5 meters it will be heard at 45 dB [21]. Each speaker's complex speech tone (pitch) or fundamental frequency (f0) lies in the range of 100–150 Hz for men; approximately 180–250 Hz for women; and, around 300 Hz for children (exact averages vary by researchers; however, the general trends are consistent). Consonants in English speech are above 500 Hz. The energy from vowels diminishes rapidly above 1 kHz. It is not possible to increase the sound levels of consonants as one can with vowels; hence, some aspects of speech cannot be changed with increased intensity

or volume. With regard to speech frequencies, most speech sounds occur around 2 kHz with the range of sounds occurring from 125 Hz to 8 kHz [21].

Difficulty with perception of sounds initially occurred when AB was in his forties and later progressed as his hearing thresholds increased. When in quiet environments, AB was able to function and adequately perform his research duties and engage in most conversations with no noise or minimal noise. However, as his hearing loss increased, in research, AB relied on the perceptual judgments of others in ascertaining sound discrimination and differentiation (i.e., use of graduate students with normal hearing). Use of amplification for discriminating participant responses and the ability to play-back responses were helpful.

Conversationally, AB was able to engage in conversation in quiet and in minimal noise without difficulties. AB's ability to discriminate sounds in noise became increasingly more difficult. Conversation in noisy environments were not possible. AB relied on visual cues, repetition, and understanding of topics to assist understanding. These strategies did not alleviate or generally improve understanding. AB's spouse tired of having to repeat herself and others tired of AB's miscommunications due to his hearing loss.

In his 50's AB experienced more hearing loss difficulties in both professional and conversational environments. AB relied more on graduate assistants in his research environment for auditory discrimination of sounds. AB continued to use previously recorded speech stimuli that was created for his experiments, thus, not needing to create new stimuli (which would require intact hearing, speech perception, and speech discrimination abilities). AB discontinued child phonology studies which involve extensive sound discrimination. Hence, AB's research was constricted by his hearing loss.

Conversationally, AB in his 50s withdrew more and had difficulty hearing and understanding others. Use of subtitles with movies became a regular feature. He consistently asked for conversation to be repeated. Even after several repetitions he still would not grasp the entire intent or message. He engaged more in attempts to read lips and to use word cues in the messages to guess at unclear words. AB's frustration with communication increased as well as those around him.

2.3 Rehabilitation

Rehabilitation began when AB conceded to using amplification (i.e., hearing aids) when he was in his late 50's. AB first attempted to make use of local government services in an attempt to obtain hearing aids (i.e., Health and Human Services). This attempt was not successful. Although, AB was ready to purchase hearing aids individually, the cost for bilateral, behind-the-ear (BTE) aids were prohibitive.

AB and his wife attended an international conference for speech-language pathologists and audiologists. It was at this conference that colleagues informed AB that the same hearing aids sold and used in the U.S. could be obtained for one half of the cost. AB's hearing was tested when he was 57 and it was at this time that he purchased his first pair of behind-the-ear (BTE) hearing aids. Over the course of five years AB continued to use his BTE aids until the point where he wears the aids 100% of the time.

AB continues to use compensatory strategies to conserve existing hearing, to make use of amplification and existing technology, and modifies his environment to enhance listening skills. Hearing conservation strategies include: (a) education about hearing; (b) reducing exposure to loud noise; (c) using hearing protection in noisy environments; (d) using hearing amplification; and, (e) participating in routine hearing evaluations [22]. AB has studied hearing loss through his

professional affiliation as a speech-language pathologist. AB uses hearing protection in extremely noisy environments (i.e., ear plugs or head phones). AB wears his hearing aids regularly, makes use of closed captioning when available, and smartphone use. His hearing aids are smartphone capable; thus, AB is able to adjust different listening levels within the app program. Conversationally, AB adjusts his distance to speakers (i.e., moves closer when appropriate); AB maintains eye contact and looks at the speaker to increase visual and vocal cues; AB attunes more to key words in deciphering ambiguous words; and, AB can adjust his hearing aids via his smartphone to better hear in noisy environments.

3. Conclusion

Noise induced hearing loss is a common disorder that has many health consequences [1–4]. NIHL has many health consequences ranging from auditory processing deficits, attention and cognitive loss to social isolation. Traumatic brain injury, hearing loss, and auditory processing deficits are interwoven. Individuals who experience TBI or CTEs will most likely experience trouble with speech in noise, trouble with taxing auditory tasks, and trouble overall with speech processing. Age related hearing loss (ARHL) affects most individuals after 60 years of age. A non-hearing-impaired individual at 60 years of age will experience a mild hearing loss. If a person experiences noise induced hearing loss at an early age; then combined with ARHL, the effects can be compounded.

AB's speech in noise difficulties, resulting from his noise induced hearing loss (NIHL), were reduced through the use of hearing aids, use of aural rehabilitation strategies of paying attention to the speaker's lips, limiting loud and noisy environments, and practicing proper hearing conservation. Strategies to address AB's age related hearing loss (ARHL) consisted of wearing his hearing aids, noise conservation strategies, and scheduling regular audiological exams. It should be noted that some ARHL and NIHL strategies overlapping occurred.

AB is an adult male, currently 63 years of age. He was identified as having a noise induced hearing loss (NIHL) at 21 years of age. Over the course of 36 years, AB has documented his hearing loss with six hearing evaluations. AB's loss is a bilateral, sensorineural, and a high frequency sloping loss. AB currently wears hearing aids and practices hearing conservation. His work is minimally impacted by his hearing loss since he began wearing his hearing aids five years ago. AB is able to engage more fully in activities of daily living, i.e., conversations with others. Hearing obstacles include difficulty with high frequency speech sounds, listening in noisy environments, and maintaining strict hearing conservation.

While, noise induced hearing loss is a chronic condition with no means for improvement; hearing conservation strategies become of utmost importance. Conservation strategies include education about hearing, reducing exposure to loud noise, use of hearing protection, use of hearing amplification and making sure that continual hearing evaluations occur.

Conflict of interest

The author declares no conflict of interest. The author has no financial interest, direct or indirect, in the subject matter or materials discussed in the manuscript.

Author details

Alejandro Brice
University of South Florida, Tampa, FL, USA

*Address all correspondence to: aebrice@usf.edu

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Section 2

Teamwork Approach to Hearing Loss in Children

Chapter 4

Neonatal Hearing Screening

Alejandra Itzel Contreras Rivas,
Gaston Eduardo Estudillo Jiménez, Edgar Flores Molina
and Patricio Guerra Ulloa

Abstract

Around the world 10 million people have some type or degree of auditory problem, of them, between 200,000 and 400,000 have total deafness. Estimating that a large population presents this problem from birth (61%), with an incidence of 1 to 3 of every 1000 newborns. For this reason, early implementation through the neonatal auditory sieve allows timely detection to respond early to the hearing impairment of the newborn, as the ideal age to carry out rehabilitation with the help of an auditory auxiliary and initiate Language therapy is at six months of age. Most of the international guides for the integral attention to persons with auditory disability it indicates that all newborns should be screened Auditory before his hospital discharge. The prevalence of auditory disturbances in our environment is 0.3%, a proportion that places us above national and global statistics, so it is very important to screen all newborns including those who do not have Apparent risk factors in order to establish the appropriate diagnosis, the necessary treatment and thus avoid delays in neurodevelopment.

Keywords: hearing defects, hearing loss, neonatal screening, OTOAC Sticas Emissions

1. Introduction

Hearing loss is the most common neurosensory alteration in the human being, due to the loss or alteration of the anatomical and/or physiological function of the auditory system [1]. It is estimated that worldwide 1 out of every 1000 children is born with bilateral hearing loss. To the deep and 5 out of every 1000 with other forms of deafness. In 2012, "WORLD HEALTH ORGANIZATION" estimated that 5.3% of the world's population had hearing loss, with prevalence in South Asia, Sub-Saharan Africa and Asia Pacific region. In Latin America, the prevalence of 1.6% and specifically in Mexico is estimated that around 10 million people have some type or degree of auditory problem, of which between 200 000 and 400 000 present total deafness. In addition, each year are born between 2000 and 6000 Children with congenital deafness. These numbers show that hearing disorders are an important public health problem around the World [2]. This problem was considered in the National Development plan and in the health Sectoral program 2007–2012, for which the SSA designed the neonatal auditory sieve early intervention program, backed by the standard: NOM-173-SSA1–1998, for comprehensive care for hearing impaired persons [2]. This same recommendation has been Issued by the National Institutes of Health in the USA, in agreement with the American Academy of Pediatrics [3]. The previous

documents establish to make the sieve to all the newborns regardless of their state of health before the discharge hospital, if However most of the countries only reports of children with risk factors, with few compared to healthy children. With the neonatal auditory sieve is intended the timely detection of the hearing impairment of the newborn, its objective is to attend In advance these deficiencies in the neonate, since the ideal age to carry out the rehabilitation with the help of an auditory auxiliary and to initiate the therapy of the language, is at the age of six months, since at this age begins the development of the language. Any reduction in hearing can cause communication disturbances that affect the motor, affective and intellectual development of the individual [3]. Neonatal auditory sieve has several advantages over other methods for detecting no time. Auditory sieve, is 60% less expensive study compared to the neonatal metabolic sieve, faster (lasts about two minutes), immediate response, is not painful and can be repeated as many times as necessary to confirm the outcome [4]. In auditory screening studies a prevalence of permanent congenital hearing loss of 112 by 100,000 infants has been found, with a higher proportion in those who have risk factors (62 by 100,000) than in those who do not have them (54 per 100,000) [5]. There are many different equipment in the market, the most common used in our country is the Portable Interacoustics® OtoRead™ For Sieve Addictive. Provided of a Probe Of 30 Cm o 100 cm, soft latex olives of different calibers. Otoacoustic emissions of distortion products were performed at frequencies 2–5 KHz in four bands with intense. From 40 to 70 db [6]. This is a test that consists in collecting the response of the external hair cells by a receiver placed in the ear canal (CAE), after the sound stimulation by a click, emitted by a microphone in CAE, this technique simple and fast, reproducible, objective, innocuous and reliable: sensitivity: 80–100% and specificity: 90%. It was carried out as recommended by the Commission for the early detection of hearing loss in Spain (COPEDEH).

Phase 1: At birth or before discharge hospital, criterion of the step is the obtaining of the Wave V with PPATC to 40 db or the emission of emissions otoacoustic auditory bilateral.

Phase 2: Newborns who do not exceed this phase are re-explored between the first week and the month of age.

Phase 3: Newborns who do not exceed the second phase are assessed by the audiology service for definitive diagnosis and treatment.

Peripheral hearing is the starting point for structuring expressive language. It is the basis for the comprehension, decoding and central auditory perception to be achieved after reception. These two great phenomena, peripheral sensation and cortical perception, allow the development of the oral language, characteristic and specific quality of the human [7, 8]. The sensations with which the afferent processes begin in the organ of Corti and the babbling with which the first manifesto begins efferent linguistics, are functions that are closely linked to the evolution of Abstract thinking [9]. When hearing does not exist, decreases or is lost, one, several or all psychoacoustic levels are rendered inoperative [10]. We need to be aware that there is a possibility to know if the hearing conditions of newborns are deficit from the first hours after childbirth, which is why it is imperative to act in the stages in which the unstructured as cortical are maturing and can be modeled, as the base as the basis for defining the future of more than 4000 to 6000 babies born deaf or deep hearing problems every year in most of the third world countries [11].

The audiology has its fields of action delimited with great precision, and although many of them correlate with other disciplines, it is the secondary prevention where we can focus the position of our document on the transcendence of sieve Neonatal auditory sieve [12]. The issue that concerns us, the deep hearing loss or total deafness, in many cases with primary prevention measures, it is possible to avoid the damage to the structures of the auditory system and the concomitant

Sensoperceptiva dysfunction [13]. In a percentage these measures cannot be applied, so it is essential to act in the field of secondary prevention to identify a possible problem from the time after birth, so that, continuing with the Diagnosis of certainty and early intervention, the auditory canal is enabled and the cerebral plasticity that will produce the most precious fruit of the audition, which is the language [14], is harnessed. The literature indicates that 0.1% of children are born with some type of congenital deafness [15], according to the results, the prevalence of problems Auditory in healthy newborns of our hospital was 0.3%, i.e. 3 times higher than the reported in the literature (3% reported) [16, 17].

The importance of conducting auditory screening at birth is in the timely detection, establishing early rehabilitation, lowering the cost of care for the institution and the health system in general [18, 19] in a systematic review on the prevalence of alterations in neurodevelopment in Mexico, it was identified that reports on the frequency of hearing loss, passed with methodological differences that do not allow the generalization of their results. In addition, The reports in our country are very scarce with high variability of auditory disturbances through auditory screening. However, it should be noted the findings of two studies conducted, one in low-risk population and one with high risk for Auditory problems. In the first group was observed prevalence of 0.65 for every 1000 live births, the second study estimated 2.6% of 6000 children who merited care in a neonatal intensive care unit [20, 21].

In the United States and European countries has prevalence at 5 years of age of 0.5% with estimated people of 800,000, compared to 2.6 million patients in Latin America, the big difference could be given by the prevention and identification of these alterations in Early stages of life. Unattended cases of hearing loss represent an annual global cost of 750 billion. Interventions aimed at preventing, detecting and treating hearing loss are not expensive and may result Very beneficial to the stakeholders. The greatest importance of timely detection is based in the times and degrees in the what the plasticity cerebral and the potential for linguistic development decreases in relation to the age of intervention [22]. The more time it takes for the proper intervention to begin, the more difficult it is for a good development of the oral language to be achieved, which is the basis for the integral development of the individual, which of course includes the mechanisms of written linguistic communication, with the acquisition of reading and writing as starting points of cognitive and cultural development. The critical period for that the intervention is successful is to the 18 months old. Then the potential and plasticity of the brain for the development of the language, until reaching the point where the late intervention becomes almost useless [23, 24], quickly decreases.

2. Benefits

The benefits of early detection of various medical conditions have long been found; Such is the case of auditory alterations in newborns, an entity that by its very nature is not evident until it is presented retro in neurodevelopment, mainly speech. Unfortunately the ideal age to perform rehabilitation with the help of an auditory assistant and language therapy is at six months of age. Contreras and col. [24] determined that the prevalence of congenital deafness in children without apparent (healthy) risk factors, was three times greater than that reported in the world literature, coupled with this, it is likely that in preterm infants or with various morbidities the prevalence will increase [23]. Therefore, It is essential to educate health providers at all levels of care for the newborn, and the high relevance of hearing screening with an early detection of hearing loss, as well as send it in a timely manner and To receive multidisciplinary management involving specialist in language, audiology,

rehabilitation, otolaryngology, neonatology and psychology in order to promote the increase in the quality of life of these patients, increase the Possi to integrate in a successful and productive way in the society, reduce the costs of care and the socio-economic cost that causes the country to maintain a problem like the Deafness.

Author details

Alejandra Itzel Contreras Rivas[1*], Gaston Eduardo Estudillo Jiménez[2], Edgar Flores Molina[3] and Patricio Guerra Ulloa[4]

1 The Intensive Neonatal Therapy, Maternal Childhood Hospital Miguel Hidalgo Y Costilla, Mexico

2 Department of Maternal Fetal Medicine, ISSSTE General Hospital Dr. Dario Fernandez Fierro, Mexico

3 Prenatal Care Institute, Chiapas, Mexico

4 ISSSTE General Hospital Dr. Dario Fernandez Fierro, Mexico

*Address all correspondence to: alejandracontrerasr15@outlook.es

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Chapter 5

Cisplatin Ototoxicity in Children

Penelope Brock, Kaukab Rajput, Lindsey Edwards, Annelot Meijer, Philippa Simpkin, Alex Hoetink, Mariana Kruger, Michael Sullivan and Marry van den Heuvel-Eibrink

Abstract

Cisplatin is a highly effective chemotherapy medicine used in the treatment of many childhood cancers. Like all medications, cisplatin has many side effects and as always the treatment of cancer in children is a balance between the risks of the medications used and their potential benefits. While many side effects of cisplatin chemotherapy are reversible, one major side effect is permanent and irreversible hearing loss (ototoxicity) in both ears which may worsen with time. The severity of cisplatin-related ototoxicity is associated with age and the cumulative dose received: the younger the child and the higher the total dose, the more severe the hearing loss may be. The spectrum of hearing loss varies from mild to moderate high tone hearing loss, to profound loss across the hearing range and permanent deafness. In addition to hearing loss, some children, especially adolescents, also experience tinnitus and vertigo. Cisplatin ototoxicity is one of most important of the many long-term effects experienced by children who are cured of their cancer. The burden of this toxicity may be compounded by other long-term health issues that emerge with time. This chapter will focus on cisplatin-induced hearing loss, its mechanisms, its health impact on the young person and ways to mitigate or reduce the severity of ototoxicity. This chapter has been written by a multi-disciplinary team including paediatric oncologists, audiologists, a psychologist, a health scientist and a parent of a child growing up with high frequency hearing loss.

Keywords: cisplatin, chemotherapy, cancer, children, ototoxicity, hearing loss, tinnitus, vertigo, prevention

1. Introduction

Cisplatin is a chemotherapy medicine which can cause hearing loss, tinnitus and vertigo. The most common and well documented toxicity affecting the ear is hearing loss and will be the main focus of this chapter [1, 2].

1.1 Cisplatin

Cisplatin was first successfully used in the late 1970s as chemotherapy, in addition to surgery, for the treatment of men with testicular cancer and published in a landmark study in 1980 [3]. At that time Dr. Jon Pritchard at the Great Ormond Street Hospital for Children (GOSH) in London was researching new treatments for

childhood cancer and had a particular patient with widespread ovarian cancer who would previously have been moved to palliative care. However, seeing the effect of cisplatin on testicular cancer in young men, he thought it might work on ovarian cancer in young women and got urgent permission to treat his patient with this new medication. The child's tumour had a spectacular response and shrank enough for the surgeon, at the time Professor Spitz, to successfully remove the tumour without having to perform a hysterectomy. She was cured and when she had children of her own, Jon became Godfather to her first child. The History of cisplatin and its introduction to medicine was captured by The Wellcome Trust in 2006 [4].

However, the challenge of introducing this powerful new chemotherapy to treat children with cancer was its toxicity, it was extremely emetogenic provoking severe nausea and vomiting, and was toxic to the kidneys (renal toxicity), ears (ototoxicity) and peripheral nervous system (neurotoxicity). Research into the side effects of this medicine on children at GOSH began in 1985 when Dimitrios Kouliouskas started studying the renal toxicity [5, 6].

In 1987, both in Brussels and London, a combination treatment of cisPLAtin and DOxorubicin was showing promise in the treatment of children with large liver tumours (hepatoblastoma). These tumours need expert surgery to remove the whole tumour intact; this combination was able to shrink hepatoblastomas to make surgery safer and in some cases make it possible to remove previously unresectable tumours. It was Jon Pritchard who coined the phrase "PLADO" for this combination treatment when passing a Play-Doh store on the way back to the airport in Brussels. Later that same year at the annual meeting of the International Society of Paediatric Oncology (SIOP) in Jerusalem Jon, along with Dr. Jacques Plaschkes (Paediatric Surgeon, Berne), Dr. Giorgio Perilongo (Padua) and others formed the International Society of Paediatric Oncology Epithelial Liver group SIOPEL to improve the treatment of children with liver cancer.

With increased use of cisplatin an alarming incidence of hearing loss was observed and at GOSH, Consultant Audiologist Sue Bellman noted a striking pattern seen on hearing tests (audiograms). Audiograms are a measure of the intensity of sound in decibels (dB) required for a person to hear a particular frequency measured in Hertz (Hz). The patterns seen in children with cisplatin-related hearing loss were very consistent and led to the development of an ototoxicity grading scale (the Brock Grading Scale) which could be used to evaluate the hearing loss acquired by one child and compare it to that of other children treated with cisplatin [7]. In this way different treatment regimens of cisplatin could be compared for ototoxicity. The grading scale showed that some children were more susceptible to cisplatin ototoxicity compared to others when given the same cumulative dose. This idiosyncratic and varied severity suggests possible biological or genetic susceptibility to hearing loss and has led to years of study of the genetic predisposition of patients towards cisplatin ototoxicity.

Cisplatin remains one of the most effective chemotherapy drugs for childhood cancer and is a key component in the treatment of solid tumours, specifically, malignant germ cell tumours, liver tumours, neuroblastoma, osteosarcoma and retinoblastoma, but also brain tumours, particularly medulloblastoma and ependymoma. However, the occurrence of irreversible hearing loss that occurs in approximately 50% of cisplatin-treated children, is a serious clinical challenge [8–10].

The impact of the hearing loss, tinnitus and potentially vertigo caused by cisplatin has serious consequences for the child, their family and the society in which they live [11]. Very young children with even mild forms of hearing loss have difficulty developing the skills of language leading to communication problems and reduced school performance [1]. Acquired hearing loss in adolescents with previously normal hearing, causes serious social and emotional difficulties [12].

In children with brain tumours, cisplatin-related ototoxicity is made more debilitating by damage to the hearing from surgery and radiotherapy, and ototoxicity may compound the learning difficulties caused by radiation to the whole brain.

Other platinum based medications have been developed, (carboplatin and oxaliplatin), with the aim of reducing toxicity but they do not have the efficacy in many cancers to replace cisplatin except in certain circumstances. Carboplatin, which is now widely used in childhood cancer, is less ototoxic (its main toxicity is to bone marrow), but it cannot be substituted for cisplatin without careful clinical trial evidence that it is as effective. When used in combination with cisplatin, the combined ototoxicity is greater than the sum of the two individual drugs [13]. When carboplatin is used at high dose, such as for bone marrow ablation prior to autologous bone marrow transplantation, it is ototoxic.

As it is unlikely cisplatin will be replaced by other agents to treat childhood cancer any time soon, monitoring its impact on a child's development and education, increasing awareness of its effects and support for families, and finding ways to prevent ototoxicity are the key medical needs for the foreseeable future. The results of recent oto-protection clinical trials testing agents to mitigate cisplatin hearing loss have recently been assessed and a clinical guideline published [14, 15].

1.2 Hearing and balance

Hearing and balance are the two senses that are perceived by means of the inner ear that consists of the cochlea (the organ of hearing) and the vestibular system (the organ of balance), see **Figure 1**.

Hearing is the perception of sound and the vestibular system detects motion of the head and body. Together with vision and propriosepsis, which is the internal sense of positioning within the body, these senses are elementary for orientation and sense of safety in the world. For the developing child, normal hearing is essential to learn to detect, discriminate and identify sounds, culminating in the ability to use and understand spoken language, enjoy music and identify potential harm. A normal function of the vestibular system is essential for learning to move freely and efficiently. The importance of hearing for the development of speech

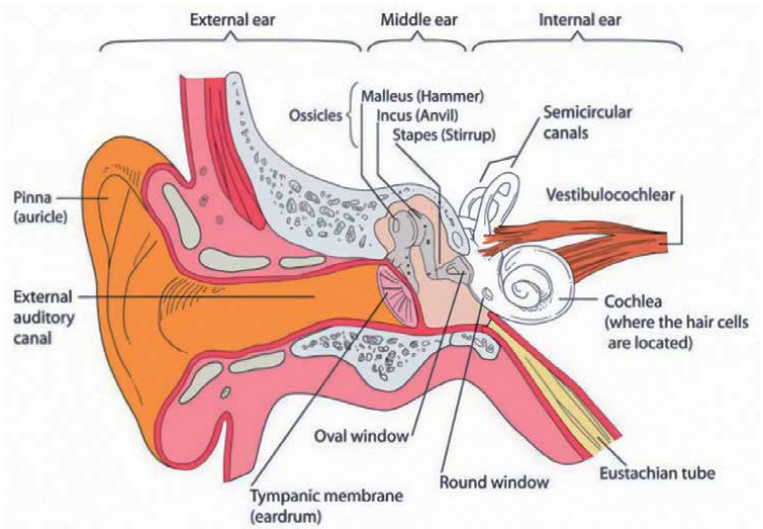

Figure 1.
The ear.

and spoken language is well recognised and in several countries national newborn hearing screening programs have been implemented to detect congenital hearing loss as early as possible, and enable timely intervention. Hearing loss has many impacts on daily auditory functioning, communication, psychosocial wellbeing, and general health, so high quality hearing care for children is best delivered by multidisciplinary teams consisting of medical specialists, audiologists, speech language therapists and (developmental) psychologists. Acquired hearing loss may have multiple causes, but one of the common causes in childhood follows treatment for childhood cancer with cisplatin.

For a sound to be perceived, it has to travel through the external ear, the middle ear, the cochlea and the auditory nervous system to the auditory cortex in the brain. Sound waves are collected by the pinna and channelled by the external auditory canal to the tympanic membrane, causing it to vibrate. The middle ear is an air-filled cavity containing the ossicles (malleus, incus and stapes). The footplate of the malleus rests on the eardrum (tympanic membrane). When the membrane vibrates in response to sound it causes movement of the malleus. This movement is, in turn, transmitted via the incus and the stapes to the fluid filled cochlea.

The normal cochlea is a coiled structure with two and a half turns. It is divided lengthways into three fluid-filled compartments by two membranes (the basilar and Reissner's membrane). These create three fluid filled spaces, the scala tympani is the lower compartment, the cochlear duct (scala media) the middle one and the scala vestibuli the upper compartment, as shown in **Figure 2**. The inner ear hearing apparatus (the organ of Corti) consists of two types of sensory hair cells, the inner hair cells and the outer hair cells, resting on the basilar membrane, also shown in **Figure 2**.

When the middle ear stapes footplate moves, pressure waves in the cochlear fluid produce movement of the basilar membrane and the inner and outer hair cells in the organ of Corti. Excitation on the surface of the inner hair cells creates a neurotransmitter impulse which is transmitted along the cochlear nerve (VIIIth

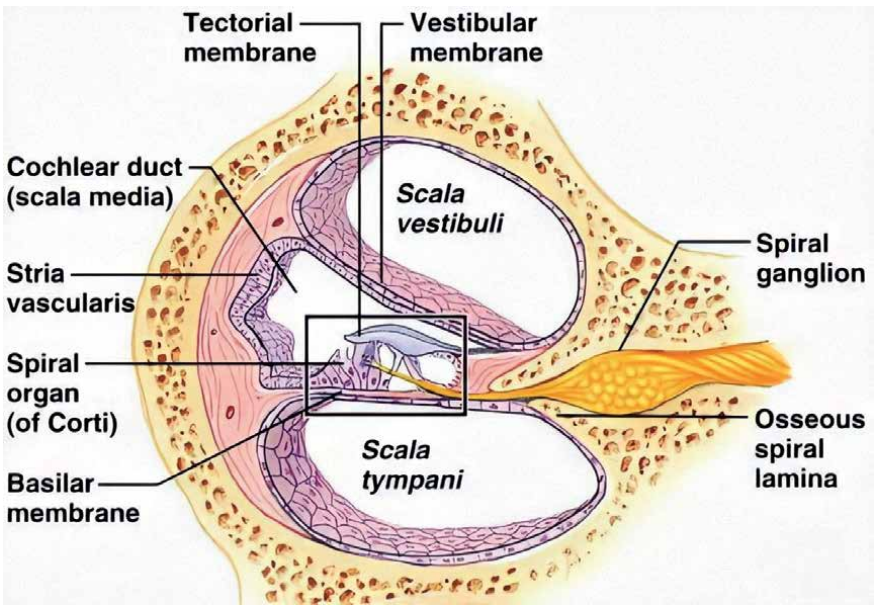

Figure 2.
Cross section of the cochlear scalae in the basal turn.

cranial nerve) to the brain stem and auditory region of the brain. Damage to both the inner and outer hair cells from cisplatin, causes loss of this signal transmission, with the highest sound frequencies lost first.

2. Cisplatin and cisplatin-related toxicity

Childhood cancer is divided into haematological cancer and solid tumours. Haematological cancers occur in the bone marrow and lymph glands (leukaemia and lymphoma) and solid tumours occur in organs such as the liver, kidneys and nerves; solid tissues such as bone and muscle; and the brain (brain and spinal tumours). Cisplatin is currently used alone or in combination with other chemotherapy to treat solid tumours and brain tumours, and only rarely for leukaemia or lymphoma.

When given to children intravenously cisplatin causes acute nausea and vomiting, and may cause renal impairment (nephrotoxicity), neurotoxicity and ototoxicity. When given to adult patients, the dose limiting toxicity is neurological (peripheral neuropathy, tinnitus and vertigo) whereas in children its major long-term effect is ototoxicity with permanent irreversible hearing loss. The severity of ototoxicity varies with age being more severe in younger children, the dose of cisplatin administered at each treatment and cumulative dose of cisplatin given during the course of treatment. However, susceptibility to these effects and their severity vary from individual to individual. Some children will develop very little toxicity despite large cumulative doses and others will develop relatively severe toxicity with only one or a few doses. The significant heterogeneity in the occurrence of ototoxicity among similarly treated patients, suggests that genetic susceptibility contributes to the occurrence of cisplatin-related hearing loss in individual children [16–19] (section 2.5.3).

2.1 Cisplatin mechanism of action

Cisplatin is a simple chemical compound made up of an atom of the platinum metal bound with two atoms of chlorine on one side (cis) and two molecules of ammonia on the other side. When in solution in the blood surrounded by a high concentration of chloride ions cisplatin remains in its neutral form. However, when cisplatin enters a normal cell or a cancer cell which has lower concentrations of chloride ions, cisplatin undergoes spontaneous hydrolysis with water. In this activated state it can enter the nucleus of a cell and become irreversibly bound into the double strands of nuclear DNA forming a cisplatin-DNA adduct (**Figure 3**).

Both normal and cancer cells have complex molecular mechanisms that have evolved to repair the damage to DNA caused by toxins such as cisplatin and other chemotherapy agents. If a cell can activate its molecular repair mechanism and successfully repair the damaged DNA, it will survive and continue to thrive, but if the damage is irreparable, both normal and cancer cells can switch on a molecular process called programmed cell death (apoptosis) and the affected cell will die. Cells can also resist the effect of cisplatin by producing free radicle oxygen molecules within the cell cytoplasm that neutralise the cisplatin molecule. The use of cisplatin in the treatment of children with cancer relies on the fact that solid tumour cancer cells are less able to repair DNA damage than normal cells, and are less resistant to cisplatin, making them more susceptible to apoptosis than the child's normal tissues. However, within the cells of some normal tissues such as within the hearing apparatus, the kidney and peripheral nerves are directly damaged by the effects of cisplatin.

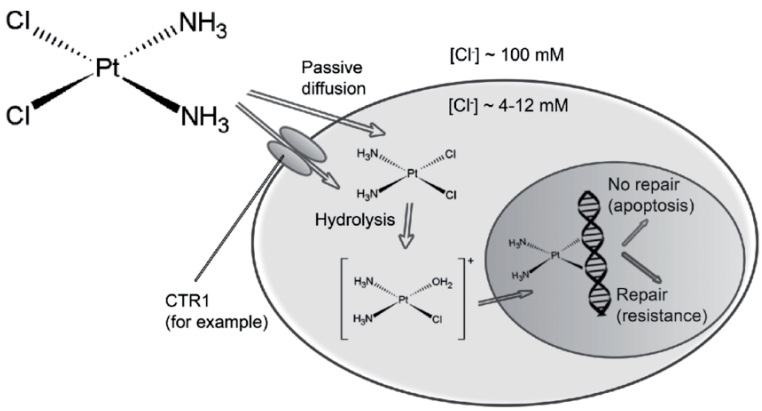

Figure 3.
Cisplatin structure and mechanism of action [20].

2.2 Cisplatin administration

Cisplatin is administered intravenously. It is infused via a central venous catheter over various times but usually between 1 and 6 hours, and given with a large amount of hydration fluid with a high chloride concentration to reduce its toxicity. The hydration is usually administered over 24 hours so the child must stay in hospital during its administration. If the child is not hospitalised throughout this time, adequate hydration needs to be managed by other means.

In the early years, cisplatin was administered for an hour following a period of hydration of about 6 hours, with another 24 hours hydration afterwards.

Times of administration of cisplatin began to lengthen in the late 1980's when it was found that lengthening the infusion time reduced the severity of the nausea and vomiting the child experienced. Cisplatin infusion times in Europe reached up to 96 hours continuous infusion. However, with the introduction of new classes of antiemetic drugs in the 1990's, specifically the HT3 inhibitors (ondansetron and others) the cisplatin infusion times were able to be reduced [20].

In some settings and for some cancers, the dose of cisplatin was split over 5 days reducing the need for 24-hour hydration and hospitalisation. So, in place of a standard dose, and very emetogenic dose of 100 mg/m^2 on one day, 20 mg/m^2 would be given on day 1 through 5.

2.3 Cisplatin and emesis

Cisplatin is highly emetogenic. The nausea and vomiting which ensues appears to be universal. Fortunately, the introduction of the HT3 inhibitors in the 1990s and additional classes of antiemetics more recently, the severity of emesis can be greatly modified in most children [20]. However, effective antiemesis requires a cocktail of antiemetics to be given at least 30 minutes prior to administering cisplatin and that the best antiemetic control is achieved from the very first cisplatin dose. Inadequate antiemetic treatment at the start of cisplatin therapy can lead to the development of anticipatory vomiting which is a particular problem in adolescents. This is when a patient starts to vomit when the idea of receiving chemotherapy is triggered for example on sight of the hospital or if they meet a

ward staff member in a shop. Once anticipatory vomiting has become established it is very difficult to control.

2.4 Cisplatin nephrotoxicity

Cisplatin is almost entirely excreted through the kidney. When in its ionised form, cisplatin is very toxic to kidneys, so to ensure cisplatin is excreted in non-ionised form it needs a high concentration of chloride ions in the posthydration fluid. Nephrotoxicity in young children is partially reversible although this may be due to further maturation of the kidney in very young children rather than actual improvement [5, 6].

2.5 Cisplatin ototoxicity

The hearing loss caused by cisplatin is permanent and bilateral and it may worsen with time. It is worse in very young children, the ear at this age appears to be more susceptible to damage compared to that in older children and adults. Cisplatin causes high frequency hearing loss which may happen following the first cycle of treatment and once acquired it tends to worsen with increasing cumulative doses of cisplatin and eventually may spread towards the lower frequencies important for speech [7].

2.5.1 How cisplatin enters the ear

Cisplatin enters the inner ear or cochlea through a number of molecular transport pathways as shown in **Figure 4** [21]. The cochlea (and vestibulum) are surrounded by several distinct barriers separating the inner ear vasculature and the inner ear fluid compartments that are filled with perilymph, endolymph or intrastrial fluid. Their anatomical sites are not yet clearly identified, but Neiberg et al. [22] summarise them as follows: "tightly coupled vascular endothelial cells form the blood-perilymph or blood-labyrinth barrier (BLB)". The same authors consider the separation between blood, endolymph and intrastrial fluid as being more complex: "tightly coupled strial endothelial cells form the barrier between blood and intrastrial fluid". This latter is separated from endolymph by epithelial marginal cells in conjunction with endothelial basal cells from the intrastrial compartment. These are also referred to as the blood-strial barrier or intrastrial fluid-blood barrier. The more general use of the term BLB covers all of these barriers.

The BLB plays an important role in cochlear homeostasis to maintain its functional integrity. As a highly specialised capillary network it selectively allows the passage of nutrients and ions in and out of the cochlea, and functions as a shield to protect the inner ear from toxic agents. However, cisplatin seems to affect the stria vascularis and might cause breakdown of the BLB [23]. The permeability of the BLB is also influenced by inflammation, diuretics, noise and a number of other factors [22]. Several organs including the liver, spleen and kidneys are able to rapidly clear cisplatin and its derivatives. Due to its unique structure, however, this ability is considered to be low for the cochlea [24]. Thus, the BLB may serve as a port of entry for cisplatin, from which it is hard to escape. Cisplatin may be retained in the cochlea for several months to years after treatment [24]. Another drawback of the BLB that is mentioned in [22] is the difficulty it poses to deliver otoprotective agents to the cochlea, as systemic delivery is highly inefficient, while local delivery is inherently invasive with limited permeability of the round window membrane.

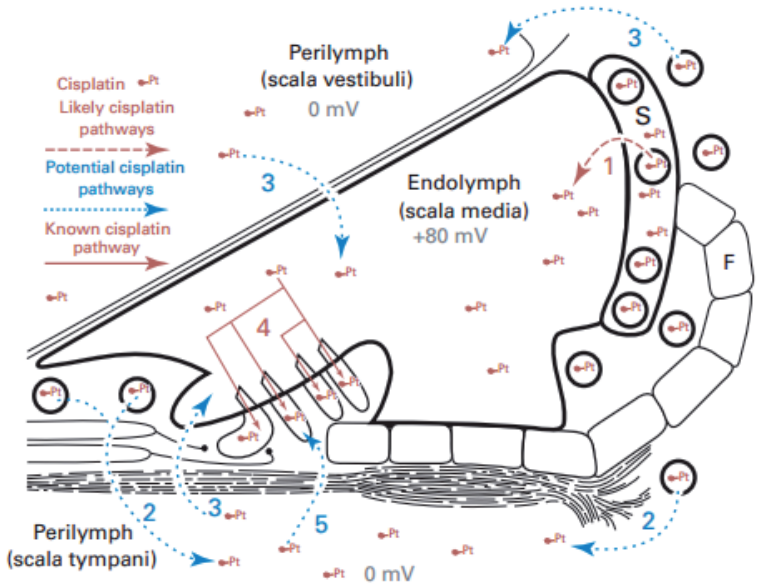

Figure 4.
Model of the cochlea and cisplatin (Pt) trafficking routes. Potential pathways for systemic Pt to cross the blood-labyrinth barrier and enter hair cells include (1) a transstrial trafficking route from strial capillaries to marginal cells, followed by clearance into endolymph; (2,3) traversing the blood lymph barrier into perilymph and subsequently into endolymph via transcytosis across the epithelial perilymph/endolymph barrier. (4) once in endolymph, Pt enters haircells across their apical membranes. (5) Pt in the scala tympani could also pass through the basilar membrane into extra cellular fluids within the organ of Corti and enter haircells across their basolateral membranes. S stria vascularis; F spirocytes in spiral ligament [22].

2.5.2 Destruction of the hair cells of the cochlea

Cisplatin causes irreversible damage to the hair cells of the cochlear apparatus located in the inner ear. Once within the perilymph cisplatin may remain permanently trapped in the inner ear and may continue to cause delayed hearing loss [24]. The molecular mechanism of cisplatin related ototoxicity and destruction of the hair cells is currently unknown. It is thought to involve the production and activation of Reactive Oxygen Species, (ROS), within the cell cytoplasm which the cell attempts to neutralise by a specific molecular mechanism. However, the capacity of the hair cells to neutralise ROS may become exhausted with time or exceeded by the cisplatin dose, leading to hair cell death. Hair cells in the cochlea are fixed in number and do not regrow, so once destroyed hearing begins to be lost. This would explain why higher doses of cisplatin given per day cause more toxicity. **Figure 5** shows how the hydrated complex is neutralised by the cell [25].

2.5.3 Genetic susceptibility to hearing impairment

Over the years, several studies have focused on genetic susceptibility to cisplatin-induced hearing loss using candidate single nucleotide polymorphism (SNP) approaches and more recently genome wide association studies (GWAS). Results to date are conflicting, as studies were often underpowered and did not included multiple testing or replication efforts. Differences in patient populations (e.g., ancestry), sample size, methods of audiometric testing and end point definitions with regards to audiological testing or classification attributable factors that may explain these discrepancies in results and have shown, that certain cohort and

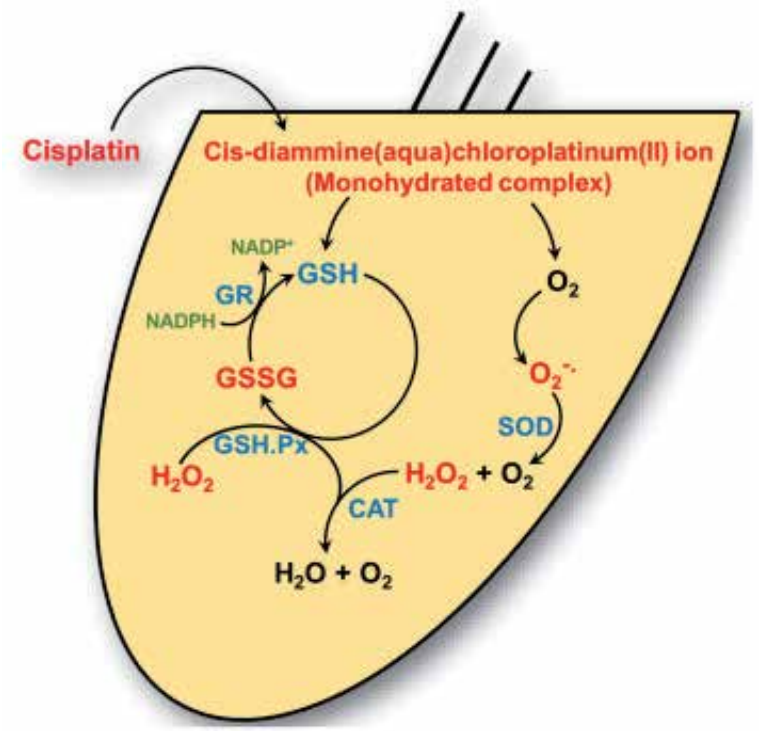

Figure 5.
Cisplatin's interaction with the cochlear antioxidant defence system. Cisplatin is converted to a cis-diammine(aqua)chloroplatinum(II) (a monohydrate cisplatin complex) upon entering the cell cytoplasm. These reactive platinum species can react with molecular oxygen (O_2) to generate superoxide ($O_2^{\cdot-}$) which is detoxified by superoxide dismutase (SOD) to hydrogen peroxide (H_2O_2) and oxygen. Hydrogen peroxide is further detoxified by catalase to water (H_2O) and oxygen. Cisplatin reactive intermediates readily bind to and oxidise the antioxidant reduced glutathione (GSH) to oxidised glutathione (GSSH). Glutathione peroxidase (GSH.Px) consumes GSH to produce glutathione disulfide (GSSG) in the process of converting H_2O_2 to H_2O. Glutathione reductase (GR) reduces GSSR to GSH by using the reduced form of nicotinamide adenine dinucleotide phosphate (NADP+) NADPH, as cofactor [24].

treatment factors (e.g. cranial irradiation, type of platinum agent, total cumulative doses and use of co-medication) may be even more important than genetic susceptibility. In addition, comparison of genetic studies to date have been hampered by heterogeneity in phenotype definitions **Table 1** [26–28].

Currently, efforts are being made to identify and meta-analyse relevant genetic variants, to enable the selection of children with a high risk of platinum related hearing loss to facilitate clinical decision making and where possible to intervene to prevent ototoxic damage. Alongside intensifying hearing screening any other intervention would require careful clinical risk assessment aided by thoughtful discussions with parents, carers and older children themselves. This could then lead to agreeing on an alternative cancer treatment plan for the child [29].

2.5.4 Hearing assessment in children

Functional hearing is represented by 'air conduction' thresholds measured using headphones, and 'bone conduction' thresholds measured using a vibrator placed on the mastoid bone. The air conduction thresholds indicate the status of the external ear, middle ear, cochlea and central auditory nervous system. The bone conduction thresholds indicate the status of only the cochlea and central auditory nervous system.

Candidate gene studies			
SNP	**Described variants**	**Reference**	**Statistically significant**
ACYP2	rs1872328	1#,2, 16#	Yes see also below in GWAS studies
TPMT	rs12201199 rs1142345 rs1800460	1#,3,4,6,12,15# 1#,3,4,6,12,15# 1#,3,4,6,12,15#	CR CR CR
COMT	rs9332377 rs4646316	1,3,4, 6,12 1,3,4,6,12	CR CR
SOD2	rs1880	13#,15#	CR
ABCC3	rs1051640	6, 15#	CR
LRP2	rs22288171 rs2075252	7#,15# 7#,8, 12, 15#	CR CR
GSTM1	null	7#,12	No
GSTM3	*B	10	Yes but no replication
GJB2	rs80338939	9	Yes but no replication
GSTP1	rs1695	5,12,15#	CR
SLC22A2	rRs316019	15#	Yes but no replication
GWAS studies			
ACYP2	rs1872328	13#	Yes GWAS n = 238 replication in historical subjects n = 68 paediatric brain tumours
		1#	Yes CGA n = 156 brain tumours
		2	Yes CGA n = 149 various CNS and solid tumours
		15#	No CGA in 900 various ped cancers
WFS1	rs62283056	14#	Yes GWAS n = 511 replication in 18.620 subjects testicular cancers
		15#	No CGA in 900 ped cancer patients

**SNPS that were tested once, but not found to be associated with ototoxicity were not included. CR = conflicting result CDA = candidate gene approach. #: studies that adjusted for multiple testing.*
(1)Thiesen, Pharmacogenetics and genomics, 2017; (2)Vos,Ppharmacogenetics and genomics, 2016; (3)Hagleitner, PloSone, 2014; (4)Yang, Clinical Pharmacology and Therapeutics, 2013; (5)Rednam, 2013; (6)Pusegoda, Clinical Pharmacology and Therapeutics 2013; (7)Choeypasert,2013;, (8)Riedeman, 2008; (9)Knoll, Laryngoscope, 2006; (10)Peters, AntiCancer drugs, 2000; (11)Brown,Cancer Med, 2015; (12)Ross, Nat Gen, 2009; (13) Xu, Nat Gen, 2015; (14) Wheeler, Clin Cancer Research, 2017; (15)Langer, EJC, 2020).

Table 1.
Relevant SNP studies on cisplatin related hearing loss in childhood cancer by candidate gene studies.*

2.5.4.1 Testing of the status of the external and middle ear

A check-up of external - and middle ear status is required to exclude any conditions causing obstruction for the sound to reach the cochlea. When sound is

obstructed from reaching the cochlea, this is called a conductive hearing loss. Causes for conductive hearing loss include accumulation of cerumen, infections or tympanic membrane perforation [30]. Otoscopy allows for visual inspection of the auditory canal, the tympanic membrane and part of the middle ear. Tympanometry may be used to indicate the presence of middle ear pathology, by measuring the mechano-acoustic properties of the middle ear system [31]. A probe is placed in the ear canal for a few seconds, which delivers a tone and changes the air pressure. The way in which the pressure changes affect the sound level developed in the ear canal can provide useful information about the status of the middle ear.

2.5.4.2 Behavioural testing of inner ear status

Several behavioural tests are available to estimate hearing thresholds in children. The reliability of these tests depends on the child's age, neurological status, development and motivation.

The usual way to assess hearing function in older children and adults is to measure the air and bone conduction thresholds, i.e. the quietest sounds which can be detected, as most hearing problems are associated with raised (poorer) thresholds. Audiometry is the process of measuring hearing thresholds at a range of frequencies (pitches). Thresholds may be measured in various ways and are usually displayed on an audiogram, which shows the thresholds at each audiometric frequency. Different types of hearing loss and their classifications can be found in a previous IntechOpen book [32]. **Figure 6** shows a typical Pure Tone Audiogram of normal hearing on the left and moderate cisplatin induced high frequency sensorineural hearing loss on the right.

The horizontal axis shows the test frequencies. Octave intervals are tested from 125 or 250 to 8000 Hz (8 kHz). The vertical axis is the level of sound in decibels - termed dB HL (Hearing Level) where the quietest levels are at the top. Thus, the "normal range" is anything down to 20 dB HL (vertical axis) and thresholds higher than 20 dB HL (lower on the audiogram) represent a clinically significant hearing loss. Where there is no conductive hearing loss the air - and bone conduction

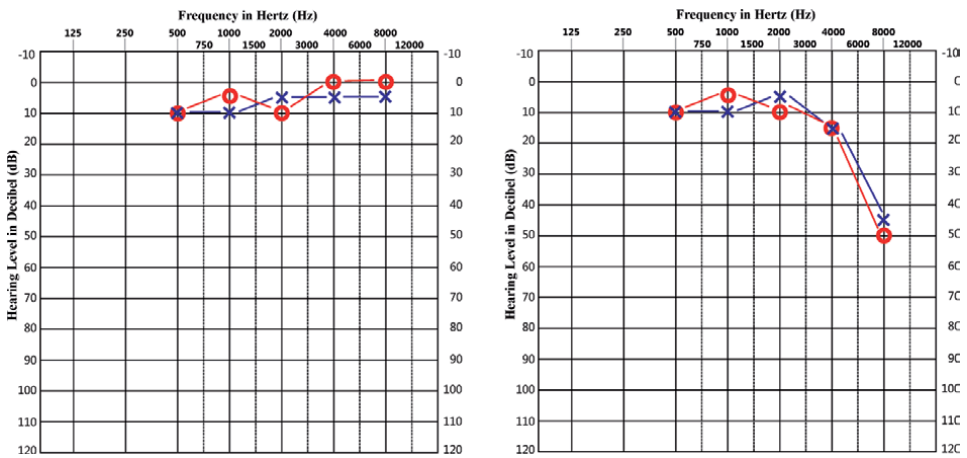

Figure 6.
An audiogram showing normal hearing on the left, and an audiogram depicting a typically symmetrical high frequency hearing loss on the right. The red line represents the results for the right ear, and the blue line the results for the left ear. The x-axis portrays the frequency of sound in hertz, and the y-axis the hearing level in decibel with acoustic reference zero for calibration given in ISO-381-1 for frequencies up to 8 kHz and in ISO-381-5 for the extended high frequencies (Meijer A.J.M. Childhood cancer related hearing loss and tinnitus. Utrecht University; 2021).

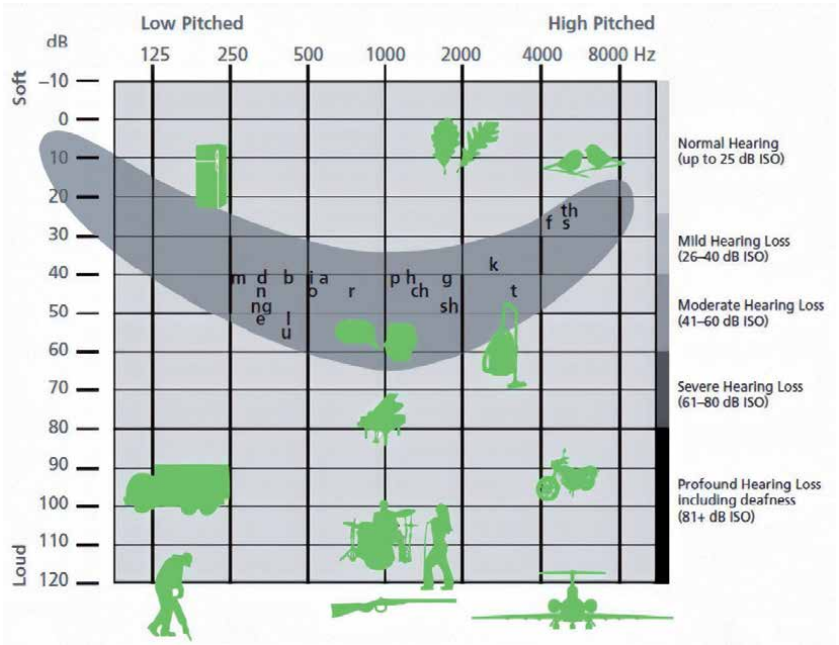

Figure 7.
The speech banana.

thresholds are more or less the same, but when there is a hearing loss the air conduction thresholds are depressed further.

Figure 7 shows the levels and conductive frequencies of a variety of environmental sounds and components of speech (the so-called "speech banana") in an audiogram format. Overlaying any audiogram onto this can indicate which sounds are audible and those which would be inaudible, which can illustrate the functional implications of various configurations of hearing loss.

For the results of audiometry to be reliable, the child has to understand the instructions and has to be motivated to comply. For children younger than 5 years of age, audiometry is generally too challenging. Therefore, several other behavioural tests are available to estimate hearing thresholds in children. The reliability of these tests depends on the child's age, neurological status, development and motivation.

Visual reinforcement audiometry is applied to estimate hearing thresholds in young children (6 months to 3 years of age). A visual reinforcer, such as an animated toy or picture is used to generate and maintain a head turn response to the sound stimulus presented through a speaker or ear phones.

To measure hearing thresholds in children aged 3 to 5 years, conditioned play audiometry may be applied. The child is conditioned to respond to a sound by performing an action (putting blocks in a box or stacking rings on a stick) [30].

Conventional audiometry has been considered the gold standard for obtaining hearing thresholds between 0.125 to 8 kHz in children of 5 years and older. The child presses a button in response to the sound stimulus. Additionally, the extended high frequencies (EHF) up to 16 kHz may be tested for identification of early ototoxic damage. EHF testing is less widely applied as special calibration of the equipment is required (A.J.M. Meier et al. in press).

2.5.4.3 Objective testing of inner ear status

For infants up to 6 months of age, behavioural tests are too inaccurate for hearing threshold estimation. To asses hearing of children of this age, objective tests are

available and widely used in programs for new born hearing screening. These tests can also be used to confirm the outcome of behavioural testing in older children, and may be applied in children/adolescents who are not able to cooperate.

A simple and fast way to objectively assess hearing is a test of otoacoustic emissions (OAE), in which a soft probe is placed into the ear canal and the OAE or "cochlear echo" is recorded in response to moderate level clicks or a combination of pure tones delivered via the same probe. OAEs reflect the function of outer hair cells and are only produced in ears with normal hearing or a mild loss of 20–30 dB HL. Presence of an OAE response confirms normal or near-normal hearing. Absence of a response indicates the possibility of a hearing loss and the need for follow-up testing, though it is often due to temporary factors such as excessive head movement or middle ear fluid.

The main follow-up test in this age group is auditory brainstem response (ABR) testing. Disposable electrodes are attached to the baby's head and rapid clicks or tone pips are delivered to the ear by an insert probe. The electrodes detect field potentials generated by the lower auditory pathways (cochlea and brainstem), producing a characteristic waveform response. The intensity of the stimuli is reduced until the waves are no longer visible, providing a close approximation to behavioural hearing thresholds. When the equipment is well calibrated and click stimuli are used, hearing thresholds around 3 kHz can be estimated, type of hearing loss can be determined (conductive or sensorineural) and integrity of the VIIIth cranial nerve and lower brainstem can be assessed. ABR is preferably measured during sleep, but in some situations sedation must be applied ([30], A.J.M. Meier et al. in press).

2.5.5 Monitoring of ototoxicity in children

As cisplatin-induced ototoxicity in children may have a negative impact on speech-language development and quality of life, early detection of hearing loss by audiological assessments is important. Monitoring during and after cancer therapy facilitates audiological management including counselling of patients and family, and support of hearing function if necessary (hearing aids, assistive listening devices, speech and language therapy) [33]. During therapy, monitoring may also provide the opportunity to modify cisplatin dose, depending highly on the availability of an evidence-based alternative, and whether or not cisplatin is the backbone of treatment. For example, dose adjustment may not be applicable in patients with liver tumours, for whom cisplatin is the key component of survival [34].

2.5.5.1 Timing and frequency of testing

A baseline assessment before start of cisplatin treatment, where possible, is important to identify pre-existing hearing loss, and is accompanied by questions on medical history including previous ear and hearing problems, family history, a check for dysmorphic features and presence of tinnitus. The timing of monitoring and the testing schedule during cancer therapy highly depends on the protocol and patient-specific circumstances. Serial assessments can be considered for patients who receive cisplatin, including a check of middle ear and inner ear function, and presence of tinnitus. A post-treatment assessment is used to identify hearing loss or to record progressive changes in hearing status, often performed within three months after cessation of treatment (A.J.M. Meier et al. in press). It may be necessary to continue monitoring up to several years after treatment to detect a delayed onset of hearing loss. Surveillance is advised annually for young survivors, every other year for older children, and every five years for adolescents and young adult survivors [35].

2.5.6 Grading of hearing loss in children

When cisplatin was first used in young children at GOSH there were no appropriate grading scales with which to compare ototoxicity measurements taken from children receiving the same or different treatments including cisplatin. There were the common toxicity criteria of adverse events (CTCAE) and the American Speech-Language Hearing Association (ASHA) criteria, but both compared hearing measured after treatment to baseline hearing. These approaches can be used in older children where baseline hearing can be established. In very young sick children it is difficult to get a reliable baseline and the tests used at a very young age are not the same as the tests used later on. Sue Bellman, the audiologist at the time at GOSH studied the particular pattern of hearing loss which the children were developing. She designed a scale which was published by Brock in 1991 and became known as the Brock grading [7]. Brock grading was later thought not to be sensitive enough and was developed further and a new scale published by Kay Chang in 2010 [36]. There followed a consensus meeting at the annual general meeting of SIOP in Boston and the SIOP scale was introduced and published in 2012 [21]. Grading can be done from the audiogram locally but when comparison of grading is required for the purposes of studying the toxicity of one treatment regimen with another in a clinical trial then central review of audiograms is necessary to assure consistency and quality. This is particularly the case in international clinical trials where the audiogram needs to be uploaded to the trial database for review.

2.5.7 The developmental and psychological impacts of hearing loss

The developmental and psychological impacts of deafness on children are diverse and substantial. In addition to the primary influence of hearing loss on the acquisition of language and literacy skills, children with any degree of hearing loss are at increased risk of experiencing social, emotional and behavioural difficulties as well as potential influences on quality of life, identity and self-esteem. All these consequences are well documented for children with congenital hearing loss, with research typically focusing on children with severe or profound deafness, and recently, those who have received cochlear implants. Research findings reveal a highly complex picture, with a large number of factors interacting to result in the difficulties presented by any individual child, including for example their language and communication skills, the cause of their deafness, their educational provision, and parental socio-economic status. The picture is somewhat less clear for children who have a mild or moderate hearing loss (often referred to as minimal hearing loss, and the largest group of children affected by ototoxicity), or those who acquired a loss during childhood due to illness directly (for example meningitis), or as in the case of ototoxicity, due to the treatment of illness. However, there is increasingly empirical evidence that is relevant in relation to the developmental and psychological impacts of ototoxicity-induced hearing loss.

The most significant impact of hearing loss is during infancy and early childhood, when language skills are developing at their fastest but delays may go unrecognised or untreated until the child enters school [37]. Thus age of exposure to ototoxic drugs is of particular importance, since even if the hearing loss is confined to the high frequencies, it can have subtle but significant impacts on speech perception and therefore speech production and intelligibility [38, 39]. Audibility and recognition of high-frequency speech sounds (s, f, th, sh, h, k, and t) and perception of fricative phonemes (e. g./s/) supports phonological and morphological development in young children with normal hearing and children with hearing loss [39]. Delays in language development acquired at this time may be hard to reverse, even with appropriate amplification and speech therapy [40].

A review of the literature on minimal hearing loss (comprising 69 articles, 6 of which included children with high-frequency hearing loss) concluded that although some individuals appeared to have no observable speech-language or academic difficulties, others experience considerable problems [37]. Those children that perform in the normal, average range on tests of language skills and academic attainments may in fact be under-performing in relation to their cognitive potential (IQ). In addition, children who appear not to have been negatively affected in terms of language and academic development, may still present with significant psychosocial problems. As a group, children with any degree of hearing loss, as well as those specifically with minimal hearing loss, exhibit higher rates of behaviour problems such as noncompliance, aggression, hyperactivity, impulsivity, and inattention than their hearing peers. They also have more emotional problems such as lower energy levels, higher stress and poorer self-esteem.

The psychosocial impact of hearing loss is also seen in terms of the effect on quality of life. A systematic review of 41 articles [41], showed that children with hearing loss generally report a lower quality of life than their normally-hearing peers. Their meta-analysis on four studies employing the Paediatric Quality of Life Inventory (PedsQL), revealed statistically and clinically significant differences in PedsQL scores between children with normal hearing and those with hearing loss, in the Social and School domains. Recently, a study reported detrimental effects of hearing loss on quality of life in children and adolescents who suffered hearing loss following ototoxic treatment compared with those whose hearing was unaffected [11]. All the areas assessed were impacted, including the ability to communicate with family and peers, level of independence, interactions with peers and emotional well-being. Long-term follow-up of childhood cancer survivors indicates significant hearing loss as predictive of poorer outcomes for school, employment and independent living [42].

As a result of these developmental and psychosocial consequences of ototoxicity-induced hearing loss it is essential that children are not only closely monitored in terms of their hearing thresholds, but also the wider language, learning, social, emotional and behavioural impacts. A range of interventions may be needed, including speech and language therapy, classroom and teaching accommodations and strategies to maximise access to speech and peer interactions, as well as therapeutic interventions to address emotional and behavioural problems.

2.5.8 Resource challenged nations and cisplatin hearing loss

The Global Initiative for Childhood Cancer (GICC) which was launched in 2018 by the WHO in partnership the International Society of Paediatric Oncology has the goal of improving the Global survival of children with cancer to 60% by 2030. As child cancer services develop and more gain children access cancer care, it will be necessary to develop policy and services to address the long term effects of chance treatment [43]. Cisplatin, is included in the WHO Essential Medicines List for Children (2017), but severe acquired hearing loss in child cancer survivors may have very significant impact on learning and future education opportunities of survivors and increase the health burden in families [44, 45]. Studies from low-and middle-income countries report the prevalence of hearing loss in community screened children as about 10%, while it is 23% for children with co-morbidities, such as HIV, tuberculosis, chronic suppurative otitis media and impacted cerumen% [46, 47]. Adding cisplatin as childhood cancer treatment may therefore increase the prevalence of hearing loss, which increases the need for early identification in the context of limited resources. Community health care workers have been successfully trained to assist and implement screening for hearing loss in communities, which should be used to assist in continuous assessment of hearing in children, surviving childhood cancer after cisplatin treatment and return

to their communities [45]. These identified children should be referred back to the major urban treatment centres for further more sophisticated hearing assessment and management. However, it should be noted that in Sub-Saharan Africa, and in the most populous parts of South East Asia there is a general lack of audiologists and limited access to testing and hearing support, which may hamper rehabilitation. These resource-constricted countries should therefore establish partnerships with developed countries and non-governmental organisations to assist them in the management of childhood cancer survivors with hearing loss due to cisplatin [48].

2.5.9 The parent's perspective

A parent with a child going through treatment is always trying to find the balance between a desperate longing for their child to be cancer free whilst enduring the least possible short and long-term side effects. At the start of treatment, when doctors explain the risks of potential hearing loss when using cisplatin, it can be hard to fully appreciate and understand the long-term impact for your child. At this stage of treatment many different outcomes are as yet unknown. This is especially true if the child receiving treatment is very young and unable to communicate verbally. The impact of having to wear hearing aids and other assistive listening devices is unknown and therefore almost impossible to comprehend. Whilst going through treatment the support given by doctors and nurses is invaluable. Once treatment ends access to that level of specialised support ends too. Parents are delighted to have a child free from cancer but all too often they are left to deal with the consequences of long-term side effects on their own. This can mean that young children learning to speak, read and write are not given adequate learning support since parents do not always know how best to help them or even what kinds of basic learning support to ask for. At a young age the child will not know in what circumstances they find it difficult to hear and parents need to be aware of every situation in order to be able to help the child develop coping strategies. This is especially true in nursery and primary school settings where a child could quickly feel overwhelmed. It would be easy for that child to be incorrectly labelled as reclusive, of low ability or naughty in class. As the child gets older, they will be able to deal with situations more easily themselves but will easily get tired and quickly zone out. Parents might need to advocate for their child and make the school aware of their needs. Interventions could include sitting at the front of exam halls, increasing teacher awareness in situations like sports pitches, playgrounds, swimming pools and in noisy classrooms. It is easy for a child with hearing loss to retreat from interactions or to become frustrated and then behave poorly. Parents need assistance and information to know how best to help and support their child. Children need to be encouraged to ask for help rather than be singled out or stigmatised.

2.5.10 The search for otoprotectants

As soon as it was known that cisplatin caused irreversible hearing loss researchers began to look for drugs to protect against this side effect. Different medications have an impact at different points in the metabolism of the cell **Figure 8** [49].

2.5.10.1 Preclinical studies of ototprotectants

The most promising pre-clinical studies have come from Edward Neuwelt's team in Portland Oregon [50–52]. They have been working on Sodium Thiosulfate (STS) and N-Acetyl Cysteine (NAC). As can be seen in **Figure 8** these 2 drugs can act at different points both inside and outside the cell.

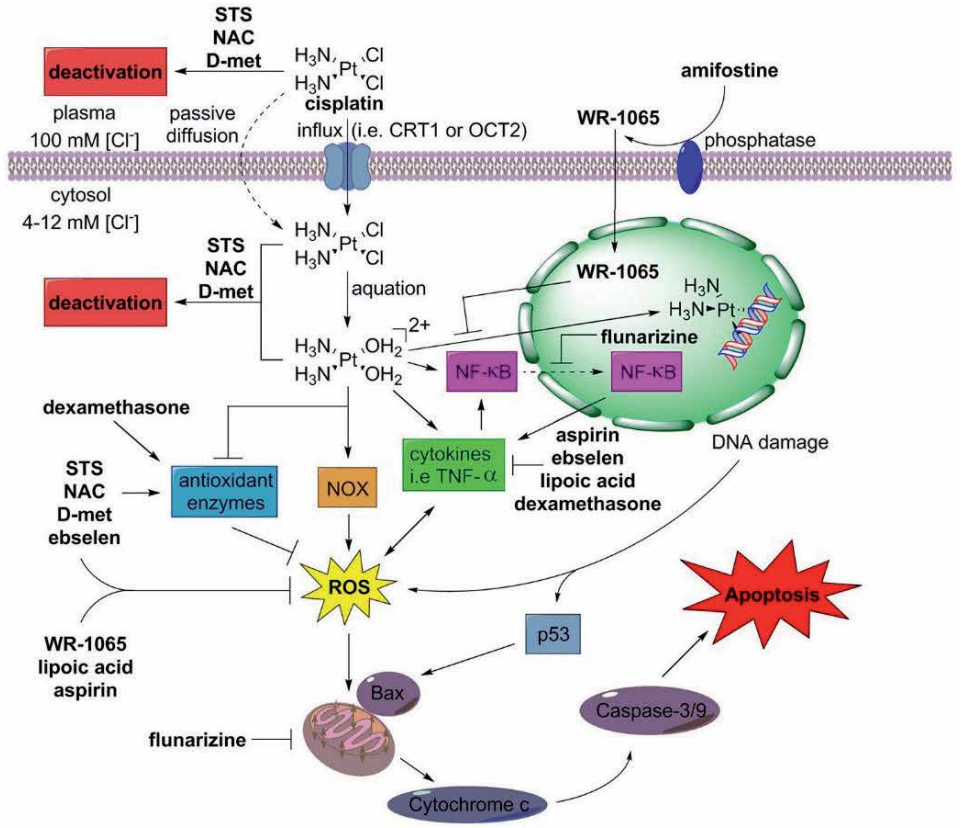

Figure 8.
General mechanistic pathways of cisplatin-induced cytotoxicity in auditory cells and the mechanistic pathways by which the otoprotective clinical candidates combat cisplatin toxicity [47]. https://doi.org/10.1021/acs.jmedchem.7b01653.

2.5.10.2 Clinical trials of otoprotectants in children

In 2019 a clinical guideline paper was written by a multidisciplinary team led by Lillian Sung and David Freyer [15]. The conclusion of this paper was that to date the most promising otoprotectant is STS, see **Table 2** taken from this paper. STS is close to being licenced both in North America and Europe. The evidence for the use of STS in children comes from two phase III trials [53, 54] which both showed that the incidence of hearing loss can be reduced by 50% in children receiving STS as a 15 minute infusion given 6 hours after the cisplatin infusion ends.

2.6 Cisplatin neurotoxicity

In adults, peripheral sensitive neurotoxicity which ranges from paresthesias to ataxic gait is the dose limiting toxicity of cisplatin [55]. This means that when patients develop severe neurotoxicity the dose of cisplatin needs to be adapted or stopped. In young children neurotoxicity is rarely observed.

2.7 Hearing conservation from the public health perspective

Cisplatin hearing loss is considered to worsen with time. It is not clear whether this is due to ongoing toxicity from platinum retained in the cochlea or the addition of further assaults on the ear or both. Hearing educational programs for the young

	Studies (n)	Patients (n)	Effect size *	95% CI	I^2 (%)	Value
Amifostine vs no treatment						
Any ototoxicity	5	465	RR 0.96	0.71 to 1.29	49%	0.78
Severe ototoxicity	4	223	RR 0.85	0.34 to 2.12	0%	0.72
Sodium diethyldithiocarbamate vs no treatment						
Severe ototoxicity	2	255	RR 0.73	0.08 to 6.44	56%	0.77
Sodium thiosulfate vs no treatment						
Any ototoxicity	2	205	RR 0.51	0.37 to 0.71	0%	<0.0001
Intratympanic acetylcysteine vs no treatment						
Threshold at 4 kHz	2	62	MD-2.7	−14.9 to 9.5	0%	0.66
Threshold of 8 kHz	2	62	MD-1.6	−14.8 to 11.6	0%	0.81
Intratympanic dexamethasone vs no treatment						
Threshold at 4 kHz	2	92	MD-0.7	−5.8 to 4.5	0%	0.80
Threshold at 8 kHz	2	92	MD-8.7	−18.1 to 0.7	34%	0.07
Continuous cisplatin infusion vs bolus cisplatin infusion						
Any ototoxicity	2	78	RR 1.60	0.62–4.13	0%	0.33

*RR = risk ratio MD = mean difference *RR less than 1 and MD less than 0 favour intervention.*

Table 2.
Data synthesis of trials for cisplatin-induced ototoxicity prevention.

are few and far between [56]. It is clear that children who have received cisplatin as part of their therapy for cancer need to be supported but also educated as they go through follow up to conserve their hearing. It is possible that at the end of treatment ototoxicity damage is not yet apparent to the young person as it may only affect the higher frequencies out of their speech range. With time however as hearing worsens as a result of the toxicity, possibly in interaction with noise induced hearing loss [57], it may reach the speech frequencies and become apparent. Hearing conservation strategies should be introduced to the parents and child at an early stage and should encourage exclusion/reduction of factors which can lead to damage to residual hearing. Not all of these factors can be excluded however it is only fair that parents and patients are made aware of the additional risk to hearing that they bring. These include: loud sounds and noises; other ototoxic medication e.g., aminoglycosides; unhealthy diets; intracranial pressure changes for example as can occur with certain sports such as scuba diving; barotrauma; head injury and exposure to radiation and proton beam therapy. Where possible children and adolescents should be discouraged from listening to loud music through headphones over long periods of time, encouraged to wear protective ear plugs if exposed to loud noise, wear protective head gear when cycling; use a head rest/child safety car seat adjusted to height.

To raise awareness of policy makers to address the problems of preventable hearing loss worldwide, the WHO World Health Assembly adopted a resolution in 2017

(WHA70.13) to provide guidance for member states for the integration of ear and hearing care into national health plans. In response The World Report on Hearing has been developed (https://www.who.int/activities/highlighting-priorities-for-ear-and-hearing-care), proposing a set of interventions for prevention, screening, rehabilitation and communication.

2.8 Future challenges

A better understanding of the predisposing genetic factors and how to influence them as well as the introduction of licenced otoprotectants will hopefully reduce the incidence of acquired ototoxicity. In the meantime children who have already developed hearing loss or other ototoxicity need expert support, audiological intervention as well as encouragement, acceptance, patience and tolerance to support them fully socially integrating.

3. Conclusion

Cisplatin ototoxicity is a serious medical problem in children with cancer whos' cure depends on the use of this drug. Progress has been made on understanding the mechanisms causing the toxicity and some of the predisposing factors. Expert counselling and management of the hearing loss, tinnitus and or vertigo is very important for all children. Understanding and adaptation at home, school and in the work place can facilitate better integration and outcomes for people suffering from acquired toxicity. Otoprotective drugs are being researched to reduce the severity of hearing loss and some will hopefully soon be licenced for use. However further research is needed in all areas to improve the quality of life for children who acquire this challenging side effect of treatment.

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Conflict of interest

Penelope Brock has been a consultant with Fennec Pharmaceuticals since 2017. All other authors have no conflict of interest.

Author details

Penelope Brock[1*], Kaukab Rajput[1], Lindsey Edwards[1], Annelot Meijer[2], Philippa Simpkin[3], Alex Hoetink[4], Mariana Kruger[5], Michael Sullivan[6] and Marry van den Heuvel-Eibrink[2]

1 Great Ormond Street Hospital for Children NHS Foundation Trust, London, UK

2 Princess Máxima Centre for Pediatric Oncology, Utrecht, The Netherlands

3 Independent Researcher, London, UK

4 University Medical Centre, Utrecht, The Netherlands

5 Stellenbosch University, South Africa

6 Royal Children's Hospital, Melbourne, Australia

*Address all correspondence to: peppybrock@gmail.com

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Section 3

Teamwork Approach to Hearing Loss Comorbidities

Chapter 6

Hearing Loss in Chronic Kidney Disease

Sampson Antwi and Mohammed Duah Issahalq

Abstract

Chronic kidney disease (CKD) is assuming public health significance worldwide largely driven by the surge in diabetes mellitus, hypertension and obesity. CKD patients, particularly those from resource restraint regions of the world, face huge challenge in terms of accessibility and affordability to care. Besides these challenges in care, several other co-morbidities often exist among these patients in addition to the primary disease like diabetes and hypertension. Yet, these "subtle" co-morbidities are often overlooked by Caregivers. Hearing loss is one of such co-morbidities CKD patients face but it is often overlooked. The situation is worse among children who often cannot express themselves. The etiology of hearing loss among CKD patients are multifactorial. It is hoped that this neglected aspect of care for patients with chronic kidney disease will receive the needed attention for holistic care of the CKD patient.

Keywords: chronic kidney disease, co-morbidity, hearing loss, aetiopathogenesis, Oto-renal syndrome

1. Introduction

1.1 Structure and function of the ear

The ear is the organ for hearing. The human ear consists of three parts: 1. the external ear 2. the middle ear 3. the inner ear. The inner ear, also called the labyrinth, consists of the vestibular apparatus for balance; and the cochlear for hearing.

The external and middle ear portions of this hearing apparatus are responsible for conducting sound energy from the exterior and transforming it into mechanical energy towards the inner ear. The inner ear then converts the received mechanical energy into electrical energy. The cochlear component of the inner ear is the end-organ for hearing. The organ of Corti within the cochlear is the functional processing unit for hearing aspect of the inner ear. This organ is very sensitive to the chemical environment. Changes in the physiological environment of the organ of Corti cause toxic damage to it (ototoxicity).

Variety of factors contribute to functional deterioration of the inner ear. These include aging, chemicals, medications and certain diseases both congenital and acquired [1].

1.2 The kidney and the inner ear (labyrinth)

The kidney is the organ primarily responsible for the elimination of toxic metabolites from the body and thereby creating the required milieu for the internal organs, including the inner ear, to function optimally.

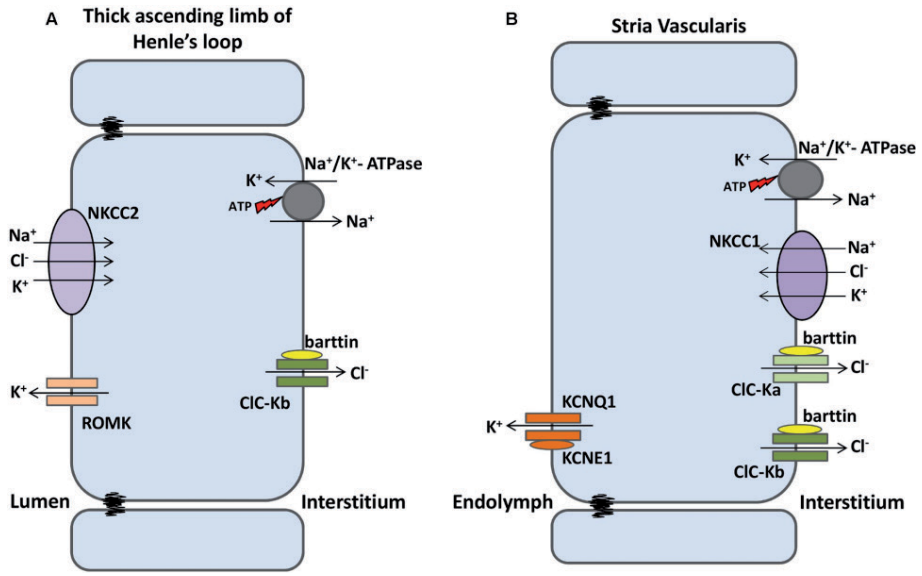

Figure 1.
ClC-K channels are expressed in kidney and inner ear. (A) At the nephrons, luminal NKCC2 transporters build up Na^+, K^+ and Cl^- into the cells. K^+ flows back to the lumen through ROMK1 channels; Na^+ and Cl^- are reabsorbed to the bloodstream separately through Na+/K+ ATPase and ClC-kb channels, respectively. (B) In the Stria Vascularis, Na^+, K^+ and Cl^- are transported into the cells by basolateral NKCC1 transporters. Na^+ and Cl^- are recycled back to the interstitium by Na+/K+ ATPase and both ClC-Ks isomers, respectively. K^+ flows through KCNQ1/KCNE1 channels and accumulates into the endolymph, a condition required for sensory transduction in inner hair cells. Figure courtesy Poroca DR et al. [4].

Diseases of the kidney have detrimental effect on the inner ear, not only because of buildup of metabolic toxins in the blood to affect the functions of the labyrinth, but also the fact that the functional unit of the kidney, the nephron, has structural and functional similarities with the stria vascularis in the labyrinth [2, 3]. These similarities make both organs vulnerable to similar agents and genetic disruptions in utero [2, 3].

1.2.1 Ion channels and transporters expressed in both the inner ear and kidney

ClC proteins are a large family of proteins that mediate voltage-dependent transport of Cl – ions across cell membranes [4]. They are controlled by the CLC gene family. They comprise the CLC-K channels, Cl – channels and Cl–/H+ antiporters. A critical subunit of the CLC-K channels is the protein barttin. These channels and transporters are expressed in both the inner ear and the kidney. [4–6] (**Figure 1**).

The CLC-K channels form homodimers which additionally co-assemble with the small protein barttin. ClC-K/barttin localizes at the basolateral membranes of both the thin and thick ascending limbs of Henle's loop, and in marginal cells of the stria vascularis of the inner ear [5]. In the kidney, they are involved in NaCl reabsorption; in the inner ear they are important for endolymph production (see 2.1.1.3 below).

2. Hearing loss in chronic kidney diseases

The kidney and the inner ear both suffer from the adverse effects of diseases like diabetes mellitus, hypertension and aging.

Several reports have indicated that hearing loss is more prevalent among CKD patients than the general population in different parts of the world [7–11]. In a Korean study by Seo1 JY et al. involving 5,226 participants ≥19 years of age whose estimated glomerular filtration rate (eGFR) and hearing threshold were measured, the authors found the odds of hearing impairment to be 1.25 times higher (95% confidence interval: 1.12–1.64, p-value <0.001) in participants with an eGFR <60 mL/min/1.73 m^2 (chronic renal failure group) than in those with an eGFR ≥60 mL/min/1.73 m^2 (normal or mildly impaired renal function group) after adjustments for age, sex, smoking, alcohol, body mass index, diabetes mellitus, hypertension, dyslipidemia, and microalbuminuria [7]. Among the risk parameters of CKD associated with hearing impairment, linear regression analysis adjusted for age and sex determined that each increase of serum creatinine or blood pressure was positively associated with an increase in hearing threshold (p-value <0.01) [7].

2.1 Etiology of hearing loss among patients with chronic kidney disease

The causes of hearing loss among patients with chronic kidney disease are multifactorial, ranging from genetics through uraemic complications to medication side effects [9, 12–14].

2.1.1 Genetic causes

2.1.1.1 Hereditary nephritis

Hereditary nephritis (Alport's syndrome) is a recognized cause of CKD among adolescents and young adults. Alport's syndrome is characterized by progressive kidney failure (mainly from second decade), sensorineural hearing loss and characteristic ocular findings. Cecil Alport first described the disease as hereditary haematuric nephritis with hearing loss in a family whose affected males died in adolescence [15]. The disease is caused by a defect in the gene that codes for basement membrane type IV collagen [15]. The consequence of this genetic defect is a thickened and often split basement membrane giving a characteristic "basket weave" pattern. The disease has variable pattern of inheritance but 85% of cases are X-linked and most or all of those results from mutation of COL4A5, the gene located on chromosome Xq22 that codes for the α5-chainof type IV collagen. Autosomal-recessive inheritance occurs in perhaps 15% of cases, and autosomal-dominant inheritance has been shown in a few cases with associated thrombocytopathy and in rare cases without platelet defects [15]. The disease initially manifests as asymptomatic microscopic haematuria, sometimes with superimposed episodes of gross haematuria. Progressively worsening proteinuria and end stage renal disease (ESRD) may eventually develop, although the rate of progression is quite variable [15].

Affected individuals have bilateral high-frequency sensorineural hearing loss [15]. Nonetheless, some affected individuals with the X-linked nephritis progressing to ESRD may be without hearing loss, an occurrence which might lead to missed diagnosis.

In Alport's syndrome, the similarities in connective tissue structure (collagen type IV) between basement membranes of glomeruli and the stria vascularis of the inner ear account for the affectation of both organs in most cases [15, 16].

2.1.1.2 Branchio-Oto-renal (BOR) syndrome

In Branchio-Oto-Renal (BOR) syndrome, there is concurrent occurrence of ear and renal abnormalities. Renal abnormalities include bilateral renal agenesis,

bilateral hypoplasia or dysplasia, unilateral renal agenesis with contralateral hypoplasia or dysplasia, ureteropelvic obstruction, and vesicoureteric reflux. Renal function ranges from normal to severe reduction in glomerular filtration rate [17]. The ear abnormalities range from preauricular pits, malformations in the external, middle, and inner ear; and hearing loss [7, 17].

2.1.1.3 ClC-K in renal salt loss and deafness (Bartter syndrome type IV)

ClC-Kb/barttin (see **Figure 1**) is mainly expressed in basolateral membranes of the thick ascending limb of Henle's loop, where it is involved in the reabsorption of salt and, consequently, water [18]. In this part of the nephron, the Na + electrochemical gradient (created by basolateral Na+/K+ pump) drives the secondary active transport of NKCC2 (present in the apical membrane), accumulating Na+, Cl−, and K+ into the cell. K+ is extruded back to the lumen through ROMK K+ channels (also present in the apical membrane), whereas Na + and Cl − are reabsorbed by the interstitial fluid through the Na+/K+ pump and ClC-Kb channels, respectively. Thus, the end product of this system is the reabsorption of NaCl into the blood stream (**Figure 1A**). In the inner ear, both ClC-K isomers are expressed in the basolateral membrane of marginal cells of the stria vascularis. This multilayered epithelium is responsible for both the high concentration of K+ and the positive potential (about 100 mV higher than normal extracellular fluids) of the endolymph of the scala media, both of which are important properties for hearing. In marginal cells—the more apical layer in the stria vascularis—Na+/K+ pumps and NKCC1 transporters build up K+ and Cl − inside the cells. ClC-K/barttin channels recycle Cl − back to the interstitial fluid, while apical KCNQ1/KCNE1 K+ channels secrete the excess of potassium ions into the endolymph (**Figure 1B**) [19]. In agreement with the transport models involving ClCK/barttin channels, mutations in the gene encoding ClC-Kb cause salt-losing Bartter syndrome type III [20], characterized by hypokalemia, metabolic alkalosis and secondary hyperaldosteronism with normal or low blood pressure [21]. Mutations in the gene encoding barttin cause Bartter syndrome type IV that combines the salt wasting with congenital deafness, since both ClC-K proteins are non-functional in the absence of barttin [22]. When disruption occurs in only one of the ClC-K channels, as it does in ClCKb mutations in Bartter type III, hearing is preserved; the other isomer channel still provides the necessary Cl − recycling. Deafness occurs only on disruption of both ClC-K channels or upon disruption of barttin [22, 23].

2.2 Medication toxic effect

Over 450 medicines are reported to be ototoxic [24]. These include both prescription medicines such as antibiotics, cancer medications, anti-malarias, and diuretics; and over-the counter medicines such as Non-Steroidal Anti-Inflammatory drugs (Pain killers). In most cases, this type of ototoxicity is an acute, short-lived side effect; if the patient stops taking the medication, the symptoms typically recede [24]. This is not the case, however, for aminoglycoside antibiotics and platinum derivatives used as cancer drugs which may be associated with permanent hearing loss [25]. The mechanism of drug-induced ototoxicity is varied.

2.2.1 Aminoglycoside antibiotics and high-ceiling diuretics

For the patient with CKD, the medications of importance in causing ototoxicity are the aminoglycoside antibiotics, used commonly in treating urinary tract infections and septicaemia which are quite frequent in such patients and also

furosemide; a high-ceiling diuretic commonly used in treating fluid overload and pulmonary oedema in CKD patients. Though the ototoxic effect of aminoglycoside is known among many medical practitioners, the lack of diagnostic facilities in many centers across the world lead to the neglect of full assessment for this potential side effect. Lack of treatment interventions for hearing loss in many regions take away the interest in evaluation for this side effect.

The ototoxicity of furosemide is often overlooked by physicians and nurses. Furosemide toxicity commonly occurs when the medicine is administered as intravenous push medication and in a faster fashion.

2.3 Hearing loss among hemodialysis patients

Chronic kidney disease patients in End stage who are on hemodialysis are another cohort of CKD patient who suffer from hearing loss.

Several reports indicate that sensorineural hearing loss (SNHL) is considerably more prevalent in patients with chronic renal failure (CRF) than in the general population. It ranges from 28% to 77% [26, 27].

Although all frequencies can be affected by CRF, hearing impairment at high frequencies is most common [28]. In addition to antigenic similarity [29], the cochlea and kidney have similar physiological mechanisms, namely, the active transport of fluid and electrolytes achieved by the stria vascularis in the cochlea and the glomeruli in the kidney [3].

It was previously confirmed that the cochlea is affected by the systemic metabolic, hydroelectrolytic, and hormonal alterations that are associated with CRF [30].

Several variables may contribute to the etiopathogenetic mechanisms of hearing loss in CRF including factors related to the severity and duration of the disease, electrolyte disturbances, ototoxic drugs, age, comorbid conditions such as diabetes mellitus and hypertension, and hemodialysis [31–33].

In an Iraqi study by Haider K et al. to determine the effect of hemodialysis on the hearing threshold in patients with chronic renal failure (CRF), 59 patients were followed up for 1 year with a pure-tone audiometric examination every 6 months [34]. At the beginning of the study, 39 patients (66.1%) had sensorineural hearing loss (SNHL). During the 12-month follow-up, 6 more patients developed SNHL giving a point prevalence rate of 76.3% at the end of the study. The hearing loss was more evident in the higher frequencies. Of the studied patients, 64.4% showed deterioration of the hearing threshold. The mean hearing threshold at the beginning of the study was 29.2 ± 21.1 dB versus 36.9 ± 17.3 dB at the end of the study ($P < 0.001$). No significant relation was found between age, sex, serum electrolytes, blood urea, and duration of CRF and hearing loss. Multivariate analysis showed that the duration of hemodialysis was the only significant independent predictor of SNHL [34].

3. Preventive healthcare strategies of sensorineural hearing loss

Because of the global burden of patients receiving chronic hemodialysis therapy, coupled with the high prevalence of hearing loss among this cohort which are often overlooked [26, 27], it is proper to highlight on the need to create awareness on preventive measures of hearing loss. Also, worldwide, 120 million people are estimated to be suffering from disabling hearing loss (>40 dB, average 0.5–4 KHz) [35]. Primary preventive measures should include genetic counseling targeted at families known to carry diseased genes. In the prenatal period, efforts should be made to address maternal problems like premature deliveries, and low birth weight through

improved antenatal care services. Perinatal/neonatal asphyxias, neonatal jaundices which requires exchange transfusions, neonatal meningitis etc. should be keenly addressed. There should be intensification of immunization programmes particularly those against meningitis, measles, mumps and rubella in selected populations.

There should be careful and judicious use of ototoxic drugs such as furosemide and aminoglycoside antibiotics in the clinical settings, avoiding combination of the two groups where possible. There should be education on the risk of self-medications, use of herbal products that may be both ototoxic and nephrotoxic.

Education on overcrowding in the daycare centers, poor housing systems, bottle feeding, malnutrition etc.

There should be better management of acute respiratory infections, noise control and the appropriate use of hearing protection. Education of individuals, communities and governments is an essential prerequisite to implementation [35].

Neonatal/early childhood hearing screening should be instituted for early identification, diagnosis, treatment and rehabilitation of high-risk patients.

There should be early identification and management of comorbidities like hypertension and diabetes in the adult population.

Among the dialysis population, awareness must be created and screening programmes instituted where possible.

Above all, rehabilitation programmes for affected individuals should be implemented to improve the quality of life of such individuals through the use of hearing aid and implants.

4. Conclusions

Hearing loss is not uncommonly associated with chronic kidney disease yet this co-morbidity is often overlooked by Health Care givers. The aetiopathogenesis of hearing loss in CKD patients are multifactorial; from genetic mutations that affect both the kidney and the inner ear due to similarities in structural proteins, through ototoxic medications commonly used in CKD patients, to the toxic effect of uraemia. It is hoped that this neglected aspect of care for patients with chronic kidney disease will receive the needed attention for holistic care of the CKD patient.

Conflict of interest

The authors declare no conflict of interest.

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Author details

Sampson Antwi[1*] and Mohammed Duah Issahalq[2]

1 Department of Child Health, Kwame Nkrumah University of Science and Technology, Kumasi, Ghana

2 Department of Otorhinolaryngology, Kwame Nkrumah University of science and Technology, Kumasi, Ghana

*Address all correspondence to: kantwisampson@gmail.com; antwisampson.sms@knust.edu.gh

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Chapter 7

Brainstem Auditory Evoked Potentials in Type 2 Diabetes Mellitus

Rajesh Paluru and Devendra Singh Negi

Abstract

Diabetes mellitus is a group of metabolic diseases characterized by hyperglycaemia resulting from defects in insulin secretion, insulin action or both. Diabetes affects many systems and produces complications in the human body, in those complications one is diabetic central neuropathy. The pathological mechanisms involved in the central neuropathy include chronic hyperglycaemia, hypoglycaemic episodes, angiopathy and blood–brain barrier dysfunction. Diabetic central neuropathy is detected by using of brainstem auditory evoked response (BAER), Visual evoked potential (VEP), somatosensory evoked potential (SEP). These abnormalities are present at different levels and may appear before appearance of overt complications. The central nervous system abnormalities are more frequent in patients with peripheral neuropathy but evoked potentials can be abnormal even in patients without neuropathy. The BAER is a physiological recording technique to study the auditory pathway and does not require subject's attention and generates waves during the first 10 ms after the sound stimulus. Each BAER wave is generated by the activation of a sub-cortical component of the auditory pathway with 90% sensitivity and 70–90% of specificity.

Keywords: Brainstem auditory evoked response, central neuropathy, hearing impairment, inter peak latency, type 2 diabetes mellitus

1. Introduction

Diabetes mellitus causes both peripheral and central neuropathy, but the peripheral diabetic neuropathy manifestations are more frequently discussed in the literature than the central diabetic neuropathy [1]. The central nervous system has wide, divergent afferent and efferent connections to integrate and transduced the whole body functions like homeostatic adjustments of food intake, energy expenditure, and nutrient metabolism [2].

The auditory nervous system is a complex and intricate structure and performs many tasks in daily life; it analyzes, synthesizes, commands sensory information and carries out decisions; it is measured by using a powerful tool, auditory brainstem evoked response, is capable of both detection and diagnosis of brainstem lesions [3]. The auditory nervous system consists of ascending and descending pathways. Ascending pathway has the classical and non-classical pathways. The classical auditory pathways are known as the tonotopic system because they have

distinct frequency tuning and the neurons are organized anatomically according to the frequency to which they are tuned. Non-classical pathway used the dorsal nuclei of the thalamus and that project to secondary auditory cortex rather than primary auditory cortex. Again the non-classical pathway divided into two separate systems, the diffuse and the polysensory pathways. Descending pathway has the corticofugal and the olivocochlear pathways. Descending auditory pathways are organized mostly parallel to the ascending pathways extending from the cerebral cortex to the cochlear hair cells [4].

Evoked potentials are helpful very much to study the diabetic change in central neural structures [5]. Diabetic central neuropathy is detected by using of brainstem auditory evoked response (BAER), Visual evoked potential (VEP), somatosensory evoked potential (SEP) [5, 6]. These abnormalities are present at different levels and may appear before appearance of overt complications. The central nervous system abnormalities are more frequent in patients with peripheral neuropathy but evoked potentials can be abnormal even in patients without neuropathy. The pathological mechanisms involved in the central neuropathy include chronic hyperglycaemia, hypoglycaemic episodes, angiopathy and blood–brain barrier dysfunction [7].

The BAER is a physiological recording technique to study the auditory pathway and does not require subject's attention and generates waves during the first 10 ms after the sound stimulus. Each ABR wave is generated by the activation of a sub-cortical component of the auditory pathway [8] with 90% sensitivity and 70–90% of specificity [9]. Despite its fall from favor as the initial test of choice in suspected brainstem or VIIIth cranial nerve disease, important clinical roles for BAER still exist. It should be remembered that BAER assess functions of auditory pathways whereas neuroimaging studies examine structure [10].

2. Materials and methods

2.1 Research design

The research design is cross sectional study. The control group included normal subjects, T2DM patients without hearing impairment of either sex, who is not suffering from hearing problems. The sampling technique was sequential sampling.

2.2 Participants

The present study was carried out at Mediciti Institute of Medical Sciences (MIMS), Hyderabad, India during the period of 2015 to 2016. This study was approved by institutional ethical committee (FWA00002084; dated 16/03/2015). In this study three groups i.e. WoHI (n = 50), WHI (n = 50) and normal subjects (n = 10) of either sex with an age group of 35–55 were included. The participants were enrolled in the study after acquiring the informed consent.

2.3 Inclusion and exclusion criteria

Type 2 diabetic patients with (WHI) and without (WoHI) hearing impairment, both the gender was included with age limit between 35 and 55 years; minimum duration of diabetes after the diagnosis was 5 years and also ten normal subjects were included as controls.

Participants who had a history of immune/metabolic diseases like hyperbilirubinaemia/kernicterus, polyarteritis nodosa, type 1 diabetes, paraproteinaemias,

anoxia/hypoxia, sarcoidosis, rheumatoid arthritis, uraemia, Guillain-Barré Syndrome, chronic infections like Leprosy, AIDS, Borreliosis, Ramsey Hunt syndrome, using heavy metals like lead, cobalt, mercury; drugs like carboplatin, methyldopa and reserpine; neoplasma/intracranial cystic lesions, chronic middle ear diseases, cranial trauma, ear surgeries, recent surgeries, congenital problems, noise exposure, smoking, alcoholism, hypertension, stroke and hepatic encephalopathy were excluded from the study.

2.4 Sample size calculation

The sample size was calculated in the OpenEpi statistical software. In the pilot study, screening for hearing was carried out for both the ears in fifteen individuals by using pure tone audiometry. In the right ear, 9 out of 15 had a hearing impairment, and 5 out of 9 (55.5%) participants with hearing impairment had diabetes. Out of the 6 (16.7%) individuals without hearing impairment only one had diabetes. Using these values sample size was calculated as 27 each for controls and test. In the left ear, 10 out of 15 had a hearing impairment, and 5 out of 10 (50%) subjects with hearing impairment had diabetes. Out of the 5 (20%) individuals without hearing impairment only one had diabetes. Using these values sample size was calculated as 45 each for controls and test. So in the present study 50 was considered as sample size for each group.

2.5 Calculation of BMI

Height and weight were measured on the subjects in standing position. The weighing scales and the measuring tapes were calibrated periodically. BMI was calculated from the formula, BMI = weight (kg) /height^2 (mts). BMI normal values are below 18.5 (underweight), 18.5–24.9 (normal), 25.0–29.9 (pre obesity), 30.0–34.9 (obesity class I), 35.0–39.9 (Obesity class II) and Above 40 (Obesity class III).

2.6 Measurement of HbA1c

In diabetes, long-term maintenance of blood glucose is important to prevent complications. HbA1cis an indicator of the average glucose concentration in the blood over a period of four months. The HbA1c was measured by using anticaogulated venous blood with latex agglutination inhibition assay (the absence of agglutination is diagnostic of antigen provides a high sensitive assay for small quantities of antigen) with "Rx imola automated analyser (open system)". Protease enzyme in the hemoglobin denaturant reagent lyses red blood cells and causes hydrolysis of the hemoglobin. The concentration of HbA1c and the total hemoglobin concentrations are measured and HbA1c was calculated as a % of the total hemoglobin concentration. A normal range of HbA1c was 4–6.5% (normal), 6.5–7.5% (target range for those with diabetes), 8–9.5% (high) and greater than 9.5% (very high).

2.7 Measurement of pure tone average (PTA)

The levels of hearing impairment are assessed with the help of Pure Tone Audiometry and obtain pure tone thresholds during air and bone conduction testing. They are recorded graphically on the "audiogram". The audiogram is graph of a patient's hearing thresholds across the frequency octaves from 250 Hz to 8000 Hz. The audiogram provides both qualitative and quantitative information about the patient's hearing loss. Quantitative information tells about degree of loss based on the pure tone average (PTA) of AC thresholds and calculated as decibels (dB). PTA

normal ranges for hearing impairment are –10 to 15 (normal), 16 to 25 (slight), 26 to 40 (mild), 41 to 55 (moderate), 56 to 70 (moderately severe), 71 to 90 (severe), 91 and above (profound). Qualitative information tells about type of hearing impairment and helps in topological diagnosis.

2.8 Recording of brainstem auditory evoked response

The BAER is a sequential electrical potential generated in the brainstem and auditory pathway in response to stimulus and is recorded as wave forms from wave I to wave VII and these peaks are generated from different sites of the brainstem auditory pathway. It helps in analyzing presence or absence of hearing loss at the level of central auditory pathway. In the present BAER is recorded by using instrument "Biologic Navigator Pro system AEP Software version 6.3" Natus Medical Incorporated USA, 2013.

2.8.1 Stimulus types

An ideal stimulus for eliciting BEAR is a click, which is a brief rectangular pulse of 50–200 μs duration with an instantaneous onset. The rapid onset of click provides good neural synchrony, thereby eliciting a clearly defined BAER.

2.8.2 Electrode application

Skin must be thoroughly cleaned to remove excess oil, dead skin and dirt to obtain a good contact between skin and electrode. Electrodes are filled with a conducting cream and taped into place. Once the electrodes have been applied, adequacy of contact with skin is assessed by measuring electrical impedance between each electrode pair. For high quality recording, inter electrode impedance $\leq$5 kΩ is acceptable.

2.8.3 Processing of electrical activity

Electrical activity picked up by the recording electrodes within the specified time window must be processed through several stages to visualize the BAER waveform. This is because the BAER peaks are of extremely small voltage (>1 μV) and are buried in a background of interference (termed 'noise'), which includes ongoing electroencephalogram (EEG) activity, muscle potentials caused by movement or tension, and 50 Hz power-line radiation. The stages of processing include amplification, filtering, and signal averaging.

2.8.4 Amplification and filtering

The small size of the BAER peaks requires amplification to increase the magnitude of the electrical activity picked up by the electrodes. An amplifier gain of 10^5 is typically used. The problem of interference obscuring the BAER can be diminished partially by filtering the electrical activity coming from the electrodes. Band pass filters are used to accept energy only within the particular frequency band of interest and reject energy in other frequency ranges. For BAER recording, a filter setting of 30–3000 Hz is recommended to enhance the BAER when testing infants.

Filtering can only eliminate a portion of the interfering noise because of overlap between the frequency content of the BAER and the frequency of the interference. Therefore, another technique, called signal averaging, must be used to further reduce unwanted interference.

2.8.5 Signal averaging

The BAER is very small, and even with filtering, it is buried with a background of noise. Signal averaging helps to reduce this noise so that the signal, in this case the BAER, can be detected. Signal averaging is possible because the BAER is time-locked to stimulus onset, whereas the noise interference occurs randomly. That is, the signal occurs at the same points in time following onset of the eliciting stimulus, but the noise has no regular pattern. In signal averaging, a large number of stimuli are presented, and the responses to each of the individual stimulus presentations (termed 'sweeps') are averaged together to obtain a final averaged waveform. By averaging, the random noise tends to cancel out, whereas the evoked potential is retained because it is basically the same in each sweep. The greater the number of stimulus presentations used, the greater the improvement in signal to noise ratio, and the more clearly the BAER can be visualized in the final averaged waveform.

2.8.6 Procedure

The patient is made to lie down in a relaxed position with eyes closed so that no auro-palpaberal reflex could be picked up. The portion behind the ear i.e., mastoid on both sides and the forehead are rubbed gently with a conductive gel such that it allows to maintain adequate impedance for the testing. Measures are taken that there no particulars in the testing area that could cause electrical artifacts. Care should also be taken that the wires embedded to the instrument are un-tangled. Considering the test particulars, click stimulus with an alternating polarity are used at intensity levels 80, 70, 60, 50, 40, 30 dB NHL. The filter setting that is set ranges from 150 Hz–1500 Hz, with an epoch time of 10.26 ms and stimulus rate of 11.1/sec and 1024 sweeps of stimulus. The waveform thus displayed post averaging process on the screen is analyzed and the peaks I, III and V are noted. The results thus obtained are analyzed for the final diagnosis considering the absolute latencies of peaks I, III and V and inter peak latencies of I-III, III-V and III-V respectively. Waves I-VII are originated from cochlear nerve, cochlear nucleus, superior olivary complex, lateral lemniscus, inferior colliculus, medial geniculate body and auditory cortex respectively.

2.8.7 Interpretation

IPL I-III is the conduction from the eighth nerve across the subarachnoid space, into the core of the lower pons; normal is 2 milli secs and abnormal is ˃2.4 milli secs. IPL III-V is the conduction from the lower to the upper pons and possibly into the midbrain; normal is 2 milli secs and abnormal is ˃2.4 milli secs. IPL I-V is the conduction from the proximal eighth nerve through pons and into the midbrain; normal 4 milli secs and abnormal is ˃4.4 milli secs.

3. Statistical analysis

All the data were expressed as mean ± SE. The mean were analyzed by one way ANOVA (Student–Newman–Keuls method). Pearson correlation test was done to see the relationship between right and left ear inter peak latencies of wave I-III, III-V and I-V values in normal subjects, WoHI and WHI groups. Pearson correlation test was done to see the relationship between inter peak latencies I-III, III-V and I-V with age, BMI and HbA1c values in normal subjects, WoHI and WHI groups for both the ears. For all the statistics and graph plotting, SigmaPlot 13.0 (Systat software, USA) was used. $P < 0.05$ was considered as significant.

4. Results

The comparison of IPLs I-III, III-V and I-V of both the ears in normal subjects, WoHI and WHI groups were done by one way analysis of variance and it was represented in **Table 1** with their mean and standard error of mean. The comparison of IPL I-III of BAER of both the ears in normal subjects, WoHI and WHI groups were given in **Figure 1**. The IPL I-III of both the ears in WHI group was statistically different from normal subjects and WoHI groups ($P < 0.0001$), this showed that IPL I-III increased in both ears of WHI group. The correlation of IPL I-III values of both the ears in WoHI and WHI groups were given in **Figure 2**. Negative correlation is seen in WoHI group for both the ears ($P = 0.730$), whereas in WHI group it is statistically significant ($P = 0.050$).

The comparison of IPL III-V of BAER of both the ears in normal subjects, WoHI and WHI groups were given in **Figure 3**. The right ear IPL III-V of WHI group

Parameter	Ear	Normal subjects (Mean ± SEM)	T2DM WoHI (Mean ± SEM)	T2DM WHI (Mean ± SEM)	P-value
IPL I-III (ms)	Right	1.688 ± 0.059	1.895 ± 0.048	2.241 ± 0.039	Given in **Figure 1**
	Left	1.695 ± 0.056	2.027 ± 0.317	2.187 ± 0.048	
IPL III-V (ms)	Right	1.596 ± 0.044	1.896 ± 0.048	1.930 ± 0.053	
	Left	1.521 ± 0.051	1.818 ± 0.053	1.662 ± 0.038	
IPL I-V (ms)	Right	3.081 ± 0.201	4.083 ± 0.050	4.170 ± 0.058	
	Left	2.919 ± 0.174	3.845 ± 0.052	3.715 ± 0.043	

Table 1.
One way analysis of variance of IPLs in normal subjects, T2DM WoHI and WHI groups.

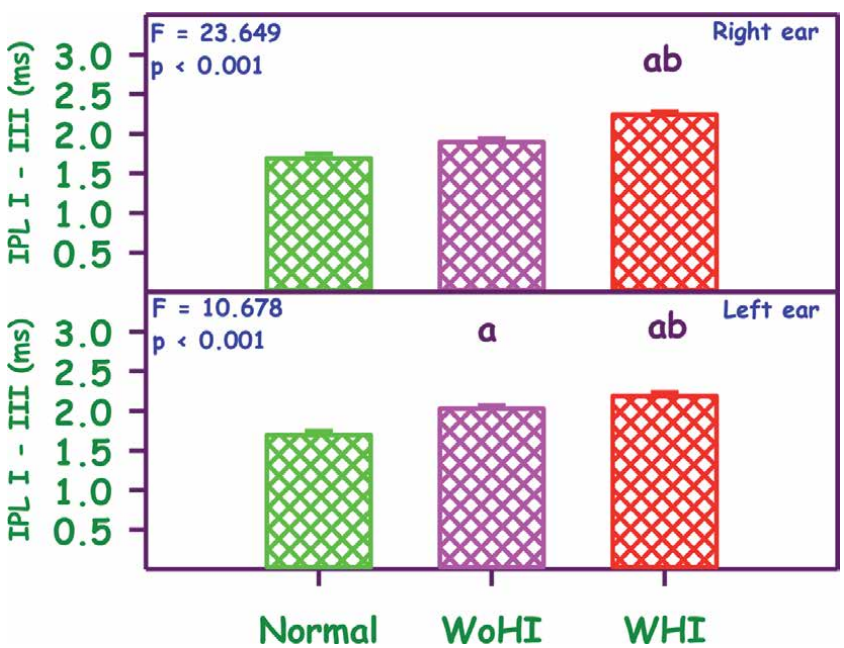

Figure 1.
The IPL I-III in normal subjects, type 2 diabetes without (WoHI) and with (WHI) hearing impairment. Mean + SE (n ± 50 each in WoHI and WHI groups, n ± 10 in normal subjects). The 'F' and P values are comparing normal subjects, WoHI and WHI of right and left ear. a – Significantly different from normal subjects; b – Significantly different from WoHI group.

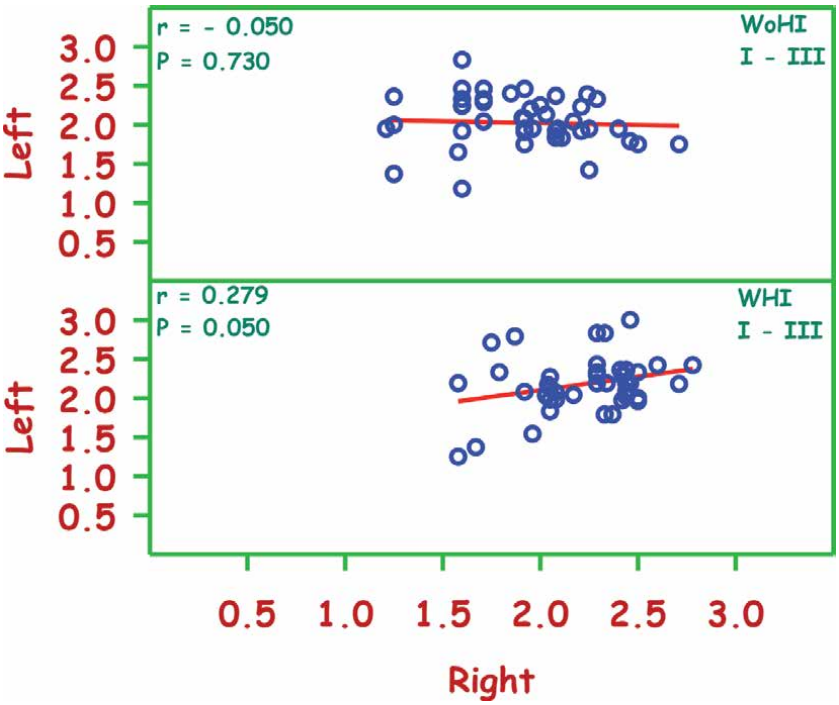

Figure 2.
Correlation of IPL I-III (ms) in type 2 diabetes, without (WoHI) and with (WHI) hearing impairment. n = 50 each. The 'r' and P values are correlating WoHI and WHI right and left ear.

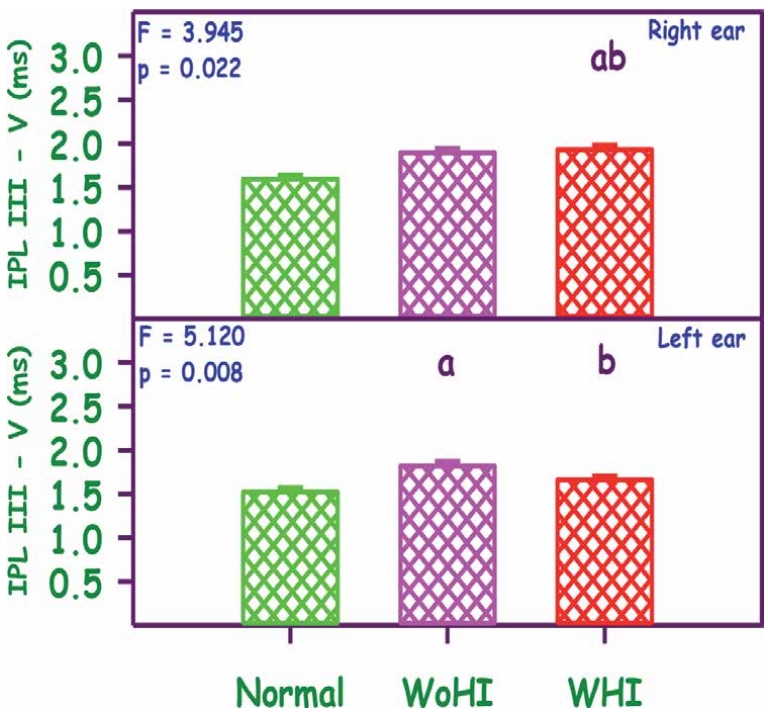

Figure 3.
The IPL III-V in normal subjects, type 2 diabetes without (WoHI) and with (WHI) hearing impairment. Mean + SE (n ± 50 each in WoHI and WHI groups, n ± 10 in normal subjects). The 'F' and P values are comparing normal subjects, WoHI and WHI of right and left ear. a – Significantly different from normal subjects; b – Significantly different from WoHI group.

(P = 0.022) were statistically different from normal subjects, WoHI group. The left ear IPL III-V of WoHI group is significantly different from normal subjects whereas WHI group is significantly different from WoHI group. This showed that IPL III-V increased in both ears of WHI group. The correlation of IPL III-V values of both the ears in WoHI and WHI groups were given in **Figure 4**. No correlation is seen in WoHI and WHI groups for both the ears. Negative correlation is seen WoHI group for both the ears (P = 0.100).

The comparison of IPL I-V of BAER of both the ears in normal subjects, WoHI and WHI groups were given in **Figure 5**. In WoHI and WHI groups (P < 0.0001), both the ears showed significant difference from the normal subjects. The correlation of IPL I-V values of both the ears in WoHI and WHI groups were given in **Figure 6**. No correlation was seen in WoHI and WHI groups for both the ears.

The correlation of IPL values and age, BMI, HbA1c values for both the ears in normal subjects were given in **Table 2**. The age, BMI, HbA1c values are not correlated with IPL values in normal subjects. The correlation of IPL values and age, BMI, HbA1c values for both the ears in all subjects were given in **Table 3**. The BMI correlated with the IPL I-V (P = 0.003) of both the ears and HbA1c values correlated with IPL I-III (P = 0.003), I-V (P < 0.001) values of both ears in all subjects. This showed that with increase in BMI and HbA1c values, the IPL values are increased in diabetic subjects.

The correlation of IPL I-III, III-V and I-V values and age for both the ears in WoHI and WHI groups were given in **Figures 7–9**. In both the groups IPL I-III, III-V and I-V values were not statistically correlated with age. In the IPL I-III, left ear (P = 0.262) of WoHI and right ear (P = 0.735) of WHI groups shows negative correlation with age. In the IPL III-V, right ear (P = 0.460) of WoHI group shows negative correlation with age. In the IPL I-V, right (P = 0.757) and left (P = 0.433) ears of WoHI group and left (P = 0.826) ear of WHI group shows negative correlation with age.

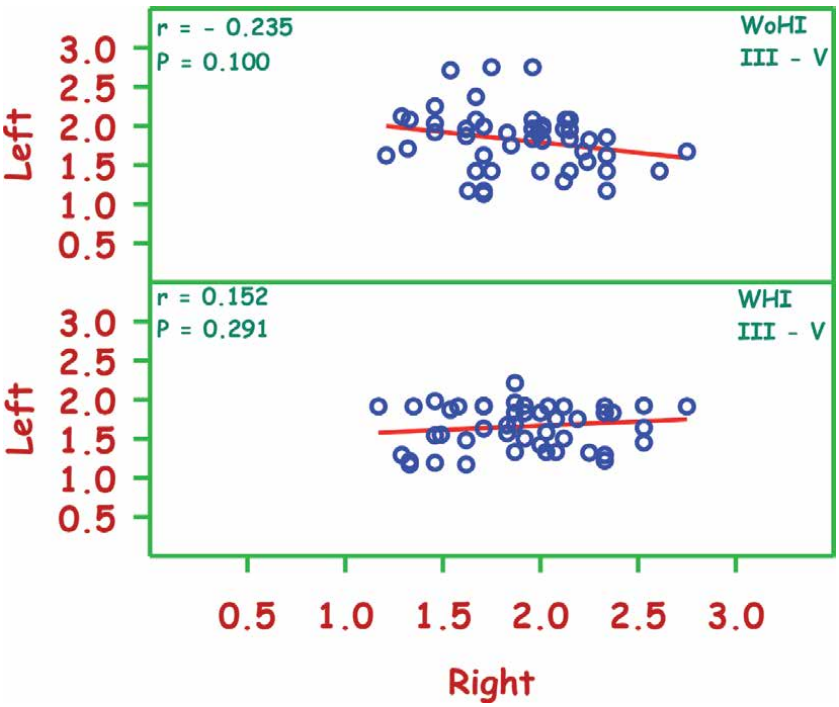

Figure 4.
Correlation of IPL III-V (ms) in type 2 diabetes, without (WoHI) and with (WHI) hearing impairment. n = 50 each. The 'r' and P values are correlating WoHI and WHI right and left ear.

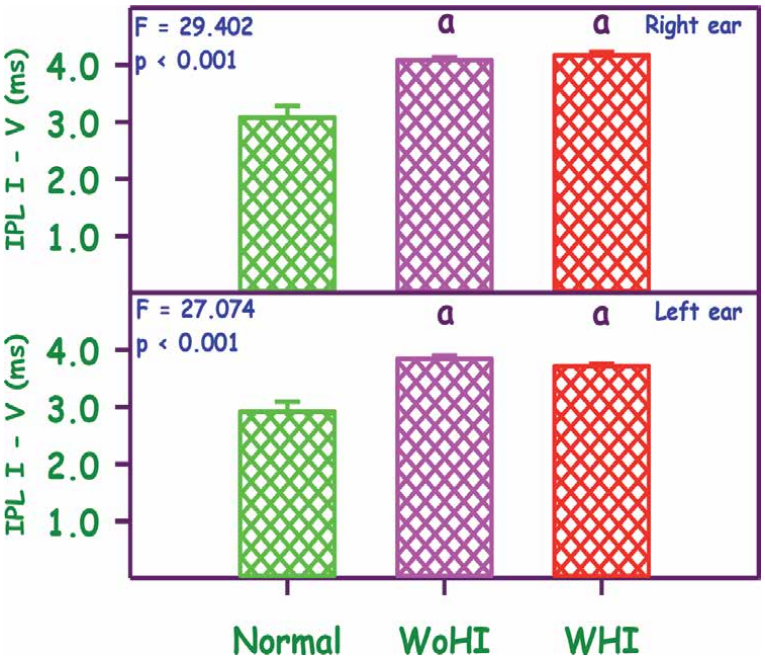

Figure 5.
The IPL I-V in normal subjects, type 2 diabetes without (WoHI) and with (WHI) hearing impairment. Mean + SE (n ± 50 each in WoHI and WHI groups, n ± 10 in normal subjects). The 'F' and P values are comparing normal subjects, WoHI and WHI of right and left ear. a – Significantly different from normal subjects; b – Significantly different from WoHI group.

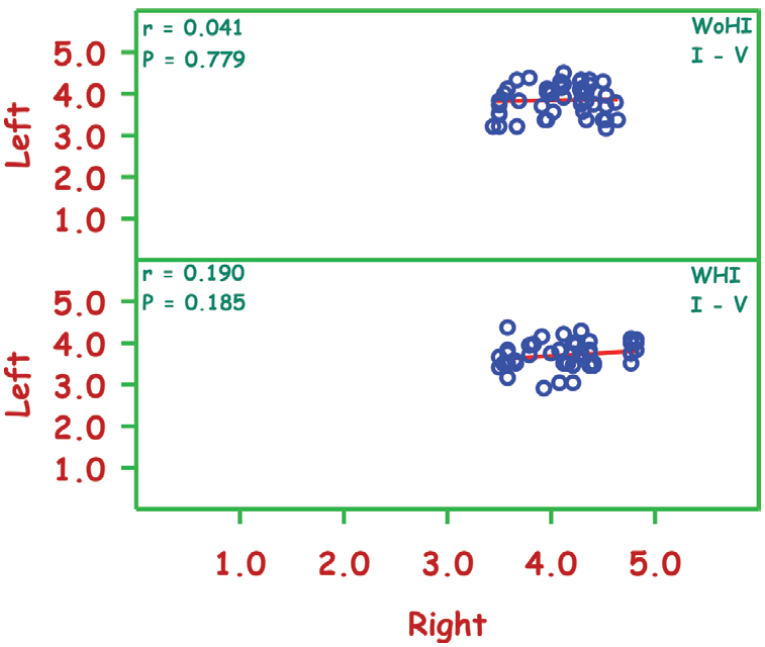

Figure 6.
Correlation of IPL I-V (ms) in type 2 diabetes, without (WoHI) and with (WHI) hearing impairment. n = 50 each. The 'r' and P values are correlating WoHI and WHI right and left ear.

The correlation of IPL I-III, III-V and I-V values and BMI for both the ears in WoHI and WHI groups were given in **Figures 10–12**. In both the groups IPL I-III, III-V and I-V values were not statistically correlated with BMI. In IPL I-III,

S.No	Independent variable	Dependent variable	Ear	r-value	p-value
1	Age (years)	IPL I-III	Rt	−0.571	0.084
			Lt	−0.523	0.121
		IPL III-V	Rt	−0.737	0.014
			Lt	−0.499	0.142
		IPL I-V	Rt	−0.705	0.022
			Lt	−0.733	0.015
2	BMI (sq.m)	IPL I-III	Rt	0.742	0.013
			Lt	0.215	0.550
		IPL III-V	Rt	0.523	0.121
			Lt	0.471	0.170
		IPL I-V	Rt	0.549	0.100
			Lt	0.496	0.145
3	HbA1c (%)	IPL I-III	Rt	−0.431	0.335
			Lt	−0.355	0.314
		IPL III-V	Rt	−0.436	0.208
			Lt	−0.282	0.430
		IPL I-V	Rt	−0.392	0.263
			Lt	−0.354	0.315

IPLs in milli seconds, Rt – right, Lt – left.

Table 2.
Correlation of independent variables and IPLs in normal subjects.

S.No	Independent variable	Dependent variable	Ear	r-value	p-value
1.	Age (years)	IPL I-III	Rt	0.081	0.397
			Lt	−0.002	0.978
		IPL III-V	Rt	0.057	0.550
			Lt	0.032	0.737
		IPL I-V	Rt	0.062	0.516
			Lt	−0.052	0.590
2.	BMI (sq.m)	IPL I-III	Rt	0.095	0.321
			Lt	−0.008	0.931
		IPL III-V	Rt	0.095	0.321
			Lt	−0.008	0.931
		IPL I-V	Rt	0.274	0.003
			Lt	0.210	0.027
3.	HbA1c (%)	IPL I-III	Rt	0.274	0.003
			Lt	0.210	0.027
		IPL III-V	Rt	0.130	0.176
			Lt	0.121	0.208
		IPL I-V	Rt	0.296	0.001
			Lt	0.296	0.001

IPLs in milli seconds, Rt – right, Lt – left.

Table 3.
Correlation of independent variables and IPLs in all subjects.

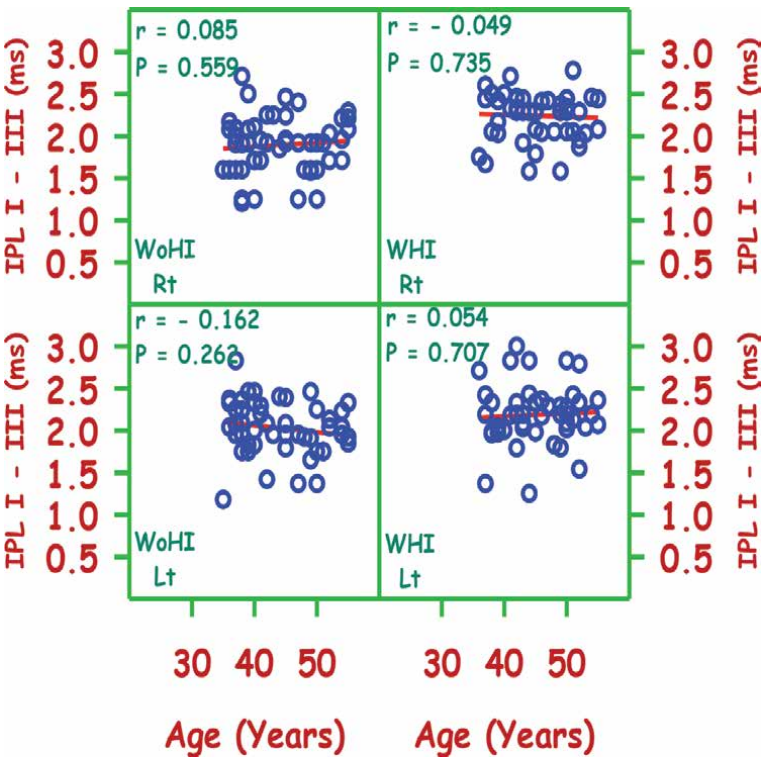

Figure 7.
Correlation of IPL I-III and age in type 2 diabetes, without (WoHI) and with (WHI) hearing impairment. The 'r' and P values are correlating WoHI and WHI right and left ear.

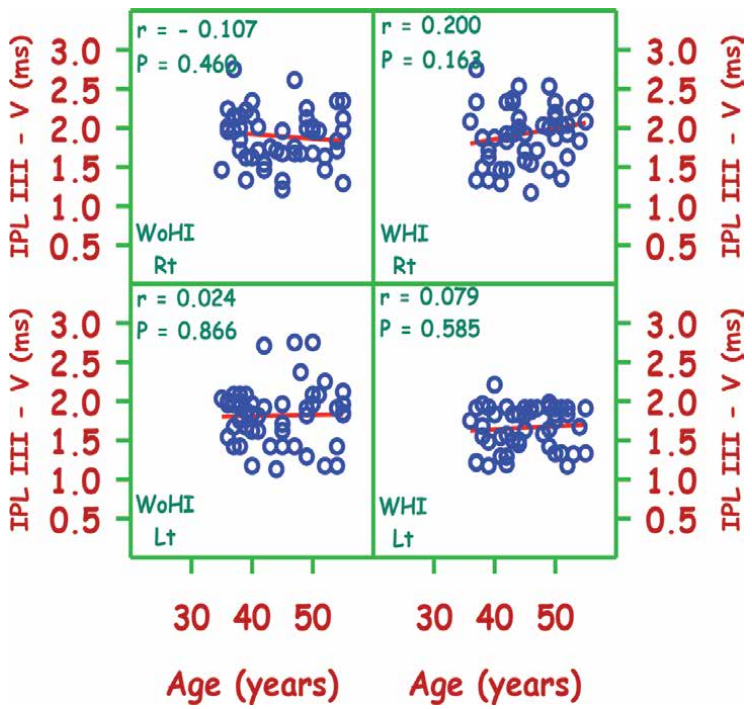

Figure 8.
Correlation of IPL III-V and age in type 2 diabetes, without (WoHI) and with (WHI) hearing impairment. The 'r' and P values are correlating WoHI and WHI right and left ear.

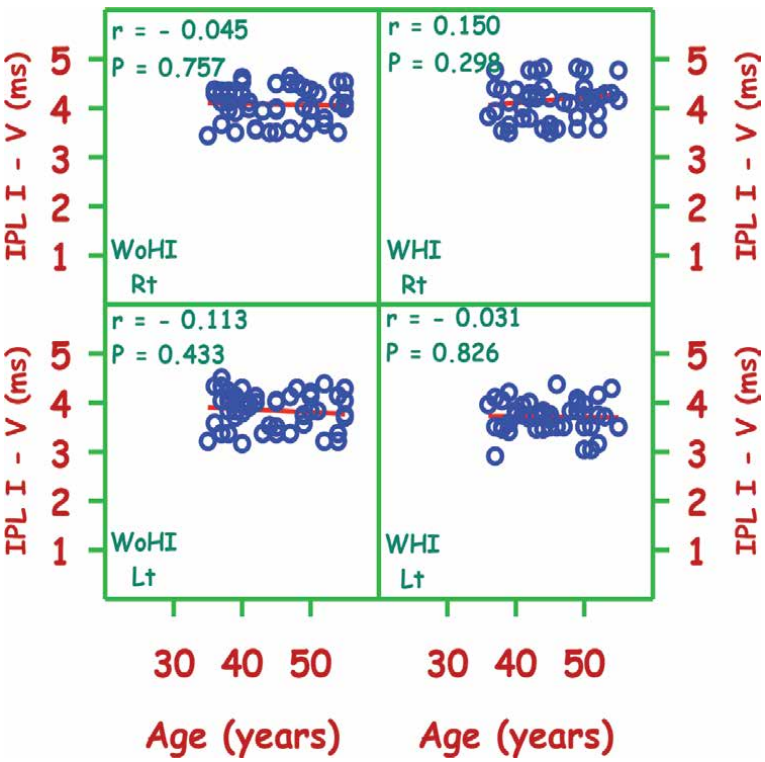

Figure 9.
Correlation of IPL I-V and age in type 2 diabetes, without (WoHI) and with (WHI) hearing impairment. The 'r' and P values are correlating WoHI and WHI right and left ear.

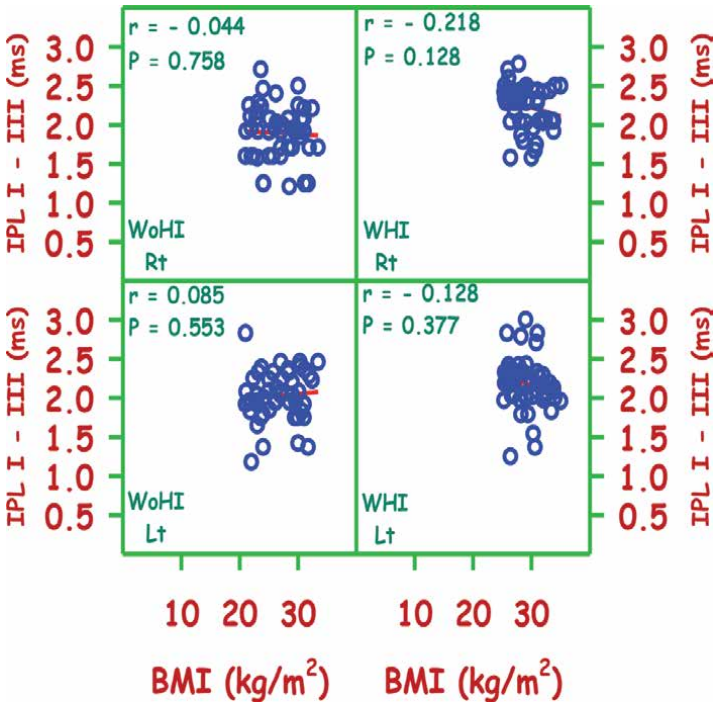

Figure 10.
Correlation of IPL I-III and BMI in type 2 diabetes, without (WoHI) and with (WHI) hearing impairment. The 'r' and P values are correlating WoHI and WHI right and left ear.

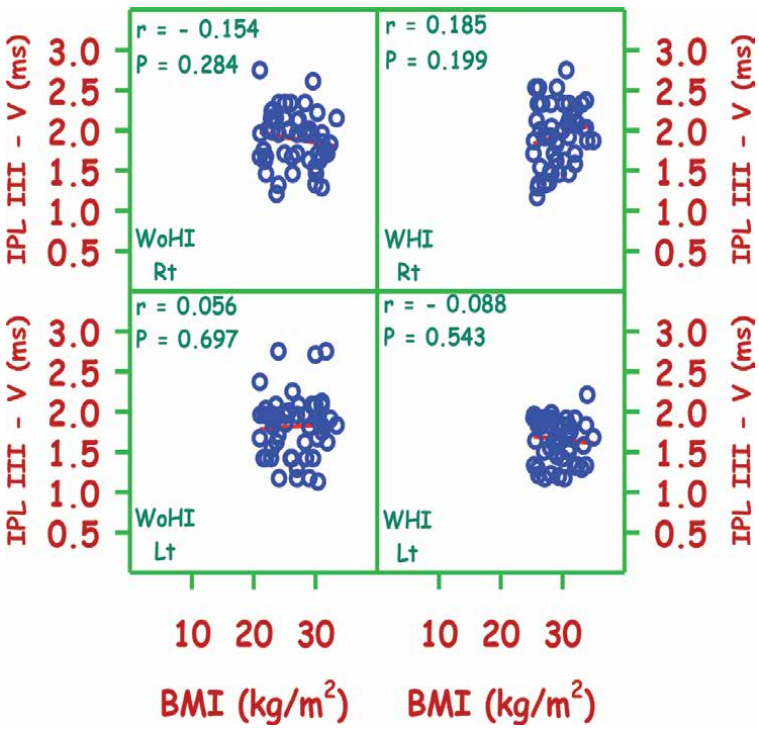

Figure 11.
Correlation of IPL III-V and BMI in type 2 diabetes, without (WoHI) and with (WHI) hearing impairment. The 'r' and P values are correlating WoHI and WHI right and left ear.

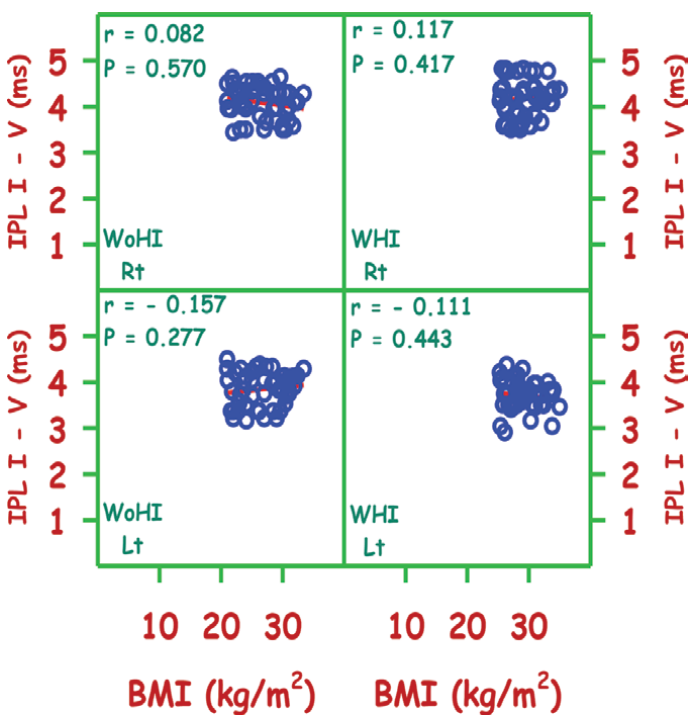

Figure 12.
Correlation of IPL I-V and BMI in type 2 diabetes, without (WoHI) and with (WHI) hearing impairment. The 'r' and P values are correlating WoHI and WHI right and left ear.

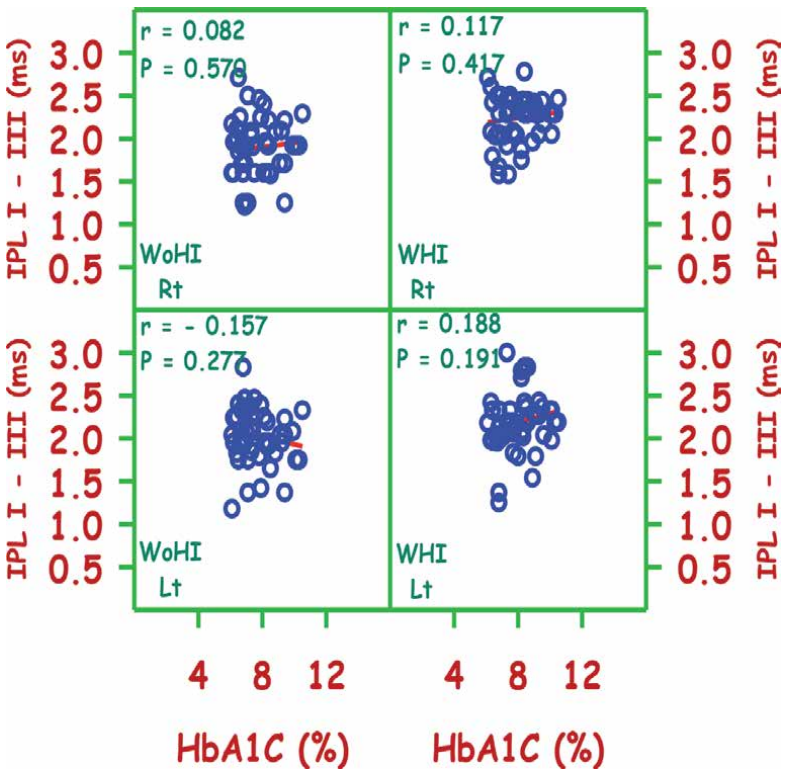

Figure 13.
Correlation of IPL I-III and HbA1c in type 2 diabetes, without (WoHI) and with (WHI) hearing impairment. The 'r' and P values are correlating WoHI and WHI right and left ear.

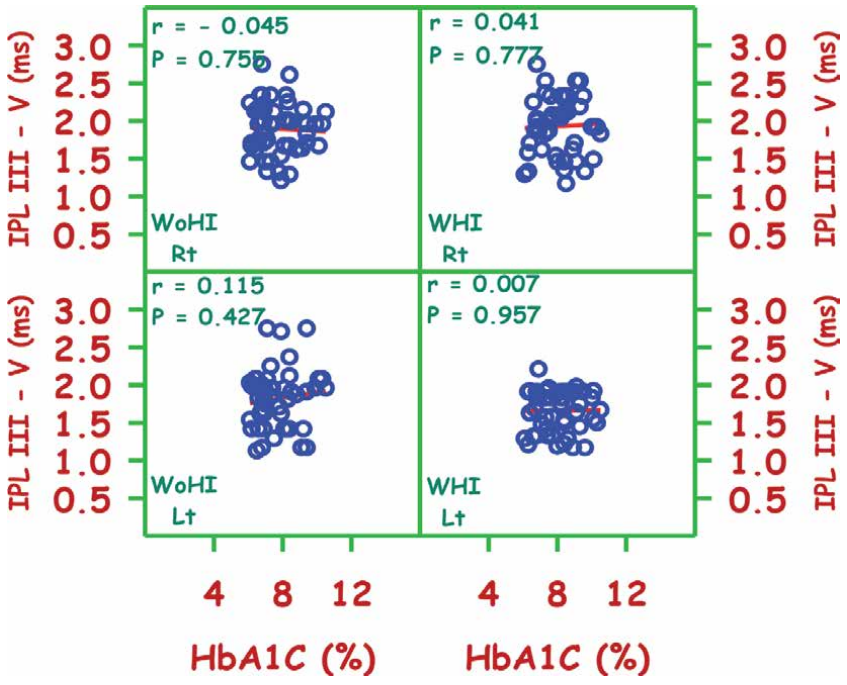

Figure 14.
Correlation of IPL III-V and HbA1c in type 2 diabetes, without (WoHI) and with (WHI) hearing impairment. The 'r' and P values are correlating WoHI and WHI right and left ear.

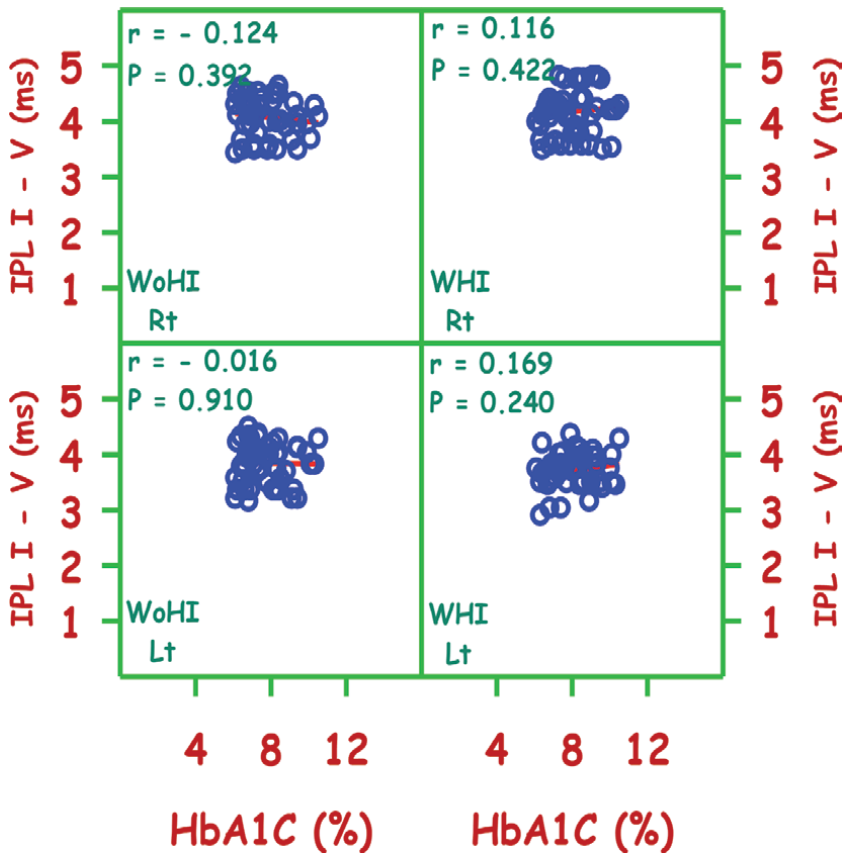

Figure 15.
Correlation of IPL I-V and HbA1c in type 2 diabetes, without (WoHI) and with (WHI) hearing impairment. The 'r' and P values are correlating WoHI and WHI right and left ear.

the right ear of WoHI (P = 0.758) and WHI (P = 0.128) group and left ear of WHI (P = 0.377) group showed negative correlation with BMI. In IPL III-V, the right ear (P = 0.284) of WoHI group and left ear (P = 0.543) of WHI group showed negative correlation with BMI. In IPL I-V, the right ear (P = 0.179) of WoHI group and left ear (P = 0.443) of WHI group shows negative correlation with BMI.

The correlation of IPL I-III, III-V and I-V values and HbA1c for both the ears in WoHI and WHI groups were given in **Figures 13–15**. In both the groups IPL I-III, III-V and I-V values were not statistically correlated with HbA1c. In IPL I-III, left ear of WoHI group shows negative correlation with HbA1c (P = 0.277). In IPL III-V, right ear of WoHI group shows negative correlation with HbA1c (P = 0.755). In IPL I-V, WoHI group right (P = 0.392) and left (P = 0.910) ears shows negative correlation with HbA1c.

5. Discussion

The BAER is a simple, non-invasive procedure to detect early impairment of auditory nerve and auditory pathway even in the absence of specific symptoms in the diabetic patients. The present study strongly recommended that BAER is carried out in all diabetic patients to detect the involvement of central neuronal pathway and periodic evaluation in of diabetes for early intervention regarding metabolic regulations.

The inter peak latencies of BAER tells about the time required for processing from one site to the next site in the auditory pathway [11]. In the present study, WHI group IPL I-III, III-V and I-V of both ears and left ear IPL III-V increased when compared to the normal subjects and WoHI group. These findings are in line with the previous research who found significant changes in the IPLs of the diabetics when compared to the controls [7, 12–16].

The prolongation of IPLs I-III, III-V and I-V are indicated central conduction delay at the level of brainstem and midbrain in the auditory pathway of diabetics. These prolongations are due to neuropathy at brainstem and midbrain level. These findings are supported by previous research [16]. In the present study, WHI group left ear IPL I-V values are decreased minimally when compared to WoHI group left ear IPL I-V values. Metformin (N, N-dimethylbiguanidine) is a widely used oral hypoglycaemic agent in T2DM; it has a potential anti-ototoxic activity. It prevents oxidative stress induced cell death and inhibition of lipid peroxidation and also scavenges hydroxyl radicals by modulating NADPH oxidase and inhibits apoptotic cascades by increasing the expression of the anti-apoptotic protein Bcl-2 [17]. This is the probable mechanism responsible for the reduced IPL values in the WHI group who are on metformin treatment.

The IPLs I-III, III-V and I-V of both the ears in WoHI and WHI groups were not correlated with the age, BMI and HbA1c values. The present study is contradicting with the previous research [18]. The HbA1c values are not correlated with the IPLs of both ears in WoHI and WHI groups. This finding is in line with the previous research [19–21] and contradicting with other studies [7]. In diabetes, hyperglycaemia results many pathological changes in nervous tissue by apoptosis, nerve energy deficits, intracellular calcium excitotoxicity, glycosylated products, oxidative stress, hypoxia and ischemia [22]. In the peripheral nervous system the myelin sheath and other nerve components are affected by hyperglycaemia [23].

In the present study, BMI and HbA1c values were correlated with the IPL I-III and I-V of both the ears in all subjects; it indicated that, with increase in BMI and HbA1c values the IPL values are increased in diabetic subjects. This finding is in line with the previous research where inter peak latencies were prolonged in uncontrolled T2DM subjects [24]. The inter peak latencies were prolonged in T2DM patients with duration of diabetes more than 7 years [24].

In diabetic neuropathy, hyperglycaemia accumulates diacylglycerol and activates PKC; this PKC causes transcription changes in the contractile proteins fibronectin, type IV collagen, and extracellular matrix (ECM) proteins in neurons and endothelial cells [25]. Due to this the affected neurons had degenerated axons, so that the amplitude of the neural conduction alters and the conduction velocity decreases in that affected nerves [26]. This is one of the reason to increase the inter peak latencies in the hearing impaired persons with T2DM in the present study. The present study is in line with the previous research with prolonged inter peak latencies in the T2DM patients [27, 28]. Another mechanism involved in the reduced neural transmission in T2DM with hyperglycaemia is oxidative stress with reactive oxygen species, these causes dendritic damage in the affected neurons with microglial activation [28–31] with prolongation of inter peak latencies.

Diabetes associated disruption between insulin activity and glucose metabolism results in decreased cerebral blood flow and oxidative glucose metabolism with impairment of neurotransmission. Diabetes has been widely associated with slowly progressive end-organ damage in brain resulting in diabetic neuropathy and/or mild to moderately impair cognitive function, both in type 1 and type 2 diabetic patients. The molecular mechanisms involved in the CNS damage in diabetes are hypothesized that AGEs formation, aldose reductase activity, oxidative stress, activation of protein kinase C and increased hexosamine pathway flux [32].

Chronic hyperglycaemia elicits pathophysiological changes to the nervous system as a result of oxidative stress, nerve energy deficits, decreased Na/K/ATPase activity and decreased neurotrophism. The damage to myelin sheaths and other nerve components as a result of hyperglycaemia occurs prominently in the peripheral nervous system but also in the spinal cord, cranial, optic and vestibular nerves. In the peripheral nervous system major myelin proteins are glycosylated, perhaps making them more prone to the effects of AGE, while in the CNS major myelin proteins are not glycosylated. The glial margin demarcates the boundary of the peripheral and central auditory systems, and is located about halfway between the cochlea and the cochlear nucleus [33]. These findings may explain why the peripheral auditory function was more affected than the central auditory nervous system in the present study. In diabetics, the IPLs I-III and I-V were positively correlated with autonomic score and large sensory nerve dysfunction. The abnormalities of waves III and V indicated an impairment of the auditory brainstem function in diabetic neuropathy [34].

The T2DM affects the cognitive function. The higher concentrations of neuron specific enolase (NSE) protein in long standing T2DM result permanent brain damage and was correlated with poor cognitive performance. Its concentration increased by oxidative stress and neuronal apoptosis and these changes reversed with insulin treatment [35]. In T2DM, the P300 event related potentials (ERPs) revealed early cognitive dysfunction which was not detected by neuro-psychometric test mini mental state examination (MMSE) and it was more prominent when the disease duration more than 5 years. When the T2DM is associated with hypertension, further increases the risk of cognitive impairment [36].

6. Conclusion

The present study explains about the inter peak latency changes of the brainstem auditory evoked potentials in T2DM. BAER was performed in normal subjects, WoHI and WHI groups for both the ears. Compared the inter peak latencies I-III, III-V and I-V between normal subjects, WoHI and WHI groups. Correlated age, BMI and HbA1c values with inter peak latencies in normal subjects, WoHI and WHI groups for both the ears. Age, BMI and HbA1c are not correlated with increase in inter peak latencies for both the ears in WHI group. The BMI and HbA1c values were correlated with IPL I-V of both the ears in all subjects.

We focused on functional changes but not anatomical changes. Because, functional changes can happen without any visible anatomical changes. For the assessment of structural changes we need CT or MRI brain which are highly cost, time consuming, radio-hazard and the subject may face inconvenience. However BAER can overcome all these circumstances. India is a country with large number of population with diabetes, insists the necessity to focus on long term hearing loss among them. BAER test is the very feasible method to perform at regular intervals for record. It could help to take necessary action to prevent hearing loss.

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Conflict of interest

The authors declare no conflict of interest.

Author details

Rajesh Paluru* and Devendra Singh Negi
Department of Physiology, MediCiti Institute of Medical Sciences,
Ghanpur, Telangana, India

*Address all correspondence to: drrajeshpaluru@gmail.com

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Section 4

Teamwork Approach to Hearing Aids Innovations

Chapter 8

Variation of Sensitivity of a MEMS Capacitive Accelerometer Based Microphone with Suspension System Topology

Apoorva Dwivedi, Prateek Asthana, Gargi Khanna and Tarun Chaudhary

Abstract

The present research seeks to improve a highly sensitive MEMS capacitive accelerometer as a probable completely implantable hearing aid microphone. The research analyses the effect of different suspension system topologies on accelerometer efficiency. The topology of folded beam suspension is considered to be the most suitable for the proposed system. The design factors such as weight, height and resonant frequency are considered to make the accelerometer an effective biomedical system which can be completely implanted with COMSOL MULTIPHYSICS 4.2 the optimized system is simulated and validated. The accelerometer occupies 1mm^2 of sensing area and achieves a nominal capacitance of 5.30 pF and an optimized capacitive sensitivity of 6.89fF.

Keywords: Microelectromechanical system (MEMS), totally implantable hearing aid (TIHA), capacitive accelerometer, mechanical amplification, microlever, sound pressure level (SPL)

1. Introduction

The universe is perceived by means of the five senses. By conjunction these five senses determine the nature of our world experience. If some meaning is lacking it removes a whole aspect of life. Similarly, the quality of life experience for people with hearing loss is significantly diminished. An individual with a completely functioning sense of hearing can hardly understand the suffering of those living with the hearing impairment. WHO reports that 15 percent of the world's adults, or approximately 766 million people, are experiencing the substantial loss of audience [1]. In India this figure is alarmingly more than 63 million, according to Varshney [2]. In most cases of hearing loss, traditional hearing aids may offer effective rehabilitation, but the societal stigma linked with wearing external hearing aids prohibits several patients from even talking about such devices. Consequently, semi-implantable middle ear and cochlear prosthetic devices are increasingly approved. Over the years, curiosity in middle ear implants has grown significantly to facilitate patients with traditional hearing aids who do not get sufficient assistance [3].

Electromagnetics-based middle ear implants [4, 5] and Piezoelectric [6, 7] have been developed for hearing loss gain. Such techniques, however, do not offer protection from damage to cochlear hair cells in hearing loss. While current cochlear implants that are partially implantable treat injured hair cells in the cochlea through direct stimulation of the auditory nerve, they remain dependent on external microphone, speech processor, and radiofrequency (RF) coils [8]. The ever-present need for invisibility has fuelled the creation of a completely implantable hearing aid to free the patient from the extreme loss of hearing without any social stigma.

Although current partially implantable cochlear implants are being increaasingly used, their usage of an external microphone, speech processor and radio frequency (RF) coils has still not addressed the issue of social stigma and embarrassment. The need to provide the users freedom from the psychological discomfort, physical inconvenience and offer improved performance has accelerated the exploration and growth of fully implantable hearing aids (FIHAs). The FIHAs, with all the elements implanted internally and using the natural sound conduction of the body, eliminate many of the issues like sound filtering, improved sound amplification, problem of feedback, ringing issues and social prejudice faced in conventional hearing aids.

The MEMS capacitive accelerometer described in the paper is designed to be placed on umbo to act as a middle ear microphone as shown in **Figure 1**. Optimizing the geometry of the device has already increased the performance of the accelerometer [9–12]. This article studies the effect of various suspension system (spring) topologies on the sensitivity of the accelerometer and then proposes the most suitable suspension system for enhanced performance. The optimized model satisfies the requisite design requirements regarding the fully implantable microphone's surgical placement.

The article consists of 5 parts. The first segment discusses the implementation of hearing aids based on MEMS which are entirely implantable. The second segment describes the development of hearing aids which are entirely implantable. The third

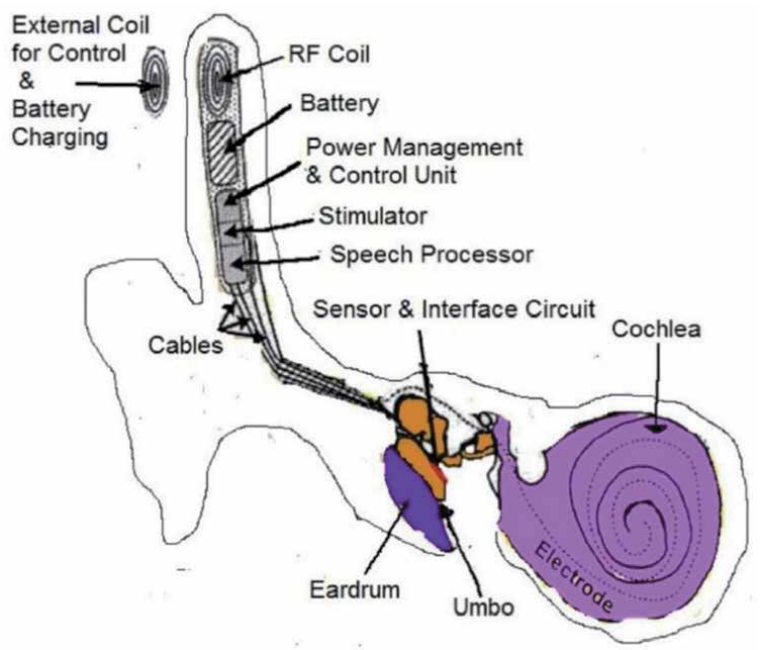

Figure 1.
Proposed fully implantable microphone in middle ear.

section addresses the sensor's operating theory and assessing the stiffness constant as a suspension mechanism for various springs. The fourth section explains the outcomes of the modelling and simulation followed by a conclusion in Section 5.

2. Development of totally implantable hearing aids

Various forms of TIHAs have been documented in the literature, such as Totally Implantable Communication Assistance (TICA) [13], Totally Implantable Cochlear Implant (TICI/TIKI) [14], Carina [15, 16], and Esteem [15–17]. Carina and TIKI, implanted in the temporal bone under the skin, experience severe body noise amplification during mastication, sound attenuation and head contact distortion due to the skin's sound-filtering effect. TICA and Esteem, when implanted in the ear canal or ossicular chain, solved those issues. Yet they are susceptible to the feedback problem between the embedded microphone and the sound source. The literature recorded MEMS capacitive sensor based microphones [18–20]. They are put straight on the umbo. Regrettably, this approach can induce a significant damping effect on the frequency response of the ossicular middle ear chain at frequencies above 1 kHz due to the loading of sensor weight on the umbo [18–20]. Yip et al. [21] have suggested a piezoelectric sensor as a microphone of the FIHA. The umbo is placed at one end of the microphone, and the middle- wall is connected at the other end. The microphone, however, suffers from the problem of feedback, because it resembles Esteem. Woo et al. [22] introduces a trans- microphone. It consists of a ventilation tube mounted in the eardrum along with a connected acoustic duct with an electret microphone at the end extending into the middle-ear cavity. The method presented potential benefits, such as comparatively quick surgery, exceptional sound collection and protection from any outside impact. The possible disadvantages, however, contain the tube dropping into the ear canal or middle ear cavity, the fluid entering the tube, and the sensitivity loss, and the cerumen covering the microphone, and inhibiting sound collection. Koch et al. [23] presents a piezoelectric transducer which is implanted into the incudostapedial joint gap. While it provides advantages such as relatively easy installation and revocable surgery, the transducer suffers from low frequency (<1 KHz) output degradation.

From the literature review it was observed that the system proposed by Young et al. [20] using the capacitive sensing scheme used provides many advantages over the other types: fairly simple mechanical structure compared to other types; henceforth easy manufacturing, excellent linearity, good noise efficiency, a reduced amount of power consumption and very small temperature-induced drift. Together with the mechanical elements, the capacitance sensing signal conditioning circuit can also be monolithically mounted on the same substratum. The only downside of Young et al.'s proposed model is the mass loading effect.

The present paper proposes changes to Young's approach by using different topologies of the suspension system taking into account their effect on device sensitivity. The impact of loading can be evaded by maintaining the sensor's total packed mass below 20 mg. In addition, the overall prototype microsystem will show a packed dimension of less than 3.5 mm for implantation on the umbo without impacting other structures inside the middle ear cavity. The tip of the umbo usually has a scale between 1.5 mm and 2 mm. The accelerometer is therefore built within a compact 1 mm/1 mm band. Absolute umbo acceleration along the primary axis is around 1 g [18–20]. As per audiologists, the loudness of regular human communication is about 60 dB SPL (sound pressure level), and the typical voice speech is in the frequency range from 500 Hz to 8000 Hz. The accelerometer is worked within the normal range of speech conversation frequency, in which the response is flat.

Consequently, the accelerometer's resonant frequency is chosen to be higher than the standard frequency range for human conversation. Yet the resonant frequency can not be too high; then the displacement of the confirmed mass decreases. The accelerometer was therefore designed to set the resonant frequency at about 10,000 Hz.

3. Working principle of the device

3.1 Structural design

The comb drive capacitive accelerometer used in this work includes four folded beams as a suspension device and a handheld finger seismic mass as shown in **Figure 2**. A comb drive structure consists of a set of pairs of capacitive fingers instead of one capacitive plate. Another set is fixed, and the other set remains movable. Further the two anchors are set also. The four folded beams bind each of the anchors to the movable central seismic mass. Let's say; x1 is the distances between the set finger and the movable finger on the left and x2 on the right.

On the umbo is set the capacitive accelerometer. The eardrum vibrates in response to incoming sound causing the umbo to vibrate along with it. The pressure coming in exerts a force on the sensor. The seismic mass with the moving fingers shifts in the direction of body force under the impact of this force, which changes the power between the moving and the fixed finger. The capacitance shift is calculated using a low noise electronic interface circuitry.

The input umbo acceleration a, causes a body force F_{ext} to act on the accelerometer with effective mass M_e.

$$F_{ext} = M_e a \tag{1}$$

The acceleration applied displaces the seismic mass by a distance of Δx from its mean spot. The force needed to displace the seismic mass is given.

$$F_{spring} = k_e \Delta x \tag{2}$$

where k_e is the effective spring constant. In the equilibrium condition when $F_{ext} = F_{spring}$, we get.

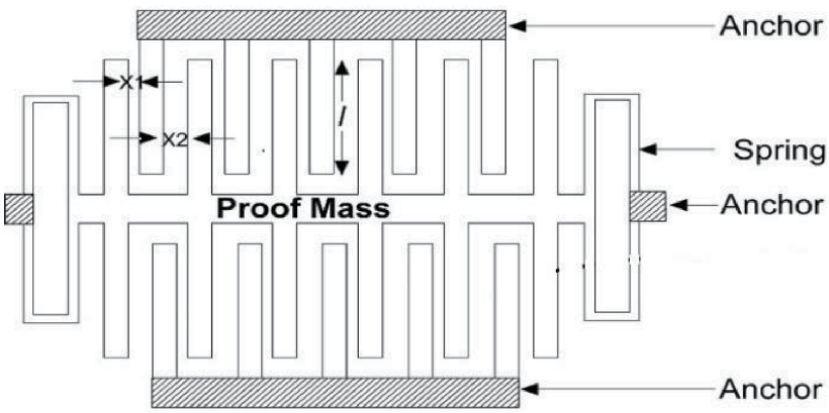

Figure 2.
Prototype of the capacitive accelerometer.

$$\frac{\Delta x}{a} = \frac{M_e}{k_e} \tag{3}$$

That also reflects the sensitivity of the unit to mechanical/displacement. The Eq. (3) shows that the device's displacement sensitivity has a direct relation to the seismic mass and an inverse relationship to the accelerometer's stiffness constant. Hence, the device's displacement sensitivity can be amplified by increasing the seismic mass and reducing the system's stiffness constant. The displacement sensitivity is inversely proportional to the square of the resonant angular frequency.

$$\frac{\Delta x}{a} = \frac{1}{\omega_0^2} = \frac{M_e}{k_e} \tag{4}$$

$$\omega_0 = \sqrt{\frac{k_e}{M_e}} \tag{5}$$

where ω_0 is the resonant angular frequency.

The resonant frequency of the sensor is given as $f_0 = \frac{1}{2\pi}\sqrt{\frac{k_e}{M_e}}$.

The values of mass and stiffness constant are determined to keep the resonant frequency at 10000 Hz.

3.2 Stiffness constant evaluation

The seismic mass can be suspended using various topology suspension systems (springs) based on 1) geometry: standard folded and round folded; 2) beam orientation: standard folded and inverted folded, and 3) series combination of springs. Each of these different types of suspension systems produces a specific accelerometer geometry which affects the sensitivity of the device.

3.2.1 Folded beam

Figure 3 indicates a folded beam-structure. The structure of the folded beam was resolved into three constituents organized in a row.

The accelerometer is composed of four folded beams as springs. The stiffness constant ($k_{1/4}$) of one such folded beam is given in Eq. (6) as.

$$\frac{1}{k_{1/4}} = \frac{1}{k_{c1}} + \frac{1}{k_{c2}} + \frac{1}{k_{c3}} \tag{6}$$

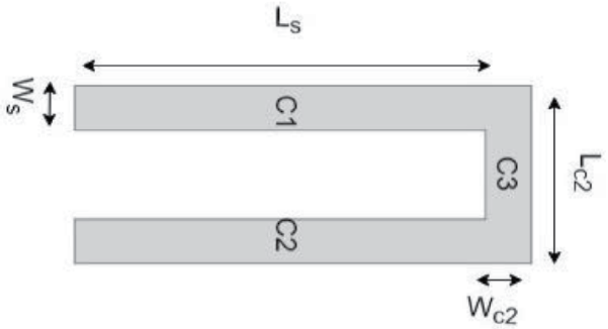

Figure 3.
A folded beam structure.

where k_{c1}, k_{c2}, and k_{c3} are the stiffness constants [23] for the constituent 1 (C1), constituent 2 (C2) and constituent 3 (C3) respectively given as.

$$\frac{1}{k_{c1}} = \frac{{L_s}^3}{12EI_s} + \frac{6(1+\mu)L_s}{5W_s} \tag{7}$$

As C1 and C2 constituents are of same dimensions, the stiffness constant of both these components are equal as given below.

$$\frac{1}{k_{c3}} = \frac{1}{k_{c1}} \tag{8}$$

$$\frac{1}{k_{c2}} = \frac{L_{c2}}{EA_{c2}} - \frac{L_s L_{c2}^2}{4EI_{c2}} \tag{9}$$

where E is the modulus of elasticity of the material, L_s is the length of the spring beam, L_{c2} is the length of the transverse bar, W_{c2} is the width of the bar, W_s is the width of the spring beam, $I = \frac{t{W_s}^3}{12}$ is the moment of inertia of component 1, $I_{c2} = \frac{t{W_{c2}}^3}{12}$ is the moment of inertia of component 2, $A_{c2} = tW_{c2}$ is the area of cross-section of component 2. W_{c2} is the same as W_s.

As the four springs have the same geometry and are made of same material, the effective stiffness constant k_e [24] is evaluated by Eqs. (10) and (11) as.

$$\frac{1}{k_e} = \frac{1}{4k_{1/4}} \tag{10}$$

$$\frac{1}{k_e} = \frac{1}{Et}\left(\frac{{L_s}^3}{2{W_s}^3} + \frac{3(1+\mu)}{5W_s} + \frac{L_{c2}}{4W_{c2}} - \frac{3L_s {L^2}_{c2}}{4W_{c2}^3}\right) \tag{11}$$

3.2.2 Inverted folded beam

The inverted folded beam, as seen in **Figure 4**, differs from folded beam only in terms of suspension orientation. The constant of stiffness is measured the same way as for the regular folded beam. In this case, it will require two supplementary support constituents identical to component 2 to connect the beam to the seismic mass and anchor. Adding both of these constituents gives us the constant stiffness as.

$$\frac{1}{k_e} = \frac{1}{Et}\left(\frac{{L_s}^3}{2{W_s}^3} + \frac{3(1+\mu)}{5W_s} + \frac{3L_{c2}}{4W_{c2}} - \frac{9L_s {L^2}_{c2}}{4W_{c2}^3}\right) \tag{12}$$

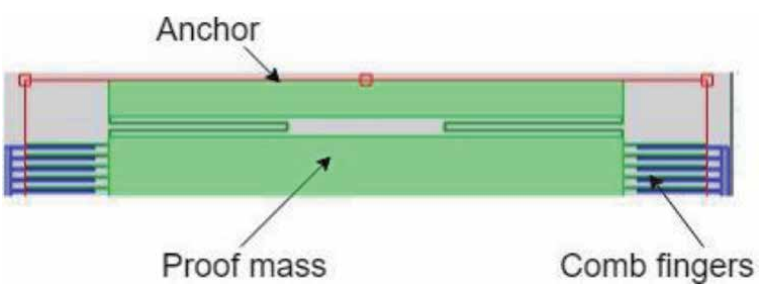

Figure 4.
An inverted folded beam as a suspension system in an accelerometer.

3.2.3 Round folded beam

A circular folded beam is made of round edges rather than rectangular edges as seen in **Figure 5**. For constituent 1 and constituent 3 the stiffness constants are identical to the regular folded beam.

The stiffness constant for the constituent 2 is evaluated by [25] as.

$$\frac{1}{k_{c2}} = \frac{24r^3}{{W_s}^3}\left(\frac{\pi}{16} - \frac{1}{\pi} + \frac{1}{24\pi}\right) + \frac{3\pi L_s^2 r}{4W_s^3} \tag{13}$$

The total stiffness constant is thus obtained by Eq. (14).

$$\frac{1}{k_e} = \frac{1}{Et}\left(\frac{{L_s}^3}{2{W_s}^3} + \frac{3(1+\mu)}{5W_s} + \frac{24r^3}{{W_s}^3}\left(\frac{\pi}{16} - \frac{1}{\pi} + \frac{1}{24\pi}\right) + \frac{3\pi L_s^2 r}{4W_s^3}\right) \tag{14}$$

3.2.4 Series combination of springs

From Eq. (4) it is detected that the displacement of the seismic mass increases with decreasing stiffness. Thus, a sequence of combinations of springs may be used to improve evidence mass displacement. Since the area of the proposed system is limited, however, the addition of a series of combinations of springs leads to a reduction in the width of the seismic mass resulting in a decrease in the seismic mass and thus a decrease in the displacement as shown in **Table 1**. Therefore a compromise is needed when choosing the combination of the pair. Some of the combinations from the sequence are shown in **Figure 6**.

The stiffness constants and seismic mass width for different arrangements of springs are given by **Table 1**. W_{pm} denotes the width of the seismic mass, W_a is the

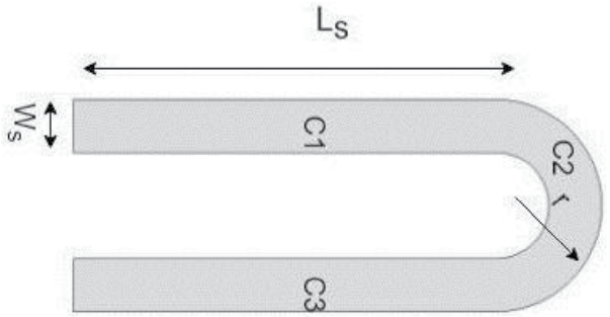

Figure 5.
A round folded beam structure.

Number of springs in series	The width of the proof mass (m)	Stiffness constant
1	$W_{pm} = 1000 \times 10^{-6} - 2(W_a + 2W_s + D_b)$	k_e
2	$W_{pm} = 1000 \times 10^{-6} - 4(W_a + 2W_s + D_b) - 2D_b$	$k_e/2$
3	$W_{pm} = 1000 \times 10^{-6} - 6(W_a + 2W_s + D_b) - 4D_b$	$k_e/3$
4	$W_{pm} = 1000 \times 10^{-6} - 8(W_a + 2W_s + D_b) - 6D_b$	$k_e/4$
5	$W_{pm} = 1000 \times 10^{-6} - 10(W_a + 2W_s + D_b) - 8D_b$	$k_e/5$

Table 1.
Proof mass widths and stiffness constants for a different combination of springs.

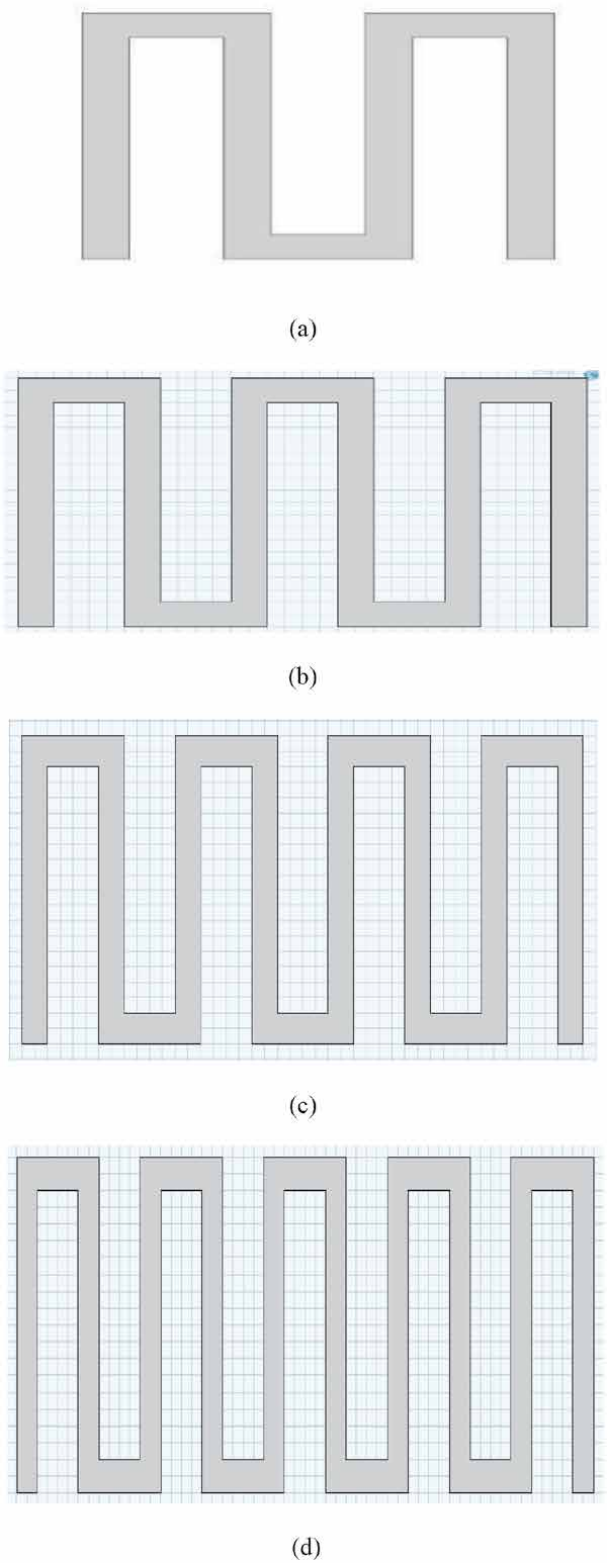

Figure 6.
Different series combination of springs (a) two springs, (b) three springs, (c) four springs and (d) five springs in series respectively.

width of the anchor, W_s is the width of the spring beam, and D_b is the gap spacing within the spring beam.

The effective mass of the folded suspension beam has been calculated by using the Rayleigh principle [24] as shown in Eqs. (15)-(17).

Effective mass due to the beam is.

$$M_{b,e} = \frac{13\rho W_s t L_s}{35} \tag{15}$$

Effective mass due to the transverse bar is.

$$M_{t,e} = \frac{1}{3}\rho W_{c2} t L_{c2} \tag{16}$$

The accelerometer's effective mass consists mainly of the evidence mass and smaller spring beam contributions. Consider the folded beam segment shown in **Figure 4**. Therefore the total effective accelerometer mass is.

$$M_e = 8M_{b,e} + 4M_{t,e} + M_{pm} \tag{17}$$

Four folded beams exist, with each beam having two lateral parts. Consequently, the whole of eight sections add to the effective mass represented in Eq. (17) by the first term. Each folded beam has a transverse section. So, as seen in the second term in Eq. (17), the mass due to the transverse section is multiplied by four times. The seismic mass contains the mass on either side of the seismic mass due to the rectangular disk, and the mass due to the comb fingers. The test of proof is.

$$M_{pm} = t\rho\left(L_{pm}W_{pm} + 2N_f L_f W_f\right) \tag{18}$$

where L_f is the length of the finger, L_{pm} is the length of the seismic mass, and W_{pm} is the width of the seismic mass. The number of sensing fingers N_f on each side of the seismic mass is restricted by the width of the central seismic mass. Depending on the various constraints, they can be calculated as.

$$N_f = \left(W_{pm} - 2p_f\right)/\left(2W_f + x_1 + x_2\right) \tag{19}$$

The seismic mass for other spring combinations can be determined along similar lines.

3.3 Capacitance evaluation

The sum of the capacitance from each side depends on the finger width W_f, finger overlap length L_{f0}, dielectric constant K, relative permittivity $\epsilon_{0,}$ device layer thickness t, the number of sensing fingers N_f and the air gap between adjacent fingers. It can be expressed by.

$$C_{t0} = \left(C_0 + C_{pm}\right) \tag{20}$$

where C_0 is the capacitance between the fixed and movable fingers as depicted by Eq. (21) and C_{pm} is the capacitance between the movable fingers and the seismic mass body as shown by Eq. (22) in **Figure 7**.

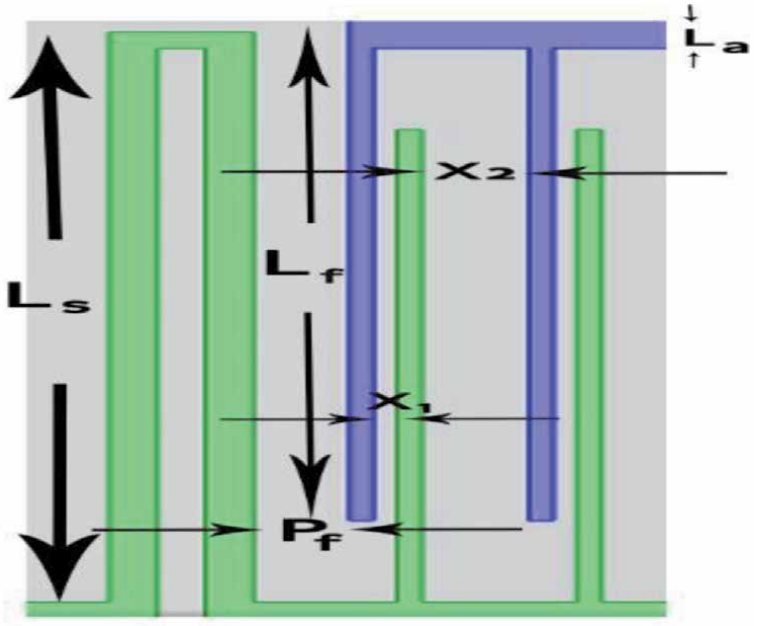

Figure 7.
Different dimensions used in capacitance formulation.

$$C_0 = \left(\frac{K\varepsilon_0 L_{f0} t}{x_1} + \frac{K\varepsilon_0 L_{f0} t}{x_2}\right) \times 2N_f \tag{21}$$

$$C_{pm} = \frac{\varepsilon_0 t W_f (2N_f + 1)}{L_f - L_{f0}} \tag{22}$$

The variation in sensing capacitance value under displacement Δx of the seismic mass is given by.

$$\Delta C = \left(\frac{K\varepsilon_0 L_{f0} t}{x_1}\frac{\Delta x}{x_1} - \frac{K\varepsilon_0 L_{f0} t}{x_2}\frac{\Delta x}{x_2}\right) \times 2N_f \tag{23}$$

Capacitive Sensitivity is given as change in capacitance with respect to applied acceleration $\Delta C/a$ (fF/g).

4. Results and discussions

The device's capacitive sensitivity depends on various geometrical parameters which conflict with each other. Simultaneous optimisation of all design parameters is essential for a highly sensitive device. An optimal problem with the accelerometer-based hearing aid that optimizes both of these variables was formulated mathematically, and simulative analysis was performed using COMSOL. As stated in the authors 'previous work [9], the various geometry parameters have been optimised. The system parameters also need to meet the constraints that need to be taken into account when designing the middle ear implantable microphone. The design constraints are:

- The average sensor length must be within 1 mm.

- The average sensor width must be in 1 mm.
- Sensor resonant frequency shall be 10,000 Hz.
- The sensor must have a total mass of less than 20 mg.

The optimized parameters of the geometry, as shown in **Table 2** [9]. The number of sensing fingers is found to be 174 on each side of the central seismic mass. The spring measurements and the seismic mass are calculated to hold the resonant frequency at about 10,000 Hz. Silicon density is 2330Kg/m3, and its elasticity modulus is 131Gpa. Silicon practically does not exhibit mechanical hysteresis. It therefore constitutes an ideal candidate material for sensors and actuators. Microsystems built and manufactured with silicon provide greater versatility than with other substrate materials. In the proposed research work the entire microsystem consisting of accelerometer and electronics interface circuitry needs to be housed in a biocompatible packaging. Recent advancements show that with minor surface modifications using laser nano texturing could increase the biocompatibility of silicon. Also, silicon compounds like silicon carbide is a promising biocompatible material. The Air is selected as dielectric medium as it offers negligible damping. The aspect ratio which is used is 12.5. Aspect ratio is the structure thickness ratio, and the finger spacing distance. Energy harvesting methodologies may be utilised to provide the power requirements for the proposed device [26–29].

4.1 Sensitivity variation with different spring topologies

Study of the device's output was carried out with different topologies for the spring. Parameters such as the resonant frequency, displacement sensitivity, capacitive sensitivity, seismic mass, and stiffness constants for the same spring beam length of 72 μm are evaluated in **Table 3**. If the number of springs in series rises, the device's displacement and capacitive sensitivity rise as a result of a steady drop in stiffness. The seismic mass and resonant frequency are finding a decrease though. The resonant frequency for our microphone needs to be outside of the usual 8000 Hz hearing range. Although the sensitivity of the device is improved, the combinations of more than one spring can not be approved for the proposed application.

Another alternative is to keep identical resonant frequencies for different combinations as shown in **Table 4**.

Geometry Parameter	Value (μm)
Length of sense finger	100
The width of sense finger	1
Gap spacing (x_1, x_2)	1, 2
The thickness of the device	12.5
Length of spring beam	72
Length of the proof mass	740
The width of the proof mass	884
Width of spring	2

Table 2.
Optimized accelerometer dimensions for the proposed device.

No of springs in combination	Resonant frequency (Hz)	Displacement Sensitivity (nm/g)	Capacitive Sensitivity (fF/g)	Proof mass (ng)	Stiffness constant (Nm/s)
1	10016	2.4771	6.4631	20.079	79.519
2	7606.5	4.2947	11.236	17.406	39.76
3	6750	5.453	14.292	14.734	26.506
4	6461.4	7.1856	15.611	12.061	19.88
5	6550.3	5.7914	15.186	9.3889	15.904

Table 3.
The parameters associated with the different series combination of springs for a similar length.

No of turns in spring	Resonant frequency	Displacement Sensitivity (nm/g)	Capacitive Sensitivity (fF/g)	Proof mass (ng)	Length of spring (μm)	Spring Constant
1	10016	2.4771	6.4631	20.079	72	79.519
2	10019	2.4753	6.4581	17.404	60	68.967
3	10033	2.4688	6.4408	14.731	56	58.536
4	10030	2.4699	6.4437	12.058	54	47.894
5	10021	2.4746	6.456	9.386	55	37.209

Table 4.
The parameters associated with the different series combination of springs for similar resonant frequency.

The orientation of the spring beam	Resonant frequency (Hz)	Displacement (nm/g)	Capacitive Sensitivity (fF/g)	Length of the beam (μm)	Proof mass (ng)	Spring constant (Nm/s)
Folded beam	10016	2.4771	6.4631	72	20.079	79.519
Inverted folded beam	10224	2.377	6.2011	72	20.079	82.867

Table 5.
Comparison of performance of the device with standard folded and inverted folded beam.

It is observed that the displacement and capacitive response are almost identical for different combinations. The length of spring beam needs to be changed to keep the resonant frequencies identical for different combinations. A decline in the seismic mass is noticed with increased number of springs in the arrangement. However, as shown in **Table 4**, no significant change in sensitivity is obtained and the arrangement is of no useful consequence. **Table 5** provides a comparison of regular folded beam sensitivities with inverted folded beam. The regular folded beam provides greater flexibility for the same length of the spring beam (72 μm) than the inverted folded beam.

The output for the spring beam length (72 μm) of folded beam and round folded beam is compared in **Table 6**. The round folded beam has an impressive sensitivity of 8.29 fF/g, an improvement over the regular folded beam. Nonetheless, this substantial improvement comes at the expense of the reduced 8849 Hz resonant frequency (very close to the standard 8000 Hz hearing range). The topology is therefore not suitable for the proposed study.

In **Table 7**, the output of round folded beam was also assessed for similar resonant frequency of 10019 Hz. The strength in this situation is significantly less

Geometry of folded beam	Resonant frequency (Hz)	Displacement Sensitivity (nm/g)	Capacitive Sensitivity (fF/g)	Length of beam (μm)	Proof mass (ng)	Spring constant (Nm/s)
Standard folded beam	10016	2.4771	6.4631	72	20.079	79.519
Round folded beam	8848	3.1736	8.2893	72	20.079	62.066

Table 6.
Comparison of performance of standard folded beam and round folded beam for the same length.

The geometry of the spring beam	Resonant frequency (Hz)	Displacement Sensitivity (nm/g)	Capacitive Sensitivity (fF/g)	Length of the beam (μm)	Proof mass (ng)	Spring constant (Nm/s)
Standard folded beam	10016	2.4771	6.4631	72	20.079	79.519
Round folded beam	10019	2.4756	6.4589	66	20.078	79.564

Table 7.
Comparison of performance of standard folded beam and round folded beam for same resonant frequency.

than the folded beam's. Therefore the option of round folded beam provides no major benefit over the folded beam.

The parameters relating to the configuration of the accelerometer are shown in **Table 8**. The table contrasts the outcomes of the experiment and of simulation. The percentage difference between the analytical and simulation results is less than 10 percent, as is evident from the table. Therefore the findings of the modeling and simulation show strong agreement.

Figure 8 provides the simulation environment for the proposed accelerometer. The First Resonant Frequency is at 10,209 Hz as shown in **Figure 9**. The average stress caused at 100 dB SPL and 10,000 Hz is 0.25 GPa, as shown in **Figure 10**. The average stress is slightly lower than silicon yield power (7 GPa). The yield strength of a material represents the highest stress that can produce without causing plastic deformation in a material. A material exhibits a defined permanent deformation at the stress. Yield strength is very critical in engineering structural design, as it must withstand the force sustained during use when constructing a part, and the part must not permanently deform. Hence the yield strength in any structure must sufficiently exceed the maximum stress produced. The yield strength of silicon (7GPa) in the proposed model is considerably higher than the average stress developed in the structure. COMSOL MULTIPHYSICS simulates the concept with optimized parameters, and validates the effects of the simulations and simulation.

Parameter	Analytical Value	Simulation Value	Error (%)
Resonant Frequency (Hz)	10018	10209	1.87
Nominal Capacitance (pF)	5.17	5.30	2.45
Displacment Sensitivity (nm/g)	2.47	2.65	6.79
Capacitive Sensitivity (fF/g)	6.41	6.89	6.97

Table 8.
Comparison of the analytical and simulation results.

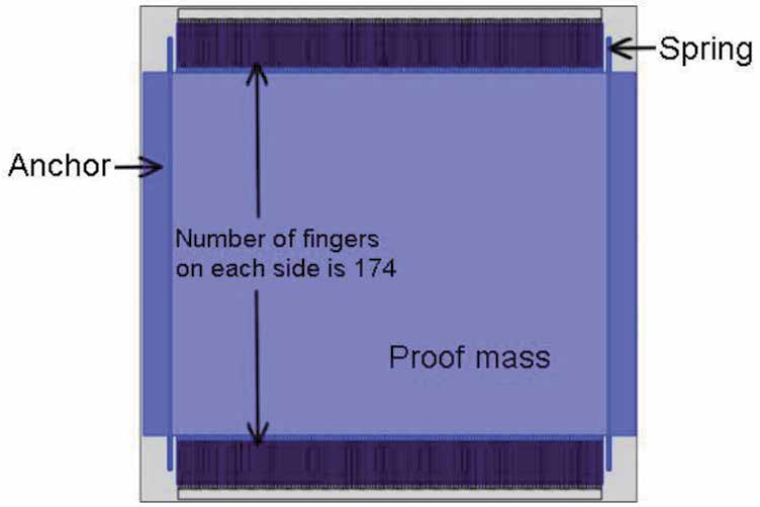

Figure 8.
The simulation setup in COMSOL MULTIPHYSICS.

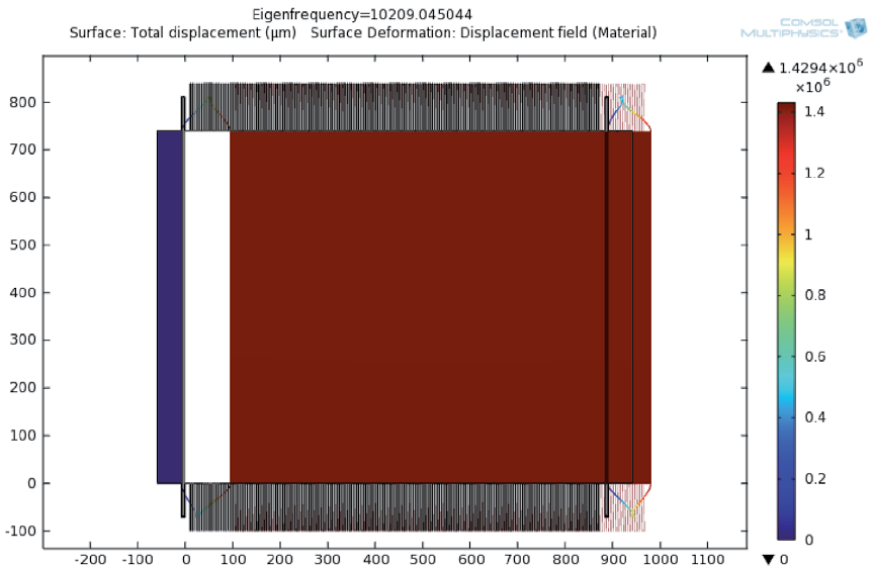

Figure 9.
The first resonant mode of the optimized model.

The proposed accelerometer is compared to previous MEMS capacitive sensors developed by Young et al. [20]. The new design shows an increase in capacitive sensitivity of 27.43 per cent over Young's research as shown in **Table 9**.

Figure 11 shows the proposed accelerometer frequency response conforming to input umbo accelerations of 0.1 g, 0.5 g, and 1.0 g. The device's frequency response is almost flat from 500 Hz to 8000 Hz (the standard conversation range) with a peak at around 10,000 Hz that reflects the accelerometer's first resonant frequency (10,000 Hz). The flat frequency response shall indicate the accelerometer's operating range.

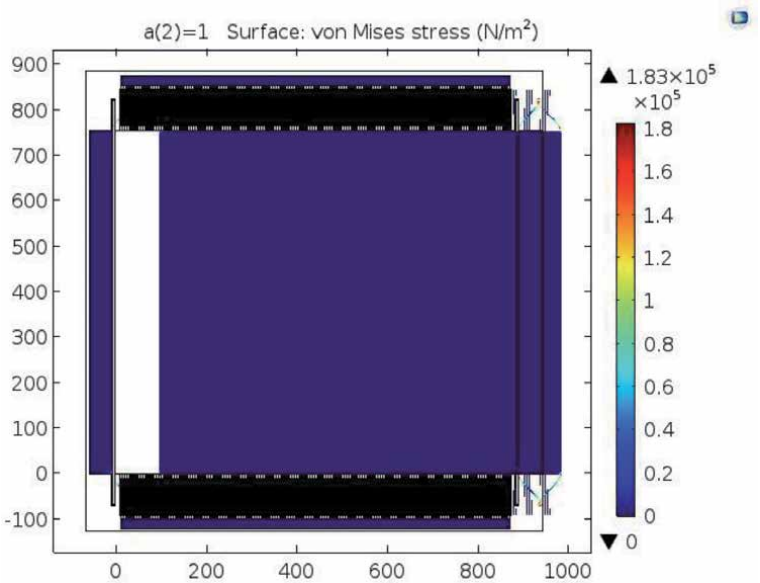

Figure 10.
Maximum stress induced in the optimized model.

Parameter	Proposed Model	Young et al. [20]	Improvement (%)
Resonant Frequency (Hz)	10209	10000	2.04
Nominal Capacitance (pF)	5.30	2.40	54.7
Displacment Sensitivity (nm/g)	2.65	2.50	5.66
Capacitive Sensitivity (fF/g)	6.89	5.00	27.43

Table 9.
Comparison of proposed model with the model of Young et al.

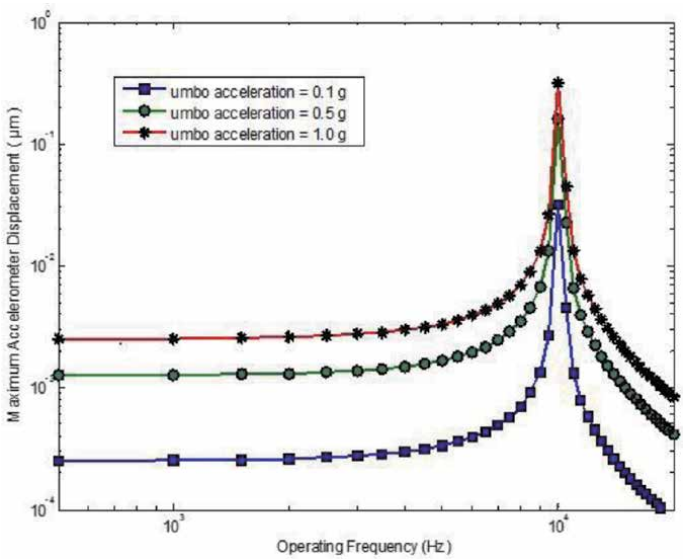

Figure 11.
The frequency response of the optimized model.

5. Conclusion

The research paper proposes an improved MEMS capacitive accelerometer to be used as a microphone for the completely implantable hearing. The effect of different types of suspension systems on accelerometer performance is being studied, and the folded beam spring topology is considered to be the most suitable for the proposed application. The analytical model was developed and validated with simulation results from COMSOL MULTIPHYSICS. The accelerometer occupies a small sensing region of $1mm^2$, an overall packed weight of less than 20 mg and a resonant frequency of almost 10,000 Hz. The accelerometer is designed so it can be inserted surgically and functions well within the standard conversational range of speech. Optimized efficiency of 5.30 pF, displacement sensitivity of 2.65 nm/ g and capacitive sensitivity of 6.89fF/g is achieved with an improvement in sensitivity of 27.43 per cent. The proposed design can therefore be suggested for possible application in totally implantable hearing devices.

Author details

Apoorva Dwivedi[1*], Prateek Asthana[2], Gargi Khanna[1] and Tarun Chaudhary[3]

1 Electronics and Communication Engineering Department, NIT Hamirpur, Hamirpur, Himachal Pradesh, India

2 Bharat Institute of Engineering and Technology, Hyderabad, India

3 Electronics and Communicaion Engineering Department, NIT Jalandhar, Jalandhar, Punjab, India

*Address all correspondence to: apoorva.dwivedi07@gmail.com

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Chapter 9

Cost-Effective Design of Amplifiers for Hearing Aides Using Nullors for Response Matching

Reza Hashemian

Abstract

This chapter starts reviewing Fixator-Norator Pairs (FNP) as an effective tool used to design analog amplifiers for a prescribed bandwidth and frequency profile. Among number of cases and applications, designing for hearing aides are particularly important, where the hearing frequency profiles, known as audiograms, are changing from person to person, and also for a person by the age. The design is mainly focused on front-end or stand-alone amplifiers. In case of a front-end the response from the amplifier can be digitized, properly controlled and adjusted to fit the digital application. Here is how the design proceed. For a given audiogram, an Audiogram Generator Circuit (AGC) is initially constructed. This AGC, usually a complete passive circuit, produces a frequency response that closely matches with the audiogram, obtained from a hearing impaired patient. The AGC is then embedded in an amplifier circuit where a fixator is placed at its output port, "forcing" the amplifier to generate the desired output frequency response profile. A flat band frequency response, for example, compensates the hearing losses and provides a uniform hearing to the patient in the entire audio bandwidth. The amplifier can be further enhanced to perform other requirements, for example, to cancel undesirable noises in certain frequencies or to magnify the voice in critical frequencies for clarity. Another alternative design methodology is also introduced in this chapter, which uses the negative feedback technique.

Keywords: Analog circuit design, audio amplifiers, feedback theory, fixator-norator pairs, frequency profiles, hearing aids, nullors

1. Introduction

Hearing aid market is definitely dominated by fully digital hearing aids. With many recent advancements in the industry the prices are also keep rising and getting almost unaffordable for some hearing- impaired patients. This chapter provides a simple and very cost effective method for the design and implementation of stand-alone analog amplifiers or pre-amplifiers for digital hearing aids. Although somewhat behind in the technology and the market, analog hearing aids can still provide some advantages in some aspects over the digital technology.

The chapter is the extended version of [1], and the objective here is to design amplifiers that exhibit frequency responses that can vary and match with any specific frequency profile in demand. In this chapter, we are considering amplifiers that are applicable to hearing aid designs. There are several main criteria associated with this design as:

- The design needs to be simple and highly modular. By this modularity, we mean to separate the active device, as an engine, from the rest of the circuit, as the controllers.
- To be easily adaptable to variations, either for different hearing-impaired patients or the natural changes happening in the hearing situation of an individual over time.
- Low cost and affordable with high quality.

2. Fixator Norator pairs and their properties in design for frequency profiles

Fixator-Noratpr Pairs and their properties in analog circuit designs are covered in [2]. A fixator, denoted by $Fx(V_j, I_j)$ or $Fx(I_j, V_j)$, symbolically shown in **Figure 1**, is a two terminal component with both its current I_j and voltage V_j specified. A nullator, denoted by $Fx(0, 0)$, is a special case of a fixator where V_j and I_j are both zero. So by definition, a fixator can be assigned to a design constraint to keep it unchanged during the design process. Then a paring norator, with its V and I unspecified, can provide the conditions in the circuit to allow the fixator to hold onto the values. Hence, a fixator and its paring norator work together to satisfy the Kirchhoff Laws [3], and they must be mutually sensitive to each other. It is important to note that, because a fixator needs to keep its variables (I and V) as designated, its pairing norator must be ultra-sensitive to small variations in the fixator in order to keep the fixator values unchanged.

A major property of a fixator is its ability to stick to a design constraint, whether fixed or variable in time or frequency, based on a pre-specified setting. For example, a fixator can be assigned to a circuit port to keep its frequency response close to a given frequency profile. In return the pairing norator must be capable of providing the necessary condition in the circuit for the fixator to operate. In short, a fixator is used to keep a design constraint as specified, shifting the problem to the

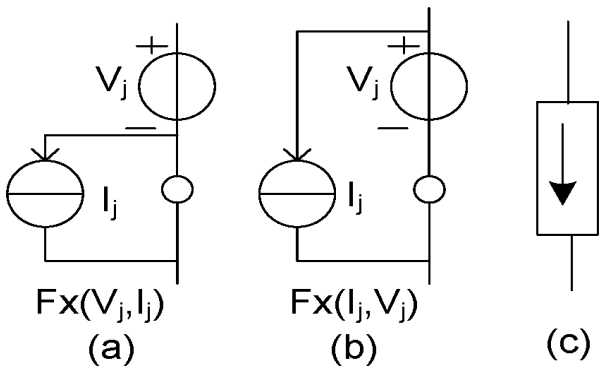

Figure 1.
Fixators; (a) a voltage fixator; (b) a current fixator; (c) the symbol.

design of a two terminal component/circuit that needs to replace the pairing norator. This is, in fact, the key property of a fixator that we are able to use in this chapter to design amplifier circuits that exhibit some specified frequency profiles and bandwidths.

Next, we are going to investigate how this property of a fixator works for us to design hearing aid amplifiers.

3. Frequency profiles matching in hearing aid applications

Consider designing an analog amplifier for a hearing aid application. Given a hearing profile (audiogram) of a hearing impaired patient, the question is how can we compensate for the hearing losses of the patient within the entire dynamic frequency range? We may go even further and design for a response that is beyond the mere compensation of the hearing losses, but enhancing or reducing the response in certain frequency areas as needed. For example, if the individual works in a factory and he/she is exposed to certain excessive sounds (noises) within certain frequencies, the hearing device must be capable of acting as a noise cancelation device [4], helping to reduce the noise as it provides amplification in other areas of the bandwidth.

This last point might be of interest to those working in the occupational technology, construction workers, and those working long hours with heavy equipment and machinery. Other applications might be in public health services such as in nursing homes to enhance certain alarms like passing vehicles, and so on, for the elderly safety. What is interesting in our analog hearing aid is that, to add those extras, such as noise cancelations or sound enhancements to the system all we need to do is to redesign the passive portion of the system without touching the active (amplifier) device.

So, we can define two objectives here: 1) compensate for the hearing losses and make it uniform within the entire dynamic frequency range, and 2) add a certain selective frequency response profile on top of the flat normal hearing. In other words, given the audiogram of a hearing impaired patient and also a desire hearing frequency profile constructed for the patient's need, how can we design an amplifier that satisfies both?

To put the problem into a mathematical perspective, suppose $H(s)$ denotes the audiogram of a hearing impaired patient, $F(s)$ is the final desirable voice spectrum that is tailored for the individual, and $T(s)$ is the transfer function of the hearing amplifier that provides such a response. Then

$$F(s) = T(s) * H(s) \tag{1}$$

To simplify the problem, we split it into two cases, just described. First, we only assume a flat frequency response for the final hearing comprehension, i.e., $F(s) = 1$ for the entire frequency bandwidth. In the second case, we try to enhance the response to follow a certain desirable frequency profile $F(s)$. We continue our design strategy for the first case here and will follow it for the second case in a later Section.

4. Design for flat frequency response

Suppose $H(s)$ is the transfer function of an audiogram, being represented by:

$$H(s) = N(s)/D(s) \tag{2}$$

Then by referring to Eq. (1) and assuming $F(s) = 1$, the amplifier response, $T(s)$, becomes

$$T(s) = H(s)^{-1} = D(s)/N(s) \tag{3}$$

So, the objective here is to design an amplifier that has a frequency response profile which is the inverse of an audiogram of our choice. In addition, this amplifier must be modular and adaptable to the changes that might happen to the hearing profile (audiogram). This change might be either due to the aging, or the amplifier may be used for another audiogram (patient) all together.

There are two known methods we can use for this functional inversion. One method is to apply the FNP technique as we introduced before, and the other method is to uses the negative feedback procedure [5], which is well known in control theory. We will introduce both methodologies in this chapter, although our preference and emphasis will be more on the former technique, as it is shown to be more reliable and accurate.

5. FNP implementation of analog hearing aid amplifiers

This implementation uses an FNP as a design tool. However, the FNP is later replaced with a high gain operational amplifier when the amplifier is constructed. Before we go into the details, here is the Problem Statement.

Problem statement – Given an audiogram of a hearing-impaired patient, design a front-end or stand-alone analog amplifier that is fully adaptable and has a wide voice dynamic range covering the audio range from 250 Hz to 8 KHz, as specified in the audiogram [1].

Design procedure – The design proposed is modular with two parts: a) a controlling circuit, generating the hearing loss frequency profile as the output, and b) an amplifier acting as an engine module for the system. The control unit must be closely equivalent to the patient's audiogram, and any performance variations, such as tuning and modifications, are done on this module, which is usually a passive circuit. Therefore, the design of hearing aid is mainly concentrated on the design of the passive control unit, leaving the amplifier undisturbed during the application. This means, once the amplifier (engine) is designed it is left unaltered, and all other variations and adaptations are done on the controlling module. This is one of the main criteria of the system, where the variations and control is concentrated on the passive unit, which is more stable and design friendly.

Let us begin our design procedure from the transfer function $T(s)$, given in Eq. (3). **Figure 2** shows an audiogram taken from the left ear of a hearing impaired patient. Notice that the hearing loss is quite large, and it is more than 60dB at high pitch voices. So, to compensate for this loss we need to use an amplifier with high gain, getting to 60 dB or higher at high frequencies. A typical amplifier suitable for this design can consist of one or two stage of Op-Amps with wide enough bandwidth. Next, we proceed with the design of the control module.

Control Unit - Our next stage of the design is to construct the controlling module for a flat comprehended hearing profile ($F(s) = 1$). The module must be so designed that it generates an output frequency profile duplicated from the selected audiogram, or simply have a transfer function close to H(s). Apparently, because of the losses in the magnitude of the response, the controlling circuit, called *Audiogram Generator Circuit (AGC),* can be totally passive RC (or RLC) circuit.

There are different methods available to construct such an AGC, and because it is a passive circuit its design and synthesis can be quite straight forward [6]. A more

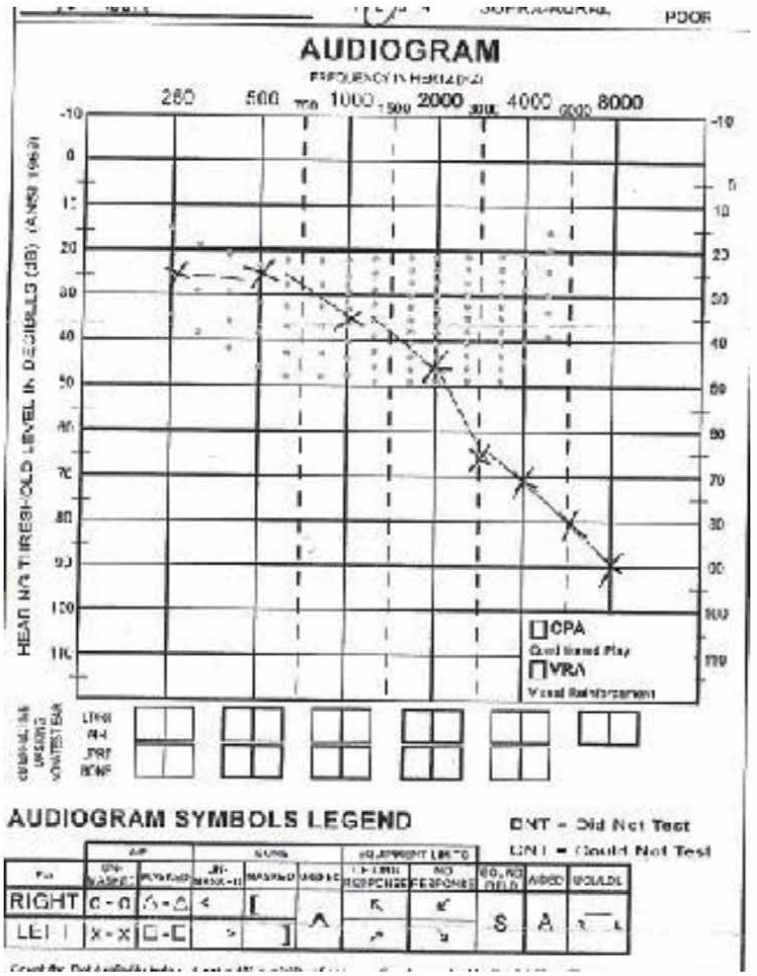

Figure 2.
Audiogram of the left ear of a patient with hearing impairment.

practical design technique is to estimate the locations of the poles and zeros for a given audiogram first, and then construct a AGC that closely displays those poles and zeros, and hence, nearly mimics the audiogram [7]. An alternative design method is also presented in [8]. Here, in this chapter, we follow an ad hoc technique where we first try to assemble an RC ladder circuit to produce an AGC with the frequency profile close to the audiogram. We then modify the circuit and add more ladder stages if necessary to get it right and accurate enough. We can always leave some room for on (application) site tuning, of course.

Another issue to pay attention to here is the phase angle. The experiment show that we need to be concern about the phase delay in an AGC as well. Because of the reactive elements (C and L) in the circuit, phase delay is generated, which causes time delay in the signal processing. In case this time delay is uniformly distributed throughout the frequency spectrum, i.e., the phase in linear vs. the frequency, then the group delay will be constant and the uniform delay only causes a constant delay between the actual voice (signal) and what is received and comprehended through the hearing aid. However, in case the time delay is dependent on the frequency of the signal, and the time delay variation is large then it may cause poor fidelity and distortion in the comprehended voice. So, for a reliable design we need to pay attention to both magnitude and the phase of the signal getting out of an AGC.

Presently, we consider two AGC circuits given in **Figure 3(a)** and **(b)**, and their symbolic representation in **Figure 3(c)**. **Figure 4** shows the magnitude frequency responses of both AGCs in comparison with the actual audiogram. To further compare the two circuits, both the magnitude and the phase Bode plots are shown in **Figure 5(a)** and **(b)**. In comparing their responses, we realize that the RC_1 module, also structurally more involved, is showing more accurate results than the RC_2 module. Notice the followings points in the response of the RC_1 module: 1) its magnitude is closer to that of the audiogram, and 2) its phase delay is almost linear, providing a nearly constant group delay. So, we have two choices to select one. Either select the RC_1 module (**Figure 3(a)**) for less distortion and better comprehended voice, or alternatively chose the RC_1 module for its simplicity.

However, we may still need to observe the roots (poles and zeros) of the modules, in case we may want to modify the responds for a better fit. To clearly identify the roots, we use a technique initially introduced in [9]. This technique converts the real axis roots (poles and zeros) of an RC circuit to roots on the imaginary axis where the sweeping excitation signal encounter with the roots and so generates

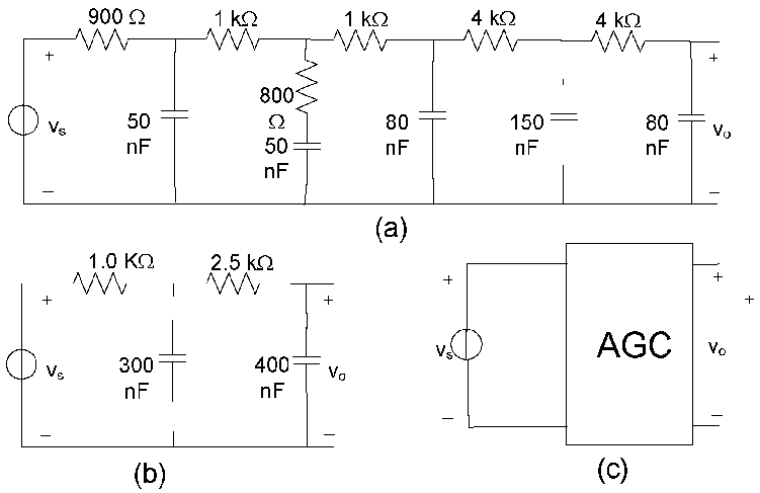

Figure 3.
*(a) And (b) two AGCs matching with the audiogram given in **Figure 1**; (c) the AGC block diagram.*

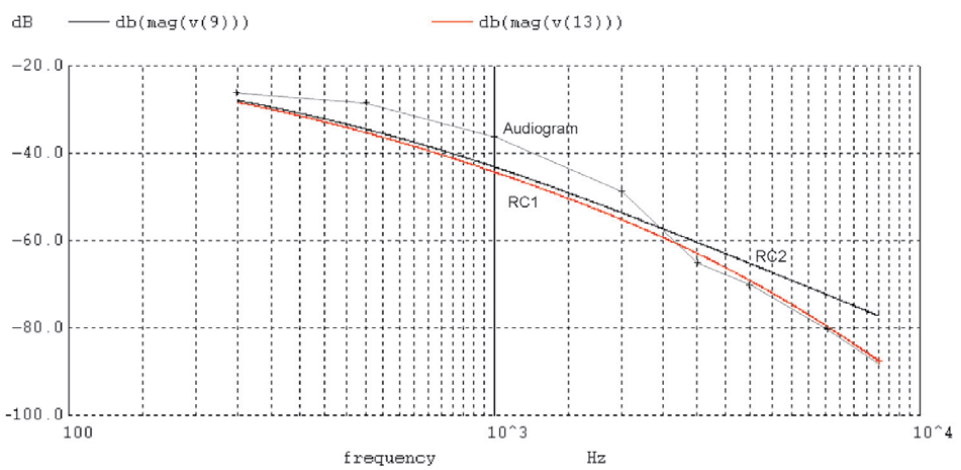

Figure 4.
Comparing the frequency responses from the two AGC candidates, RC_1, and RC_2 with the audiogram.

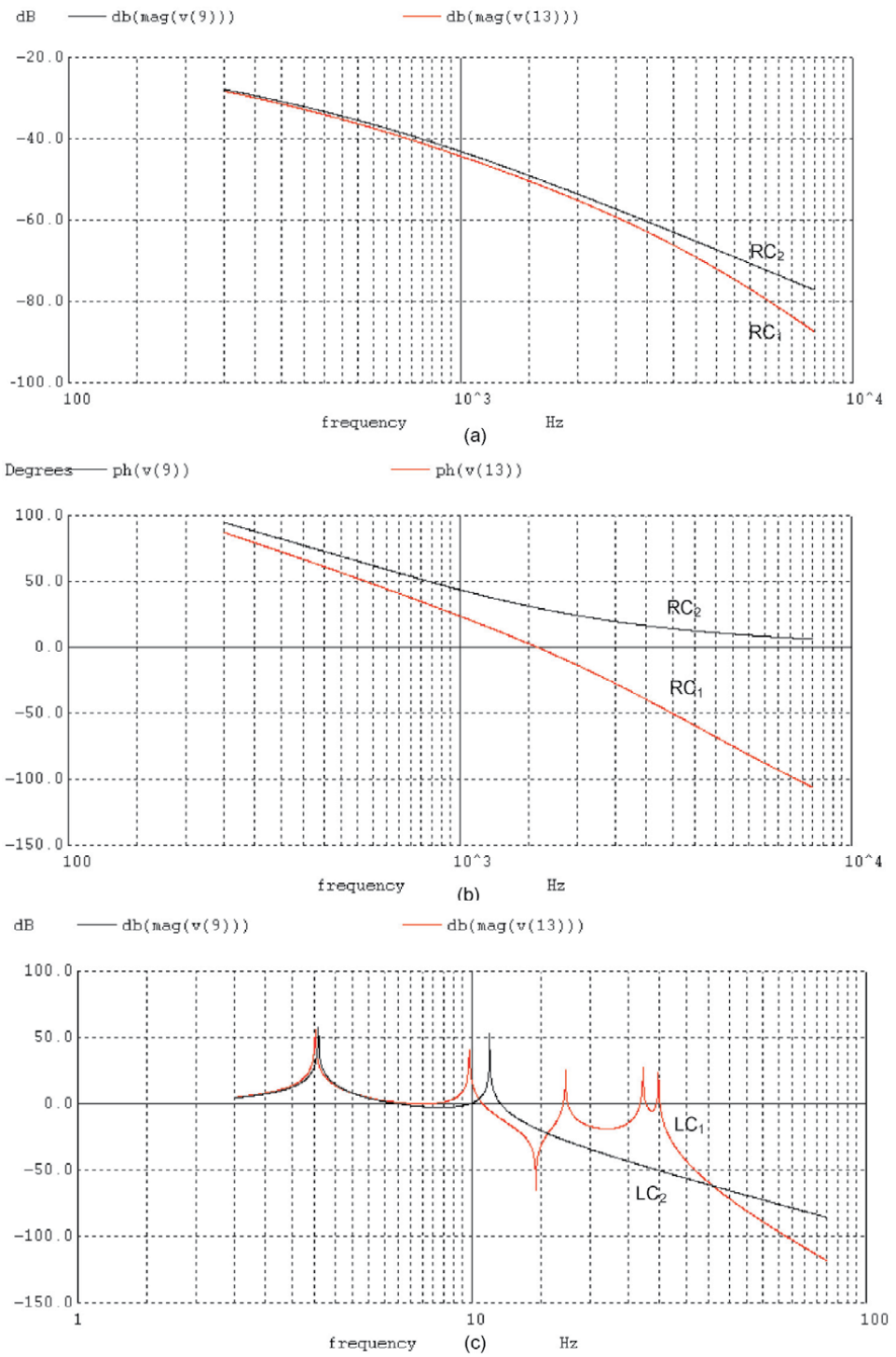

Figure 5.
(a) And (b) the frequency response of the two AGC corcuits; (c) the frequency response of the corresponding LC circuits.

peaks and notches. To implement this technique for our case we first need to create two LC circuits, LC_1 and LC_2 for RC_1 and RC_2, respectively. To create LC_1 and LC_2 we need to go through the following steps:

1. Change all resistors (R) in the RC circuit into inductors (L) with the same values.

2. The controlled sources and the controlling variables (I and V) must be of the same kind. So, for example, a voltage controlled current source VCCS must be changed to either a current controlled current source (CCCS) or to a voltage controlled voltage source (VCVS).

3. Simulate the LC circuit and generate the Bode plots, and then rescale the frequency axis.

Here is how it works.

Corresponding LC circuits – As fully explained in [9], it is simply proven that, if LC_i is the corresponding LC circuit of an RC circuit, RC_i, then for any real axis root ω_{RC} in RC_i there exist a pair of conjugate roots $\pm\omega_{LC}$ on the $j\omega$ axis for LC_i so that they are related through the relationship $\omega_{RC} = \omega_{LC}^2$, or in the log format the scaling factor is specified by

$$\log(\omega_{LC}) = \log(\omega_{RC})/2 \tag{4}$$

The advantage of getting the poles and zeros through the corresponding LC circuit is that, we can access the actual and accurate locations of the roots in terms of peaks and notches that ultimately guide us into a better design of the AGC. This means, we can study the location of the real axis roots of an AGC, make appropriate changes to the locations of the roots so that the frequency response of the AGC gets close enough to the actual audiogram (**Figure 1**). **Figure 5(c)** shows two such plots for the corresponding LC circuits LC_1 and LC_2. By observing the plots, we can extract several conclusions essential to the design. For instance, to produce a nearly constant group delay we need to create a balance between the poles and zeros of the circuit, as poles produce more lags and zeros generate more leads in the phase angle. Referring to our case of the AGCs, Bode plots in **Figure 5(c)**, we notice five poles and one zero for LC_1 transfer function that are well distributed within the bandwidth region. This, as shown in **Figure 5(b)**, produces a close to linear phase shift spanning about 200 degrees. Whereas for LC_2 the phase shift is far from linear distribution. So, the better choice for this design is clearly RC_1, although the circuit is more involved with more components. However, for the reason that is mentioned in Example 1, we choose RC_2 as the selected AGC for our design. This concludes our control unit (AGC) design.

Amplifier: Now that we have done with the AGC design, our next task is to design the amplifier and the system all together. In this design we must come up with constructing the transfer function, $T(s)$, given in Eq.(3). As we notice, the roots of $T(s)$ are the same as those of the AGC ($H(s)$) but the opposite, i.e., the poles of $H(s)$ become the zeros of $T(s)$ and vice versa. A new and rather simple method to realize $T(s)$ is to use an FNP as a tool and later replace it with real components [2]. For this implementation we start with the circuit in **Figure 6**, showing an AGC circuit with an audio input signal connection that has a unit amplitude for the entire frequency bandwidth. As expected, this input signal generates an output close to the designated audiogram. Now, we may change the problem statement and ask the following question. What do we need to connect at the input port of the AGC in order to get an output signal with unit amplitude within the audio bandwidth (250 Hz to 8 KHz)? To answer this question we refer to **Figure 6(b)**, where a

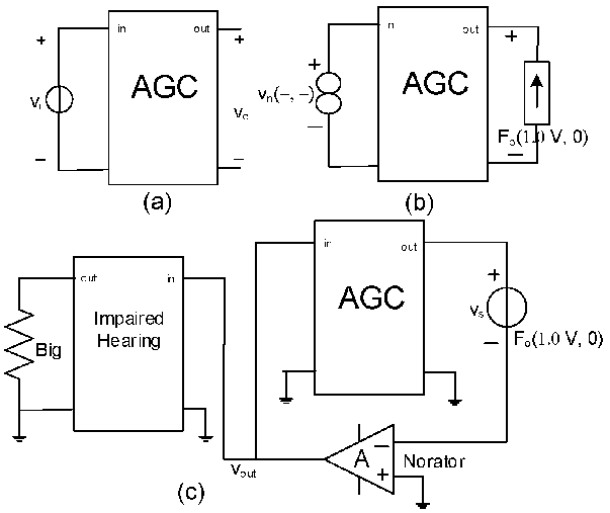

Figure 6.
(a) And (b) symbolic design of a hearing aid amplifier using an FNP; (c) a simplified equivalent circuit for test purposes.

fixator $F_o(1.0, 0)$ is providing the desired output as we stated, and a pairing norator $V_n(-, -)$ is instead added to the input port to allow this to happen. Again, the difference here is that we are now looking for a constant amplitude output from the AGC and not the input. Next we may ask, what type of the input signal the norator must provide to the AGC (replaced for the impaired hearing) so that the output is well achieved, i.e., the comprehended voice is uniformly constant? For the solution, we refer to **Figure 6(c)**. As we can see here, the norator is replaced with an Op-Amp, and as a feedback. It provides the necessary signal to the AGC for a constant amplitude output. So, if we now assume that the AGC represents the impaired hearing situation then the output of the impaired hearing is also flat as we desired, actually representing the improved hearing status of the individual.

What we need to do next is to see how we can replace the norator with a real sub-circuit, which turns out to be an amplifier, and then try to design it. **Figure 7(a)** shows a reconstruction of the complete hearing aid system presented in **Figure 6 (c)**, except the impaired hearing block is removed. To complete this design all we need to do is to design the norator amplifier. As mentioned earlier, because of the high losses that we experience at high frequencies the amplifier must provide a gain of 60 dB or more to compensate for the impairment. In this study, we selected an amplifier that uses a TI - LM318 Op-Amp with a bandwidth of 15 MHz. This Op-Amp can provide a gain of 66 dB (2000 V/V) at 8 KHz, which is well above the required value for this case study. **Table 1** provides the Electrical Characteristics of the TI - LM318 Op-Amp.

Figure 7(b) shows the amplifier constructed using LM318 Op-Amp along with its symbolic representation. With the rated gain-bandwidth product given, this Op-Amp is a very well fit to our design, although its power (0.5 W) is on the high side. There are certainly other choices of Op-Amps that can replace LM318 (not discussed here). **Figure 7(c)** is the response from the amplifier. As we can expect, this is exactly the opposite of the AGC, RC_2 frequency characteristic, shown in **Figure 5(a)**.

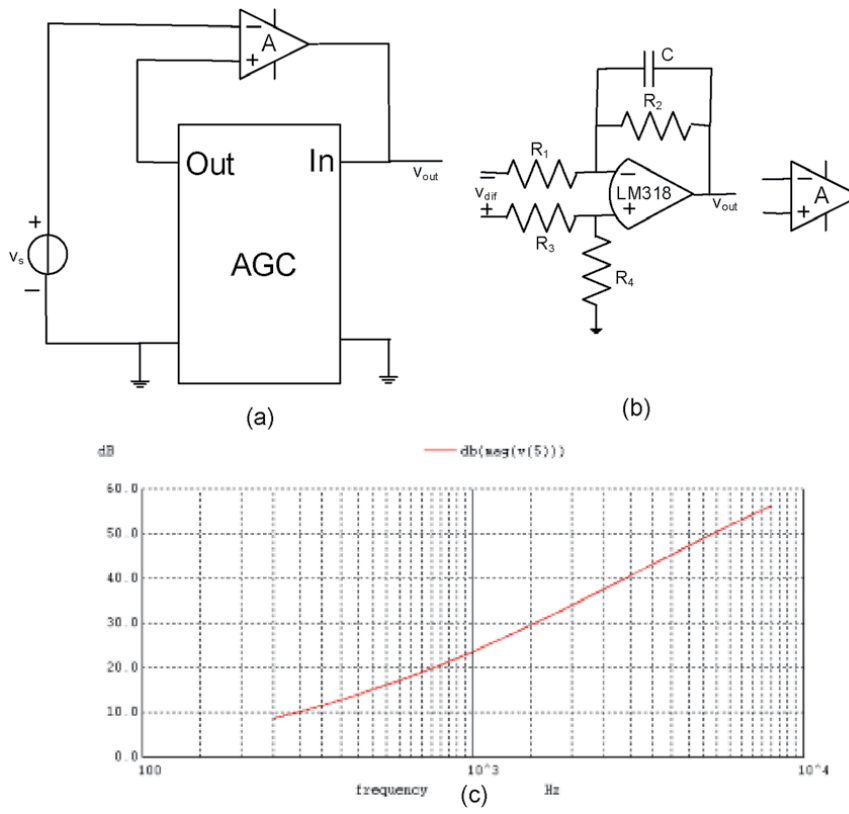

Figure 7.
(a) Hearing aid amplifier; (b) the construction of the amplifier using high gain Op-amp: (c) the amplifier frequency response.

We are now going through an examples to see how the technique practically works.

Example 1 – For this example we again take the case of the hearing-impaired patient with the audiogram given in **Figure 2**. We then construct the audio amplifier given in **Figure 7(a)** and **(b)**. However, there are some design considerations that needs to be addressed here. Our main challenge is to produce enough gain at higher frequencies (8 KHz) where the hearing loss is the most. By using TI - LM318 Op-Amp we get a small signal bandwidth of 15 MHz, which means, at 8 KHz frequency we can barely get 2000 V/V or 66 dB gain. Hence, this explains one of the reasons for selecting RC_2 instead of RC_1 for this design, which is to settle with lower gain requirement.

For testing purposes, we attach another AGC (audiogram) to the output port of the amplifier, resembling the hearing situation of the person with hearing impaired. **Figure 8** shows the combination of three parts: the input signal representing the voice received, the audio amplifier for voice processing, and the AGC model representing the hearing-impaired of the patient. As shown, the audio amplifier (hearing aid) receives the voice, amplifies it, and sends it to the patient's ear. The entire circuit is simulated and the results are plotted in **Figure 9(a)** and **(b)**, for magnitude and phase, respectively. In **Figure 9** we observe the frequency response of the amplifier that is exactly opposite of the frequency profile of the audiogram, represented by the AGC. The final result is a hearing profile which is flat for the entire frequency range.

Electrical Characteristics [1]								
Parameter	**Conditions**	**LM118-N/ LM218-N**			**LM318-N**			**Units**
		Min	**Typ**	**Max**	**Min**	**Typ**	**Max**	
Input Offset Voltage	T_A = 25°C		2	4		4	10	mV
Input Offset Current	T_A = 25°C		6	50		30	200	nA
Input Bias Current	T_A = 25°C		120	250		150	500	nA
Input Resistance	T_A = 25°C	1	3		0.5	3		MΩ
Supply Current	T_A = 25°C		5	8		5	10	mA
Large Signal Voltage Gain	T_A = 25°C, V_S = ±15 V	50	200		25	200		V/mV
	V_{OUT} = ±10 V, $R_L \geq 2$ kΩ							
Slew Rate	T_A = 25°C, V_S = ±15 V, A_V = 1 [2]	50	70		50	70		V/μs
Small Signal Bandwidth	T_A = 25°C, V_S = ±15 V		15			15		MHz
Input Offset Voltage				6			15	mV
Input Offset Current				100			300	nA

[1] These specifications apply for ±5 V ≤ V_S ≤ ±20 V and − 55°C ≤ T_A ≤ +125°C (Im118-n), −25°C ≤ T_A ≤ +85°C (LM218-N), and 0 °C ≤ T_A ≤ +70°C (LM318-N). Also, power supplies must be bypassed with 0.1 μF disc capacitors.
[2] Slew rate is tested with V_S = ±15 V. The Im118-n is in a unity-gain non-inverting configuration. V_{IN} is stepped from −7.5 V to +7.5 V and vice versa. The slew rates between −5.0 V and + 5.0 V and vice versa are tested and specified to exceed 50 V/μs.

Table 1.
Electrical characteristics of the TI - LM318 Op-amp used.

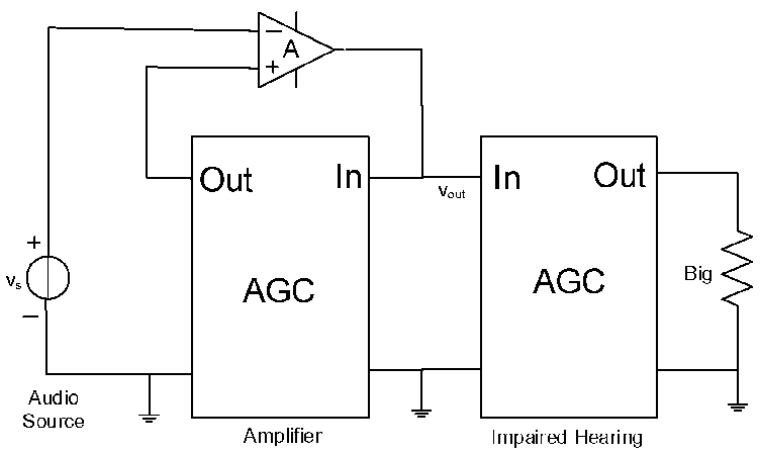

Figure 8.
A testing bench; testing the hearing aid amplifier.

Before constructing the system for laboratory testing, the circuit is simulated using WinSpice, and the following is the main portion of the code used for the simulation.

```
.control.
destroy all.
op
set units = degrees.
ac dec 1000 250 8 k.
```

```
plot ph(v(5)) ph(v(16)) ph(v(9)).
plot db(v(5)) db(v(16)) db(v(9))
.endc.
* Supplies and signal sources ********************************.
VCC       10       0       DC       5
VEE       0       20       DC       5
vi        1        0        DC        0        AC        90 m
* Combined Hearing Aid System ******************************.
rc        c        1        50
x3        4        c        10        20        5        Amp2
x4        5        7        4        AGC3
x8        5        15        16        AGC3
r3        16        0        10Meg
* AGC, Defected hearing profile ******************************.
re        e        1        50
x5        e        11        9        AGC 3
r6        9        0        10Meg
* Audiogram Generated Circuit ********************************
.subckt        AGC3        1        2        3
r0        1        2        1 k
c1        2        0        300n
r1        2        3        2.5 k
c2        3        0        400n
.ends.
* Amplifier for high gain, Gain = 5 k V/V, 74 dB ***********************
.subckt        Amp2        1        2        10        20        5
x1        1        2        10        20        3        Amp1
r1        0        4        1 k
r2        4        5        100 k
x2        3        4        10        20        5        LM318
.ends.
* Amplifier using LM318 Op-Amp, Gain = 50 V/V, 34 dB ****************
.subckt        Amp1        1        2        10        20        5
x1        3        4        10        20        5        LM318
r1        2        4        1 k
r2        4        5        50 k
r3        1        3        1 k
r4        3        0        50 k
c1        4        5        0.3p
.ends.
* LM318 Op-Amp model parameters ********************************
.include op-models.txt
.end.
```

Following the simulation, the hearing aid circuit is constructed and the tested in a laboratory setup. **Figure 10** shows the experimental bread board for testing purposes, and **Figures 11–13** are the test results at different frequencies.

The output responses of the amplifier are shown at 250 Hz, 1.0 KHz, and 4.0 KHz frequencies. Notice, that not only the magnitude changes and increases for higher frequencies, but phase delay also increases up to 82 degrees. Finally, **Table 2** shows the experimental results for the gain vs. frequencies for the amplifier.

Example 2 – Now we are going to try a different audiogram in this example, one from a person with a rather mild hearing impairment. This audiogram is given in

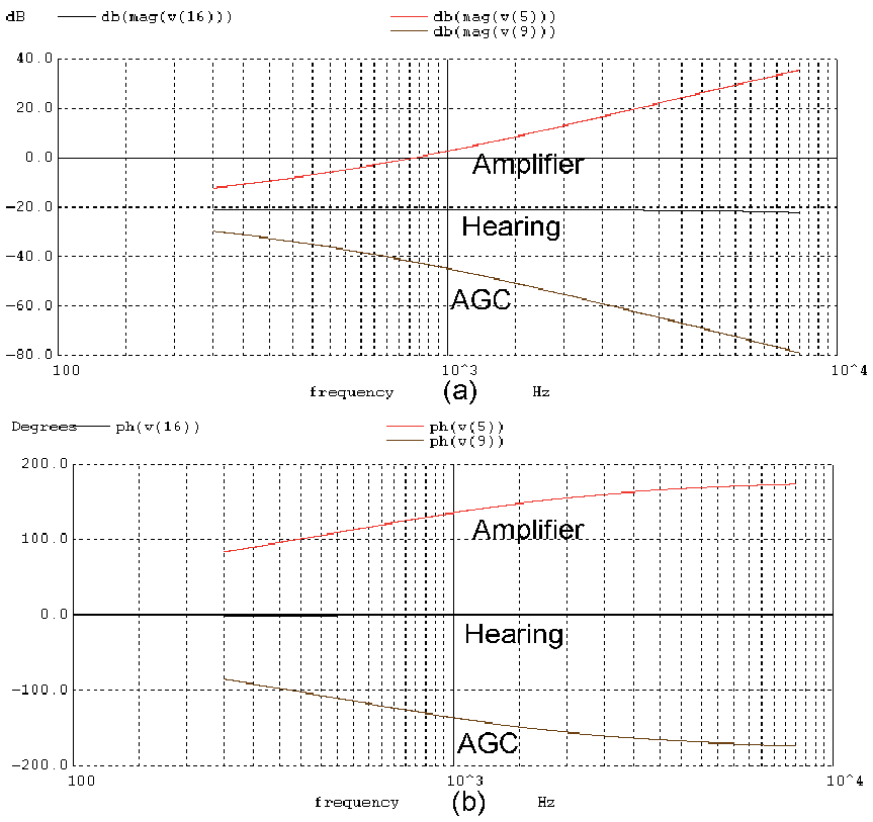

Figure 9.
Simulation results: (a) magnitude plots from the test bench in ***Figure 8****, including the amplifier response, audiogram, and the hearing profile by the hearing-impaired patient; (b) the phase responses.*

Figure 14. We start constructing an AGC model for this case, which is much similar to the one we did for Example 1. The circuit is constructed from R and C components and is then simulated for its frequency responses. **Figure 15** shown the magnitude Bode plot of the AGC. In addition, the audiogram is also added to the figure for comparison.

Our next step in the process is to construct the amplifier needed. Again, because of the modularity property the design procedure of the AGC is quite simple. All we need to do is to take the same amplifier constructed for Example 1 (**Figure 7(a)**) and replace its AGC, given at **Figure 3(b)**, with the new one created, for this example. For testing purposes, we again put all three units (the input signal representing the voice received, the audio amplifier with the new AGC, and a second AGC representing the hearing-impaired patient) together and simulate. The setup will be similar to the testing bench provided for Example 1 and shown in **Figure 10**. We then simulate the combined circuits again and plot the frequency responses. The responses from the amplifier and the one from the hearing profile, comprehended by the hearing-impaired patient, are given in **Figure 16**. Again, notice that the hearing has improved substantially by using the amplifier. As seen, the comprehended voice is quite flat just like the one we had in Example 1. Also notice that the ultimate phase angle has become flat, as well.

Further, in comparing plots in **Figure 16** with those in **Figure 9(a)**, we notice that the two amplifiers respond differently but the net results, i.e., the comprehended

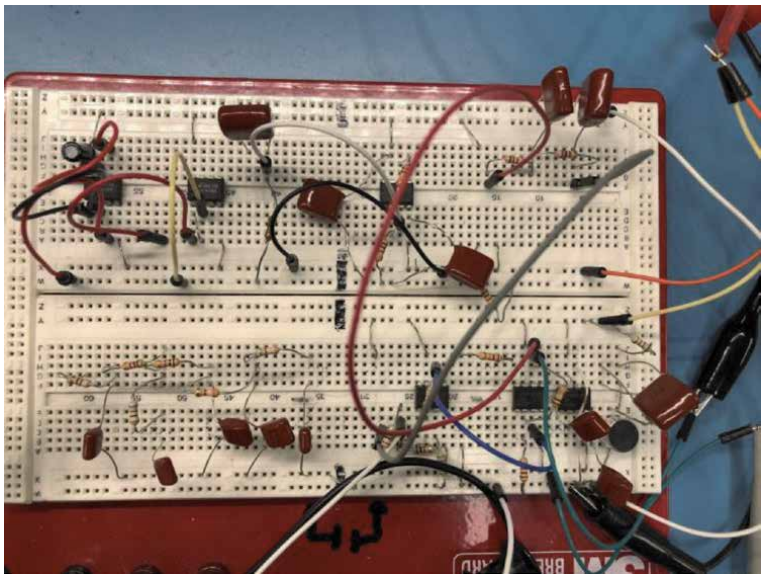

Figure 10.
A testing bench; experimenting the hearing aid amplifier.

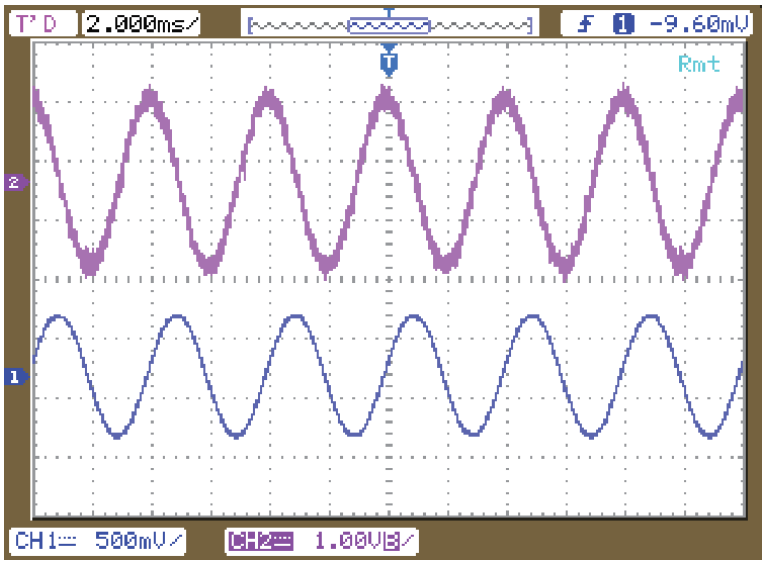

Figure 11.
Input signal (lower) and the amplifier response (upper) for 250 Hz. Note the scale difference.

voices are the same and completely flat. This shows the adaptability property of the amplifier. That is, as we discussed earlier, in shifting from one example (patient) to another all we need to do is to design a new AGC, while the amplifier unit remains unchanged, unless the ultimate gain of the amplifier in not sufficient to compensate for all the losses, recorded in the audiogram.

This brings us to the following algorithm for the construction of an adaptable amplifier for hearing aids.

Algorithm 1.

Given an audiogram similar to the one shown in **Figure 2** or **Figure 14**, we can construct an adaptable front-end or stand-alone analog amplifier that can be used to

totally remove the hearing deficiencies and provide a convenient hearing. The procedure is as follows:

1. Construct a passive AGC that represents the audiogram profile of a hearing-impaired patient as closely as possible, like the ones shown in **Figures 4** and **15**.

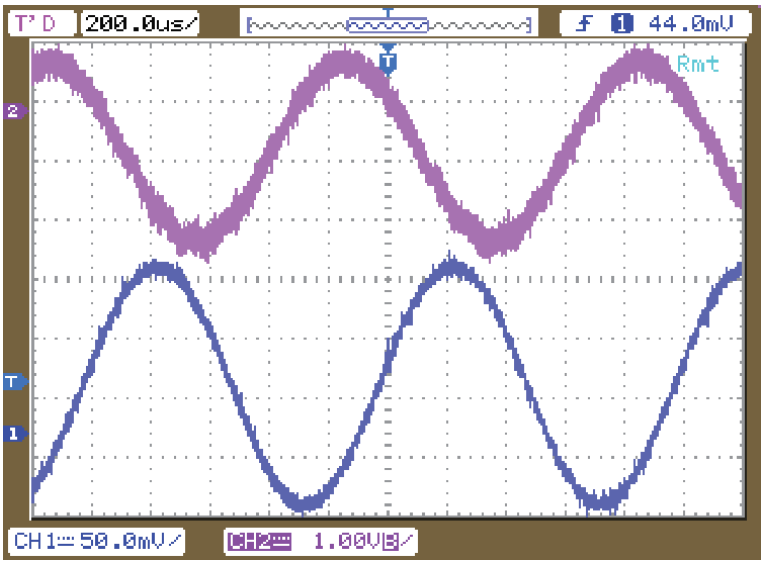

Figure 12.
Input signal (lower) and the amplifier response (upper) for 1 KHz. Note the scale difference.

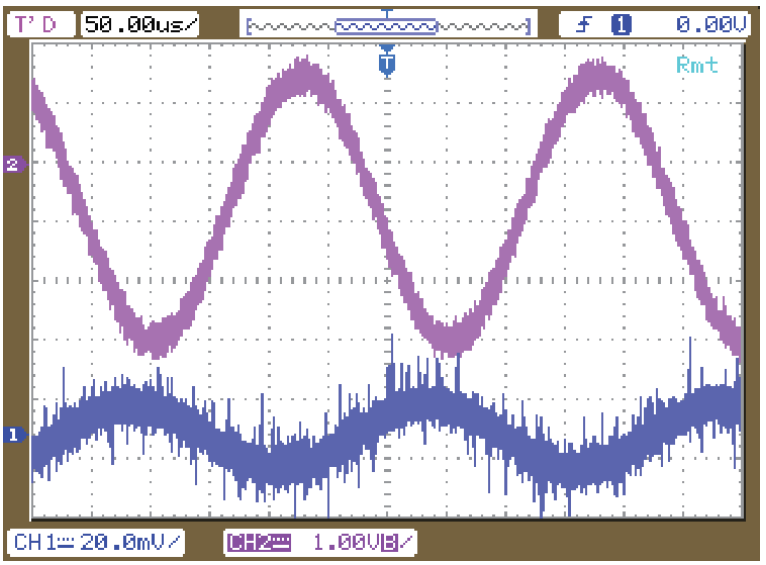

Figure 13.
Input signal (lower) and the amplifier response (upper) for 4 KHz. Note the scale difference.

Frequency Hz	**250**	**300**	**700**	**1 K**	**1.7 K**	**2 K**	**3 K**	**4 K**
Gain A_v V/V	3	4	13	20	39	65	98	200

Table 2.
Audio amplifier experimental results.

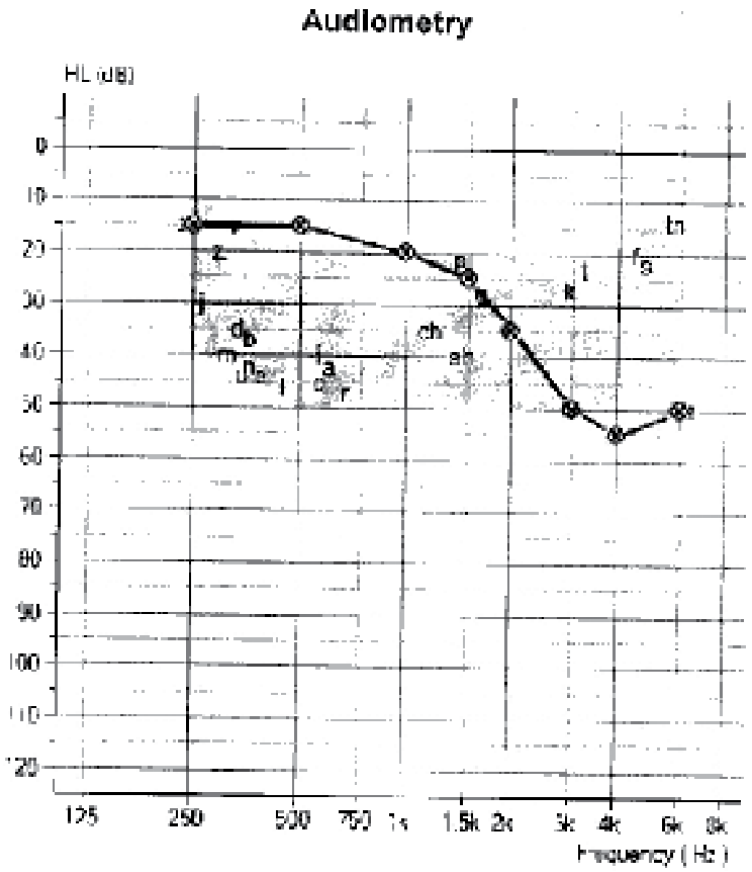

Figure 14.
Audiogram from a patient with mild hearing impairment.

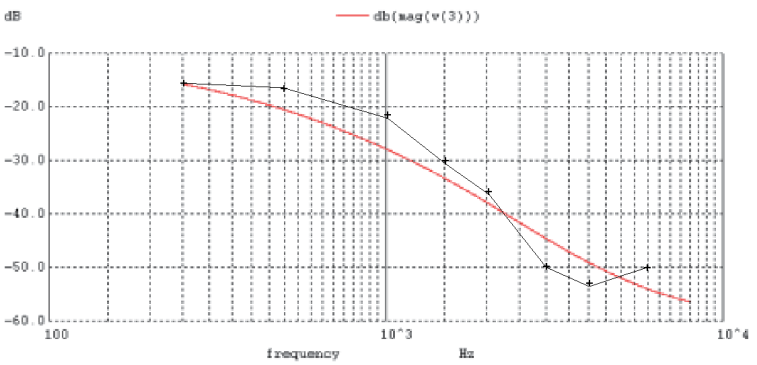

Figure 15.
The comparison between the audiogram and the frequency response of the adopted AGC.

2. Use the AGC and an amplifier with sufficient gain to construct an audio amplifier as discussed before and shown in **Figure 7(a)**.

3. The amplifier so constructed is adaptable, in a sense that for any other audiogram all we need to do is to replace the older AGC with a new one, constructed for a new patient.

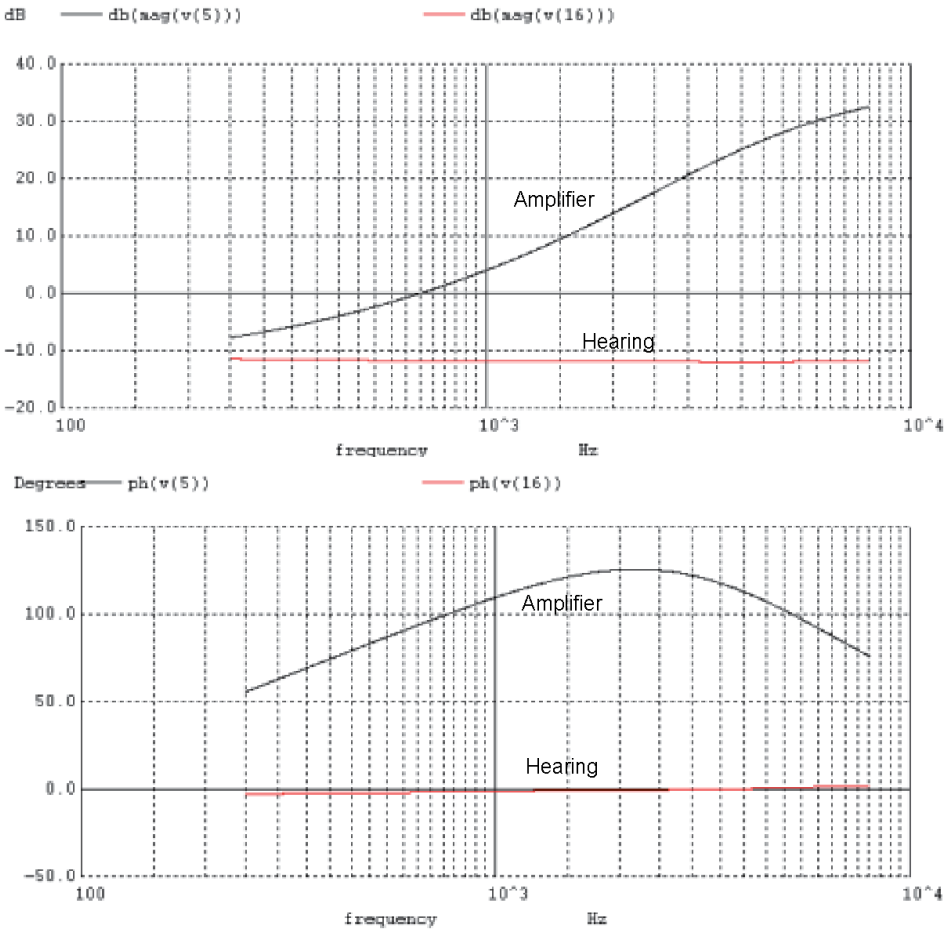

Figure 16.
Magnitude and phase responses from the amplifier and the comprehended hearing profile.

4. Simulate the entire system in a setup shown in **Figure 8**, for verification purposes.

This concludes our design procedure for hearing aids with flat responses, where $F(s) = 1$ in (1). What we need to do next is to extend the design to cover for the cases when $F(s)$ is not necessarily flat due to some preferences in the hearing quality, for example, for factory workers for whom it may be needed to reduce certain machinery noises or enhance those related to the onsite conversation.

6. Design with extra gain added

Up until now we have assumed that the comprehended voice by the patient needs to be flat, leading to the gain function of $F(s) = 1$. Now, we assume an arbitrary gain function $F(s)$ recommended for the hearing-impaired patient, suitable for his/her application.

This is done by splitting the design procedure into two parts. In the first part we again assume a flat response with $F(s) = 1$, and in the second part we modify the amplifier so constructed to generate the frequency response $T(s)$ for different $F(s)$. This modular design may also provide us with the options to switch between the

two cases during the application. Knowing how to design for *F(s) = 1* by now, all we need to do here is to go for a desired arbitrary response, *F(s)* and add it to the system. Here is the problem statement.

Problem statement – Given an audiogram of a hearing-impaired patient, as shown in **Figures 2** or **14**, design a front-end or stand-alone amplifier that is fully adaptable and has a wide voice dynamic range covering from 250 Hz to 8 KHz, as specified in the audiogram. In addition, the amplifier is supposed to produce a comprehended voice frequency profile *F(s)* that is recommended for the patient.

Design procedure – To design such an amplifier we first follow the procedure explained in the previous section, i.e., design an amplifier *N* with the frequency response of $T(s) = H(s)^{-1}$. As we discussed, this produces a flat response with *F(s) = 1*. We then follow the method explained in [8]. This method uses nullors to modify the amplifier circuit until it produces a transfer function$T(s) = F(s)/H(s)$, where *F(s)* is the desired frequency response, which is produced by a *model circuit M*. Note that *M* does not need to be a physical circuit as long as it generates an output response *F(s)*.

So, the design starts by first assuming that we already have done the first part and constructed an amplifier *N* for *F(s) = 1,* which has $T(s) = H(s)^{-1}$ transfer function, as shown in **Figure 17(a)**. Next, let us assume we have been able to find a sub-circuit *P* (usually a feedback) so that by adding *P* to *N* the circuit can be realized to perform with a transfer function $T(s) = F(s)/H(s)$, for an arbitrary *F(s)*.

In summary, for a given transfer function *T(s,)* we first design the circuit *N* for its $T(s) = H(s)^{-1}$. We then add a sub-circuit *P* to *N* and modify *P* until we get $T(s) = F(s)/H(s)$. So, our main objective here is to find the sub-circuit *P*. This is stated in a stepwise procedure, Algorithm 2.

Algorithm 2

1. Consider an amplifier *N* already designed for a flat hearing, with *F(s) = 1*. Next, try to find a model circuit *M* that produces a desirable frequency response *F(s)* that is realizable. If circuit *M* is not physically available, try to artificially synthesize *M*, possibly through a cascade decomposition method. *Note* that, because the model circuit *M* may only be needed for simulation purposes, the use of any ideal components, such as ideal controlled sources, in *M* is permissible, which makes it easier to generate.

2. Find a location in the circuit *N* such that adding a two terminal sub-circuit *P* to *N* can bring a solution to the problem, as depicted in **Figure 17(a)**[1].

3. Connect the two circuits *N* and *M* together in parallel, and keep the two output currents at zero by adding a nullator between the two outputs, as shown in **Figure 17(b)**. To match the nullator, add a norator *P* to the designated location in *N*. This norator will be later replaced with a sub-circuit *P*.

Note 1: Practically, a norator can be a high gain controlled source or an Op Amp [2, 10].

Note 2: parallel connection of *N* and *M* in **Figure 17(b)** is only valid for voltage to voltage transfer functions. However, this is not the only option we have, and other configurations can also be adopted. For example, for a case of current sourcing the connections must be in series, as appropriate [8].

[1] Here we assume the connecting nodes of *P* to *N* are already specified. Going after the best location connecting *P* to *N* adds another dimension to the problem, which is outside of this chapter.

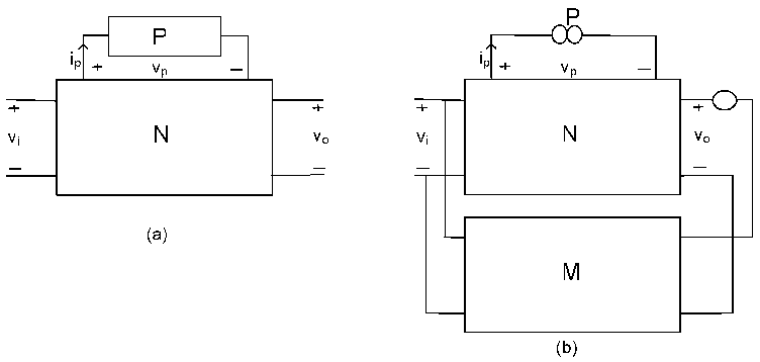

Figure 17.
(a) Circuit N *with a two-terminal* P *added; (b) realizing the two-terminal* P *by enforcing* N *to follow the desired response from* M.

4. Simulate the combined circuit. Evidently the frequency response of both circuits *M* and *N* must be identical, because of the parallel connections. So, *N* follows *M* in response. Because of the enforced response on the output of *N*, a virtual impedance function $Z_p(s) = V_p(s)/I_p(s)$ is created for the norator *P* through the simulation. This means, if we replace the norator with a two-terminal circuit that has the impedance $Z_p(s)$, then we get an independent response from *N* that is identical to that of *M*. Which means, *N* responds independently after being separated from *M*.

5. Now we need to synthesize *P* such that its impedance characteristic is close enough to $Z_p(s)$, for the specified bandwidth. Then we replace the norator *P* with the actual two-terminal *P* found. If $Z_p(s)$ is not realizable make proper approximations/adjustments to fit.

Note 3: The methodology works for nonlinear circuit as well, provided that the sub-circuit *P* does not disturb the biasing situation of *N*. This is very important point, which means that circuit *N* must be protected by coupling/bypass capacitors, if necessary.

The following example clearly demonstrates the steps given in Algorithm 2.

Example 3 - **Figure 18** shows the same amplifier designed for Example 1 and illustrated in **Figure 8** for a flat comprehended voice bandwidth (*F(s) = 1*), except here a *model circuit M* is added to the configuration. The model circuit is connected to the amplifier in parallel and through a nullator at the output port. A paring norator *P* is also added to the AGC in the amplifier. The norator is in fact a "place holder" for an actual two terminal sub-circuit *P* that must be found to replace it. According to Algorithm 2, and for simulation purposes, we now need to replace the nullor with a high gain dependent source, and for this example we have selected a CCVS, with the SPICE code given as:

```
va      2       12      DC      0
vb      11      13      DC      0
h1      13      0       va      1.0e6
```

The choice of CCVS is not unique, and in fact any of the four types of controlled sources can be selected, depending on the situation. For the present case, we first decide which variable (i or v) in the nullator is going to control the norator. We notice that the current in the nullator, although presently zero, is an effective

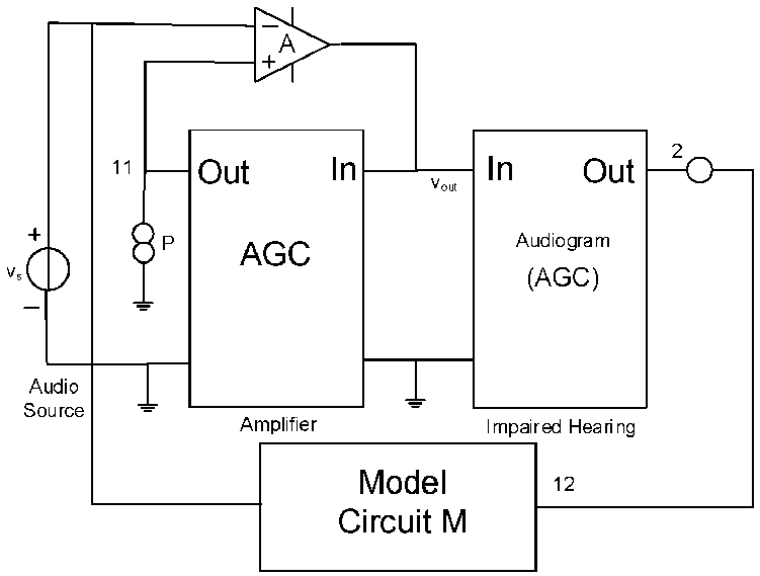

Figure 18.
*Design procedure to modify the audio amplifier for a response given by the model circuit M (see **Figure 17**).*

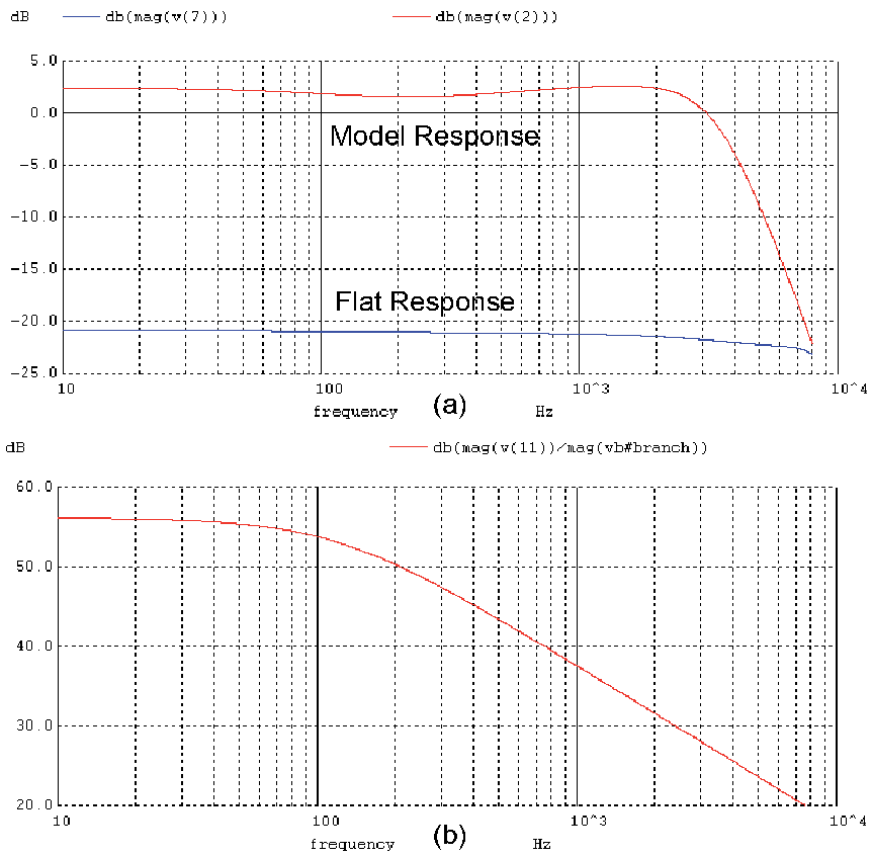

Figure 19.
*(a) Comparing the frequency response of the model circuit M with the amplifier before being modified; (b) the frequency plot representing the virtual impedance of the norator in **Figure 18**.*

candidate to control the norator. So either CCVS or CCCS can be selected. For more practical reasons, here we chose CCVS that closely resembles an ordinary Op-Amp.

The combined circuit also includes a patient's audiogram (AGC) representing his/her hearing situations. The entire circuit is then simulated and the results are plotted in **Figure 19(a)**. The SPICE code for the plots are:

plot db(v(2)) db(v(7)), the magnitude responses, **Figure 19(a)**
plot db(v(11)/I(vb)), the magnitude response of $z_p(s)$, **Figure 19(b)**

There are two response plots in **Figure 19**, one $(v(2))$ from the model circuit, and another one $(v(7))$ representing the original amplifier with the flat $(F(s) = 1)$ response. In addition, **Figure 19(b)** shows the frequency response of the virtual impedance associated with the norator, i.e., $V_p(s)/I_p(s)$. What we need to do now is to find a two terminal sub-circuit P with the impedance function $z_p(s) = V_p(s)/I_p(s)$ and then substitute it for the norator.

In search for a realizable sub-circuit P we first make the assumption that P must be a passive RC circuit. This is realistic because P is going to be part of the AGC, which is already designed with passive (R and C) components. In our search we simply notice that the norator characteristic curve (**Figure 19(b)**) appears to be a

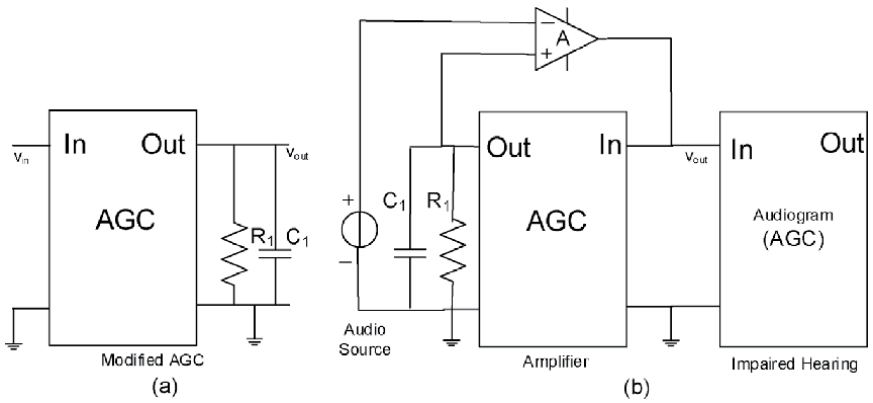

Figure 20.
Testing the modified hearing aid amplifier for the final results pertain to a hearing-impaired patient.

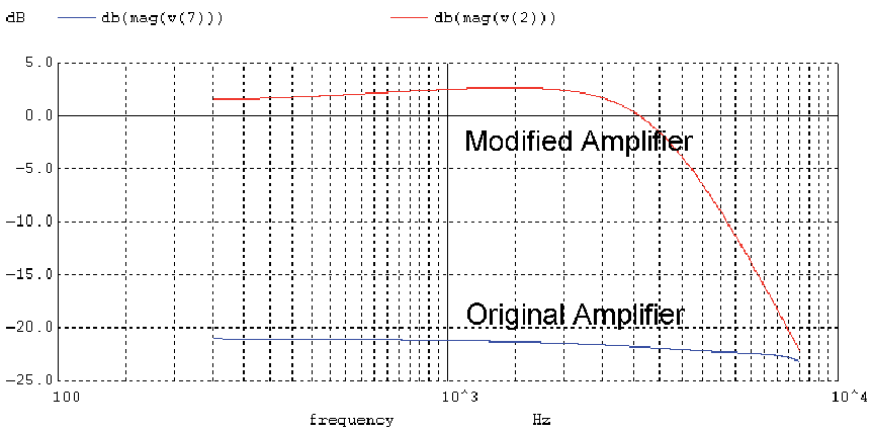

Figure 21.
Comparing the frequency response of the modified amplifier circuit with the original amplifier before being modified.

low pass filter realizable by a parallel RC circuit. The plot approaches 56 dB (631) at low frequencies and it falls at higher frequencies with break point frequency at $f_p = 118\ Hz$. Next, to find the RC circuit, we first find $R_1 = 631\ \Omega$, and then from f_p we get the equivalent capacitor $C_1 = (2\pi f_p.R_1)^{-1}$, or $C_1 = 2.1\ \mu F$. So, now the two-terminal norator P can be replaced with the components R_1 and C_1 in cascade, as shown in **Figure 20(a)**. The next step is to replace the older AGC in **Figure 18** with this modifies AGC, and then remove the model circuit all together.

Finally, **Figure 20(b)** shows a testing setup for the new hearing amplifier. After the simulation we plot the frequency response of the entire system as "Modified Amplifier", plotted in **Figure 21**. The Bode plot actually represents the voice heard and comprehended by the hearing-impaired patient. Also for comparison purposes, the result of a similar testing setup for the original amplifier with flat response ($F(s) = 1$) is also shown in **Figure 21**. A point to notice here is that, the new R_1C_1 circuit although passive, it contributes to a higher gain in amplifier and helps for an enhanced hearing. However, the price we need to pay is to assume higher gain for the Op-Amp. For example, although a gain of 60 dB is sufficient for the hearing aid with a flat response, $F(s) = 1$, it is not enough for this kind of enhanced situation. With about 20 dB gain desired here, we need to add the same amount to the Op-Amp and make it for 80 dB gain. So, here we see that the gain of 66 dB we have adopted for the Op-Amp is not sufficient any more, or we may lose some gain and precision losses at high frequencies, as we notice it in **Figure 21**.

7. Feedback implementation of analog hearing aids

As mentioned before, there is an alternative implementation technique to design hearing-aid amplifiers. This technique uses the well-known negative feedback methodology, which consists of a high forward gain amplifier inverting a transfer function generated by a feedback circuit. Consider a high gain amplifier $A(s)$ in the forward path of a feedback system, and an AGC, with the transfer function $H(s)$, placed in the feedback. The system transfer function $T(s)$ then becomes:

$$T(s) = \frac{A(s)}{1 + A(s)H(s)} \tag{5}$$

and for a special condition

$$A(s)H(s) >> 1 \tag{6}$$

$$T(s) \cong H(s)^{-1} \tag{7}$$

Eq. (7) is similar to Eq. (3) except for the constraint given in Eq. (6). This shows that the two methodologies, the feedback and the FNP, have elements in common, but different in implementation. We will discuss the major differences between the two later in this section However, let us analyze the feedback system first.

Feedback Implementation – **Figure 22** shows a feedback implementation of the hearing aid system testing setup. In the amplifier circuit part, the Op-Amp A_1 is constructed similar to what we did for FNP method in **Figure 7(b)**. For a better comparison between the feedback method and one using the FNP based design, we try to use identical components such as the AGC and the Op-Amp circuit. We then simulate the testing setup (**Figure 22**). The result of the simulation is shown in **Figure 23**. We can now compare these results with those obtained for the FNP case given in **Figure 9**. Although they look similar in general but they are different in

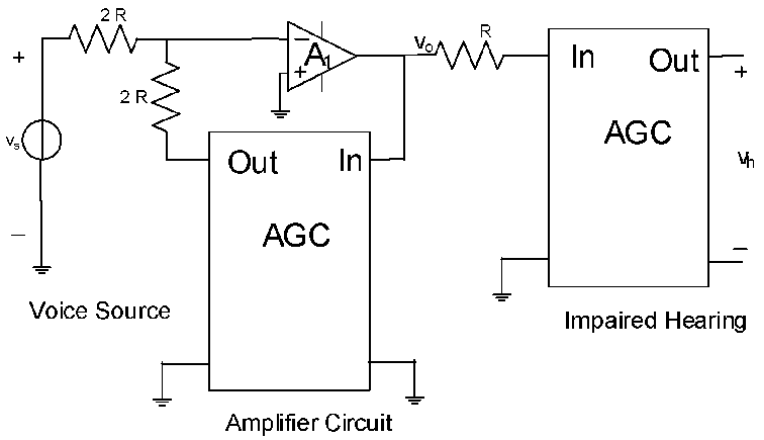

Figure 22.
A test setup for the hearing aid amplifier using normal negative feedback.

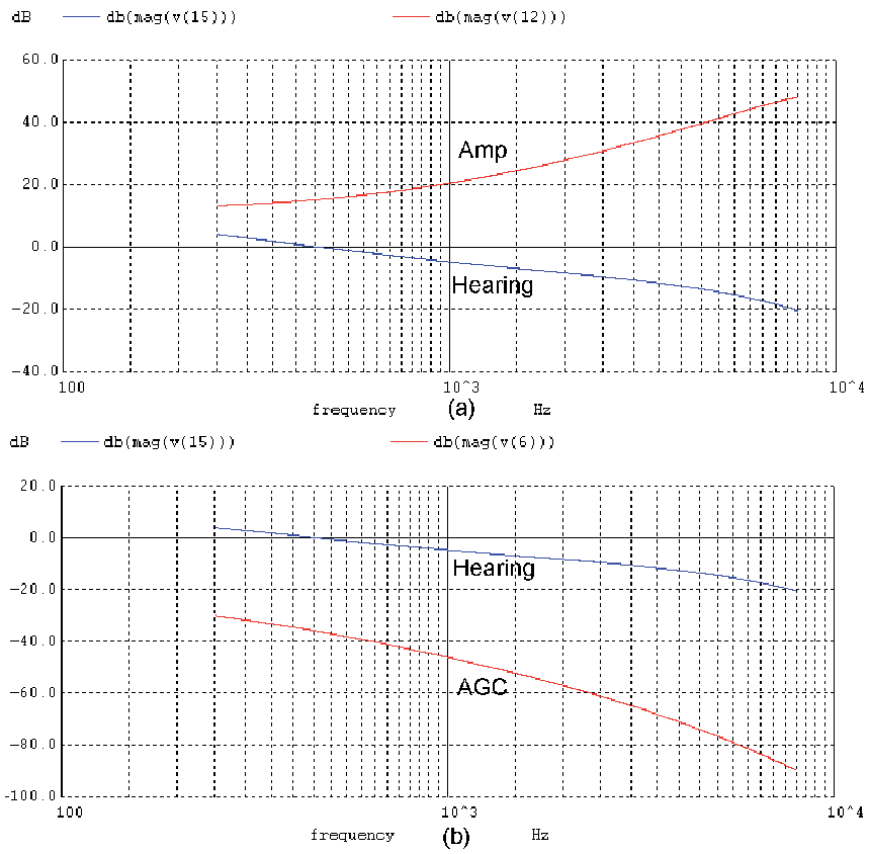

Figure 23.
Simulation results from the testing bench in ***Figure 22****; (a) the amplifier response and hearing profile by the hearing-impaired patient; (b) the frequency response of the AGC.*

performance. Notice that within the three plots (AGC, Hearing, and Amplifier) in each case the two AGCs are obviously the same, but the major difference is the following. In FNP implementation the frequency profile of the amplifiers is almost opposite of that of the AGC, whereas in the feedback case this is not true. In the

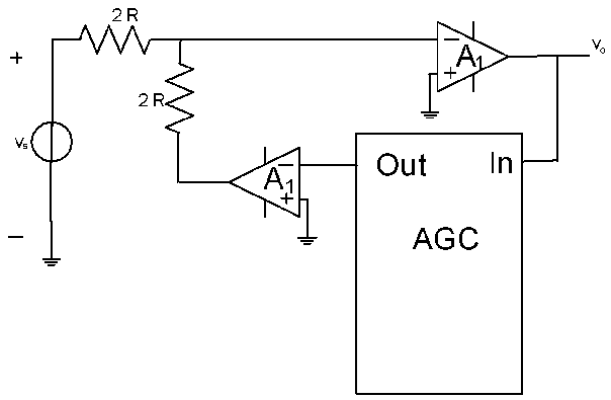

Figure 24.
Hearing aid amplifier using normal negative feedback. Another amplifier is added to prevent the AGC from being loaded.

feedback we are losing the gain for high frequencies, and that is why we are not getting a flat response at the end, as we do in the FNP case (Hearing in **Figure 9**). The consequence is that we are loosing the voice quality at high frequencies.

This, as it turns out, is due to the lack of impedance matching in the feedback case. For a passive circuit like AGC, the 2R resistive loading creates a clear variation in the AGC response because of loading. However, this is not the case for FNP methodology. Let us look at **Figure 6(b)**. Because a fixator with zero current is connected to the output port the AGC is never loaded. So it stays unchanged no matter what happens to the rest of the circuit. Back to the feedback case, one way to correct the loading problem is to use a buffer stage at the output port of the AGC circuit. This is demonstrated in **Figure 24**, where an extra amplifier is added to the output of the AGC. This of course fulfills the impedance matching and prevents the AGC being loaded. Afterwards, if we simulate the circuit we see the improvement, and the response received is almost the same as given in **Figure 8** for FNP realization.

Finally, we need to mention another major difference between the feedback method and the FNP technique. Let us revisit Eq. (7) and compare it with Eq. (3). To have the two equations identical we need to have $A(s)H(s) >> 1$, as stated in Eq. (6). This is basically a serious constraint for designing hearing aids when the corresponding audiogram (AGC) displays a large loss in higher frequencies. To make it clear, let us assume that we get satisfied with 1% accuracy for the system when we use the feedback method. This means $|A(s)H(s)| \geq 100$, for all the bandwidth. This means we always need to have the gain of the amplifier 40 dB higher than the largest inverse loss in the feedback. For example, for an AGC with 60 dB loss at high frequency we need an amplifier gain of 100 dB, instead of 60 dB, to satisfy the job, and this makes the system harder to design. The good news, however, is that if we intend to use the setup shown in **Figure 24** for impedance matching purposes then we can split the high gain requirement between the two amplifiers in the feedback loop and make it more distributed amplifier, Of course there are still some consequences involved but we ignore them here for simplicity. In any case, this shows the superiority of the FNP method compared to the feedback theory.

This concludes our design alternative using negative feedback technique.

8. Some basic comparisons with digital technology

As mentioned in Introduction, with digital high-tech so advanced the digital hearing aid dominates the market as well as the research and development areas.

However, in addition to its simplicity and cost effectiveness the analog hearing aid technique may still offer some advantages in certain areas. In particular, in comparing the two systems there are some operational factors to consider, and here are a couple of these factors. In digital technique, the incoming voice needs to go through ADC (analog-to-digital conversion), and after being processed the output signal reenters into an inverse process of DAC. This definitely adds to the *path delay* of the signal as well as reducing the *precision accuracy* of the signal due to the double data conversion. In case of analog methodology, however, we have neither of them. The signal stays analog all the way through, and the delay is just equal to the analog propagation delay of the signal through a limited number of devices.

9. Conclusion

A methodology is developed and explained in this chapter that uses nullors and FNPs to design amplifiers for certain frequency profiles. The method is applied for designing audio amplifiers for front-end or stand-alone hearing aids.

The method works as follows: For a given hearing profile (audiogram), a circuit model, called Audiogram Generator Circuit (AGC), is initially constructed. This AGC has the same, or close to, frequency response of the audiogram. Now, because of typical losses in hearing, it is shown that this AGC is all passive for a hearing-impaired patient, and it can be made quite simple and modular. Next, an FNP is used to construct an adaptable amplifier inversely following the AGC frequency spectrum. This amplifier converts the frequency profile (transfer function) of the AGC such that the poles and zeros of the AGC are exchanged and become the zeros and poles of the amplifier circuit. So, when the amplifier is used as a hearing aid, the result will be a flat frequency response for the comprehended voice heard by the patient. A second design method is also introduced in the chapter, which use the negative feedback theory. Although not a powerful as the FNP method, the feedback technique is modified for impedance matching.

The FNP design is further extended to cover the cases in which extra gain, and in general some added frequency profile is needed. This feature may help to enhance signals in certain frequencies for clear understanding, or conversely, cancel some unwanted sounds and noises. Here, it is shown how the original amplifier can be modified by adding some sub-circuits to the original AGC without touching any other part in the amplifier (such as Op-Amp circuits). Three examples of actual cases of hearing-impaired patients are worked out.

Author details

Reza Hashemian
Department of Electrical Engineering, Northern Illinois University, DeKalb, Illinois, USA

*Address all correspondence to: reza@niu.edu

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Section 5

Implementation Strategies in Public Health

Chapter 10

Childhood Hearing Loss in Developing Countries: From Multidisciplinary Team Work to Public Health

Francis Msume Banda and Britt Nakstad

Abstract

This chapter will highlight the common causes of hearing loss in children and emphasize on the fact that most of the hearing loss is due to causes that are preventable. We know that hearing loss in childhood not only impacts on the child's learning and social interaction with the child's peers and society, but also has economic implications when the child grows into an adult. Public health awareness is therefore paramount in preventing a large chunk of the hearing gloss and therefore greatly contributes to making sure that the child grows into a productive citizen of the society that the child grows or lives in.

Keywords: Hearing loss, children, pediatrics

1. Introduction

Hearing loss can be mild i.e. 20–40 decibels (dB) hearing level (HL), moderate (41–60 dB HL), severe (61–80 dB HL) or profound (81 dB HL or greater) [1, 2]. The term "Minimal Hearing Loss" refers to any of the following hearing loss categories: unilateral hearing loss (at least 20 dB HL in the impaired ear), mild bilateral hearing loss (20–40 dB HL in both ears), or high-frequency hearing loss (at least 25 dB HL at two frequencies more than 2 KHz in both ears) [3, 4]. Hearing loss is disabling if it exceeds 30 dB in the better hearing ear in children before the age of 15 years [1], or more than 40 dB in older individuals [1, 5].

Hearing loss can also be classified as conductive, sensorineural or mixed. Conductive hearing loss occurs when the child hears bone-conducted sound signals better than the air-conducted signals, and can be traced to problems in the outer or middle ear while having a normal inner ear function. Sensorineural hearing loss occurs when there is a problem in the inner ear or beyond, i.e. in the cochlea along the 8th cranial nerve or in the brain. Mixed hearing loss occurs when a child has both conductive and sensorineural hearing loss in the same ear [6]. Most cases of profound hearing loss tend to be sensorineural, which was estimated in the year 1999 to have a worldwide incidence of 1 in 2,000 live births and to affect 6 per 1,000 children by the age of 18 years [7]. In South Africa, Le Roux et al. reported that in the year 2015, approximately 95% of under-5 children with profound hearing loss had sensorineural hearing loss [8].

Hearing loss has been described as the most common disabling condition worldwide [9]. In 2018, global estimates by the World Health Organization indicated that 460 million people worldwide i.e. approximately 5% of the world population, live with disabling hearing loss, and the number is expected to exceed 9% by the year 2050 [10]. Around 7% of the people with disabling hearing loss are children and it is very worrisome to note that 5 out of every 1000 infants are born with or develop disabling hearing loss in early childhood [11].

Most of the people with hearing loss are found in developing countries [5, 12], where it has been estimated that at least 2000 infants with hearing loss are born daily [13], highlighting the grave need for more attention to hearing loss in these parts of the world.

2. Causes of hearing loss

Genetic causes account for 50–60% of hearing loss in babies [14] and approximately 80% of prelingual hearing loss [15]. In both cases, a majority of the hearing loss is sensorineural [16]. Genetic hearing loss tends to be quite prevalent in regions where consanguinity is very high, especially where marriage among first cousins occurs quite often [17, 18]. However, most hearing loss in children overall is non-genetic.

In young children, mild and moderate grades of hearing loss are most commonly caused by either acute otitis media or otitis media with effusion [19]. Chronic ear infections feature highly among the leading causes of hearing loss worldwide [11, 20]. Over 30% of hearing loss in children is resultant from diseases such as measles, mumps, rubella, meningitis and ear infections [11]. Furthermore, greater than 19% of childhood hearing loss in the world is attributable to meningitis and rubella alone [21]. Estimates indicate that bacterial meningitis is attributed to causation of at least 6% of all cases of sensorineural hearing loss in children [17, 22, 23], and ranks as the most common cause of acquired sensorineural hearing loss in infants and children [17]. Congenital rubella syndrome ranks among the foremost causes of acquired hearing loss in countries that do not have a rubella vaccination programme [24, 25].

Noise from toys, cell phones and personal listening devices is a concerning and rising cause of hearing loss among school-aged children [17]. Over time, more and more children are being exposed to hazardous levels of noise, and children's hearing levels are vulnerable to these exposures [26]. It is known that repeated exposure to loud sounds for prolonged periods irreversibly damages the delicate hair cells lining the basilar membrane of the cochlea, thereby leading to sensorineural hearing loss [27, 28]. This damage is often insidious and incremental [17, 29, 30]. It was reported in 2001 that 1 out of 12 children aged 6–11 years in the United States of America already had noise-induced shifts in their hearing thresholds [26]. The World Health organization has estimated that 1.1 billion people aged between 12 and 35 years are at risk of developing hearing loss due to noise exposure in recreational settings such as concerts and sporting events and through the use of personal audio devices [11]. Obviously, noise- induced hearing loss is largely preventable through raising awareness of risks, legislation and following safe listening practices [11].

Treatment in a neonatal intensive-care unit is another risk factor for hearing loss in children, especially during the neonatal period [31, 32]. This has been estimated to increase the likelihood of neonatal hearing loss tenfold [33], more especially if the child is admitted in the neonatal intensive care for more than 5 days [8, 34, 35] believed to be due to its frequent association with comorbid conditions known to

cause hearing loss, e.g. neonatal hyperbilirubinaemia [8, 36, 37], congenital infections [38], prematurity, aminoglycoside use, and mechanical ventilation [17], as well as any other serious illness in the neonatal period [39]. It is quite reassuring to note, from the foregoing, that most causes of hearing loss in children are treatable and preventable [9]. This has been the observation in at least two-thirds of all cases of hearing loss in the African region, where more than half of the hearing loss in the preschool population could be linked to middle ear infections and cerumen impaction [40].

3. Effects of hearing loss

Hearing is closely linked to the development of language and speech in young children [41, 42]. Significant lags in language development, cognition and academic achievement have been noted to result from childhood hearing loss [5, 17, 43, 44]. Compared to children with normal hearing, children with hearing loss have significantly lower reading comprehension, literacy skills, socio-emotional development and academic achievement [45, 46]. It has been reported that children with hearing loss often have a reading ability that is at a lower level than what is expected for the class they have been enrolled in, even by the time they graduate from high school [47]. There is increasing evidence that the mathematical scores of children with hearing loss are significantly lower compared to those of normal-hearing children, from pre-school all the way to high school [48, 49].

These facts have been observed even in children with mild and moderate hearing loss [9, 50–53]. A failure rate as high as 37% for at least one grade has been reported among students with minimal hearing impairment versus 3% for normal hearing students [3]. It has also been reported that children with minimal hearing loss often display a reduced capacity to multitask [54]. Children with minimal hearing loss, quite sadly, may only be identified much later in their education [55] because the children who have higher degrees of hearing loss tend to be diagnosed earlier, and so they are more likely to receive attention sooner than those with lesser degrees of hearing loss [56, 57]. Minimal hearing loss is, therefore, "not inconsequential" [58]. It should be brought to the fore that all the challenges faced by children with minimal hearing loss, as described here, occur among these children irrespective of the type of minimal hearing loss, be it unilateral, mild bilateral or high-frequency hearing loss [4, 59, 60].

All these observations make children with hearing loss to have a reduced chance of being enrolled into tertiary and vocational institutions [61]. A hearing assessment is therefore highly recommended for every child at the time of school enrolment, and more especially for those who have a low rate of academic performance [42].

Without early intervention, the poor academic performance of children with hearing loss persists [55], and this then leads largely to significant economic impacts both in their childhood and adulthood [10]. For instance, in the year 2000, severe to profound hearing impairment was estimated to cost the taxpayer $297 000 over the lifetime of an affected individual in the United States, and this lifetime cost was projected to exceed $ 1 million in children with prelingual onset of their hearing loss [62]. In the year 2015, annual global costs of unaddressed hearing loss of at least moderate degree in children aged between 5 and 14 years were estimated to lie between US$ 750–790 billion [63, 64]. Of these, US$ 67 to 107 billion were costs to health care systems, excluding costs of hearing devices and cochlear implants, and US$ 4 billion were costs to the education sector, including special needs. It is concerning to note that 63–73% of the total costs are incurred in developing

countries, and approximately 10% of all these costs are among the people who have hearing loss in the sub-Saharan African region [63]. In the same year, the total average medical costs in South Africa for a child in the first 5 and 10 years post–cochlear implantation were estimated at $27 000 and $40 000 respectively [8]. Adults who have hearing loss have challenges at the workplace, which can be translated into productivity costs. Globally, these costs were estimated at US$ 105 billion in 2015 [63]. The reasons for the productivity costs in people with hearing loss are manifold, and lucidly highlight the relationship between hearing ability, employment and socioeconomic status. There is overwhelming evidence to suggest that most adults with hearing loss have fewer opportunities for employment compared to those with normal hearing [65–71] and go into retirement earlier than their normal- hearing counterparts [70, 72]. Furthermore hearing loss restricts both people's career opportunities and their levels of income. Most adults with hearing loss have less income [70] as they are more likely to have completed elementary education only [71] or may not even have received any schooling at all, as it so often happens in developing countries [64]. Productivity costs contribute the biggest chunk to the costs incurred due to hearing loss [62, 63]. Both a lack of intervention services for people with hearing loss and a lack of access to the few services that are available have been postulated as being significantly contributory to the proportionally higher unemployment levels among people with hearing loss in developing countries [5].

4. Delayed diagnosis of children with hearing loss in developing countries

It is therefore very important that hearing loss in children should be identified as early as possible, in order to optimize language, cognitive and social development as well as reduce the economic impact of hearing loss as described above. However, it is sad that in Africa, a good number of children with hearing loss are diagnosed late. For instance, the only study among children with hearing loss in Botswana reported in the year 2018 that the median age at which children were first referred for hearing screening to the audiology clinic of the country's main tertiary hospital was 6.7 years [73]. This finding is rather concerning, considering that children get enrolled into standard 1 of the primary school classes when they reach the age of 6 years in Botswana. Retrospective data analysis in an audiology clinic in the Free State Province of South Africa showed median ages of 3.4 years and 3.7 years at first visit and at diagnosis, respectively [74]. Le Roux et al. characterized a cohort of children from Gauteng and Free State Provinces in South Africa and reported late diagnosis of profound hearing loss with a mean age of 1.3 years at first diagnosis. The delay in both referral and diagnosis resulted in more delays in initial hearing aid fitting, early intervention services and cochlear implant placement occurring at 1.57 years, 1.62 years and 3.6 years respectively [8]. Late diagnosis of hearing loss used to be a common occurrence in first-world countries before they introduced universal screening for hearing loss there. For example, in 1998, the mean age of diagnosis of permanent hearing loss in Germany was 6.2 years for mild hearing loss, 4.4 years for moderate hearing loss, 2.5 years for severe hearing loss and 1.9 years for profound hearing loss [57]. Though not frequent, late diagnosis does occur even in those areas of the world where a universal neonatal hearing screening programme is in place. For instance, in one region of Canada in 2018, children were first assessed for possibility of hearing loss at a median age of 3.7 months, only to be confirmed as having hearing loss at a median age of 13.8 months [75].

5. The value of early diagnosis of hearing loss

Early detection and treatment of children with hearing loss lead to great improvements in health-related quality of life [76], and very effectively mitigate the negative impact of hearing loss on the child's speech, language, educational achievement, and vocational outcomes [5, 8, 10, 55, 65, 77]. Children who are identified as having hearing loss by the time they reach the age of 6 months and receive appropriate intervention have significantly better language scores than those who are identified at a later age, irrespective of sex, socioeconomic status, ethnicity, associated disabilities and severity of the hearing loss [41, 40, 78]. Furthermore, these early-identified children go on to have average language scores that fall within the normal range by the time they reach the ages of 1 to 5 years, matching the scores of their peers who have no hearing loss [5, 13, 41, 44, 56, 78–82]. This observation gets even better when the children are identified between the ages of 0 and 2 months [79].

It is now confirmed that when identification of and intervention for childhood hearing loss occur before the child reaches the age of 6 months, he/she performs as much as 20 to 40 percentile points higher on school-related measures (vocabulary, articulation, intelligibility, social adjustment, and behavior). There is, therefore, an urgent need to identify infants with hearing loss as early as possible, preferably before they reach the age of 6 months so that appropriate interventions can be instituted the soonest [41, 83, 84].

6. Caring for children with hearing loss requires a multidisciplinary approach

The care of children with hearing loss requires a multi-disciplinary approach so that they are enrolled into multiple early intervention services i.e. habilitative, rehabilitative, or educational programmes as soon as possible while they are still within the most sensitive time period for optimal language and communication development. Children need over 20,000 hours of parent-infant interactions and listening experience in the first 5 years of life to create a neural framework for both spoken language and literacy of the child [85].

These intervention services include the fitting of hearing aids and frequency-modulation devices (especially for children with bilateral sensorineural hearing loss) and cochlear implants, coupled with special auditory training, of which sign-language education plays a vital role [17, 86]. The proper management of a child with hearing loss requires the availability of specialized medical staff like pediatricians, family physicians, audiologists, otolaryngologists, educators of the deaf, speech language pathologists and medical geneticists to work in concert [45].

6.1 Provision of hearing aids

Guidelines on childhood hearing loss developed by the World Health Organization recommend that children with moderate to severe hearing loss in the better ear in the frequency range of 500 Hz to 4 kHz should be prioritized for hearing aids and services as these are the children who are expected to derive the most benefit from hearing interventions [87]. There is a dire shortage of hearing aids for people with hearing loss worldwide, and the current rate of manufacturing is only enough for 10% of people requiring the hearing aids utmost [5]. This is quite a worrisome state for developing countries, where approximately 20% of people with hearing loss qualify for hearing aids [5], and yet the available hearing aids are enough for only 3% of these people [64].

6.2 Fitting of cochlear implants

Cochlear implants are generally reserved for those children who fail to derive substantial benefit from hearing aids and sustained auditory training. It has been reported that both the quality of life, speech performance and the academic performance of such children improves impressively following cochlear implantation, with better results observed when the implantation is done at a younger age [17, 88]. For instance, it has been shown that after one year post- implantation, children who receive cochlear implants at an early age achieve significant improvements in speech perception compared to those who receive them later, regardless of the cause of or the age at onset of hearing loss [89]. Similarly, it has also been demonstrated that the performance of children with hearing loss is directly proportional to the length of cochlear implant use and inversely proportional to the age at which the implant is placed, with the children implanted between the ages of 12–36 months outperforming those implanted at 36–60 months [76, 90]. Better still is the finding that the academic performance of children with cochlear implants can fall within 1SD of that of their normal hearing peers, and more than half of these children can enroll into college in later life [91]. In addition to all these benefits, the use of cochlear implants has also been proven to be a cost-effective strategy in the management of hearing loss in children in developing countries of sub- Saharan Africa and Asia [92, 93].

6.3 Early enrolment into speech and language therapy

Teaching sign language to children with hearing loss, coupled with provision of captions and sign language interpretation on television are very beneficial to children with hearing loss [5]. Children with hearing loss who become proficient in sign language very early end up achieving better reading skills [94, 95], receptive and expressive language excellence and better academic performance overall, be it in English reading comprehension, mathematic prowess, et cetera [94]. It is therefore very important that children with severe to profound hearing loss should be enrolled into special education services as soon as they are diagnosed in order for them to be taught sign language early.

7. Public health measures for childhood hearing loss

There are great challenges in developing countries that militate against the early diagnosis and adequate provision of intervention services for children with hearing loss. For instance, most of these countries have both a dearth of the recommended services and meager utilization of those services that are available [96–98]. These countries also have a chronic shortage of specialized personnel that are needed to manage the child with hearing loss vis-à-vis their huge population burdens [96]. In view of these grotesque economic and resource limitations, it is quite prudent for developing countries to focus more on public health, since hearing loss can be avoided through proven cost- effective public health measures [5].

7.1 Making childhood hearing loss a public health priority in developing countries

Owing to its unseen nature, hearing loss in childhood does not attract the attention, in terms of public health funding and services, that is commensurate with the short- and long-term effects that it causes, and should rank among the top public health priorities in developing countries [99]. Up to two-thirds of childhood hearing

loss is preventable through public health actions, like strengthening maternal and child healthcare programmes including immunization, implementing infant and school-based hearing screening at the time of enrolment as well as for those children who consistently have low academic performance, training healthcare professionals in hearing care, making hearing devices and communication therapies accessible, regulating and monitoring the use of ototoxic medicines and environmental noise and raising awareness to promote hearing care and reduce stigma [11].

7.2 Intensification of childhood immunization programmes

Data from more developed countries suggest that the incidence of acquired sensorineural hearing loss has waned owing to better neonatal care as well as sustained robust immunization programmes [17]. In these countries, a good case in point is the marked reduction in the incidence of congenital rubella syndrome following the introduction of the rubella vaccine, with a drastic reduction in congenital rubella syndrome cases by 99% between1969 and 1999 in the United States [100], and from about 50 per year between 1971 and 1975 to just over 20 per year between 1986 and 1990 in the United Kingdom [101]. Furthermore, the incidence of childhood bacterial meningitis in the developed world has reduced significantly with the use of immunizations against *Haemophilus influenzae* type B and *Streptococcus pneumoniae* [19, 102]. The pneumococcal conjugate vaccines have been found to be immunogenic even in children as young as 2 months old [19], and not only have they been noted to have decreased the occurrence of childhood meningitis, but also that of otitis media, where S pneumoniae is the most common bacterial pathogen [103]. Thus a sustained focus on childhood immunization programmes in developing countries should go a long way in preventing both conductive and sensorineural hearing loss in children.

7.3 Introduction of hearing loss screening programmes for children

Both the American Academy of Pediatrics' Joint Committee on Infant Hearing, and the American Academy of Audiology have published guidelines that recommend early detection of and intervention for infants with hearing loss [45, 104]. They place emphasis on the goal of early detection and intervention for hearing loss, which is to maximize linguistic competence and literacy development for children who have hearing loss so that they do not fall behind their hearing unimpaired peers in communication, cognition, reading, and social–emotional development. It is henceforth strongly recommended that all infants should be screened for hearing loss by the age of 1 month. The infants who fail this screening should be referred to audiologists for a comprehensive audiological evaluation before the age of 3 months without delay. If hearing loss is confirmed, the baby should receive appropriate intervention before the age of 6 months [45]. This recommendation has led to the call for and establishment of universal hearing screening programmes in most developed countries, with the notably impressive reduction in the mean age of diagnosis of sensorineural hearing loss from 12 to 18 months to utmost 6 months, thus enabling timely enrolment into early intervention services [105–108] whose benefits have already been described above. Countries which have instituted universal newborn hearing screening have seen dramatic increases in the number of children identified early with hearing loss who achieve normal cognitive ability [41]. Therefore, developing countries need to strongly consider introducing universal newborn hearing screening programmes in their health systems in order to identify children with hearing loss early and enroll them into appropriate intervention services, as data from developed countries continues to prove that the identification

of hearing loss by 6 months of age through universal newborn hearing screening programmes, followed by appropriate intervention, is not only cost- effective in the long- term [109, 110] but is also the most effective strategy for the normal development of language in infants and toddlers with hearing loss [84, 110]. There are challenges with the implementation of universal newborn hearing screening programme in developing countries. In South Africa, for example, despite the efforts of the Professional Board for Speech, Language and Hearing Professions of the Health Professions Council of South Africa (HPCSA) to introduce universal newborn hearing screening in the country and screen 98% of all newborn infants by 2010 [111, 112], hearing screening is still not yet standardized and is being implemented in a haphazard manner, with most health institutions doing the screening at an individual level and mostly targeting those neonates with risk factors for hearing loss [113, 114]. The reasons cited for this state of affairs include the Department of Health's prioritization of life-threatening illnesses instead of hearing loss (thus affecting budgetary allocations) and shortage of health personnel like audiologists [113, 115, 116], as well as a shortage of equipment [117]. It appears that these are the main issues in other developing countries as well [77]. However, it would still be a good step for developing countries to start with targeted screening of infants with risk factors for hearing loss and then escalate to universal screening in future because targeted screening has also been proven to be cost-effective [63, 109, 118], although it may miss close to half of neonates with hearing loss, especially those who may not have obvious risk factors for hearing loss [119]. Given the above challenges regarding the introduction of hearing screening programmes in developing countries, it would be very beneficial if these countries would also focus on improving parental awareness of important speech and hearing milestones in children. No parental concern about hearing loss in a child should be ignored but should rather necessitate immediate scheduling for hearing screening by clinicians to assess for hearing loss [120], as parents often begin to suspect hearing loss in their children way before it is confirmed [3, 45], with a high positive predictive value [121].

As discussed earlier, bacterial meningitis is a leading cause of sensorineural hearing loss in children [17, 22–24]. There are indications that this kind of hearing loss occurs very early in most children with bacterial meningitis [122] and does not improve with the passage of time [123]. It is therefore incumbent on developing countries to make sure that every child who is diagnosed of bacterial meningitis is screened for hearing loss [24].

Developing countries must seriously consider making it mandatory that every child should have a hearing screen at the time of school enrolment. The South African government has taken a commendable lead among African countries by gazetting a school health policy that requires every child to be screened for hearing loss before starting the foundation phase of learning [124]. It would be great if other developing countries would follow suit. The school health policies should go further to require screening for hearing loss for every child whose academic performance is consistently below par [42], on one hand because the magnitude and multiplicity of the academic challenges that children with hearing loss encounter often tend to be much more grotesque than the severity of their hearing loss [17], and on the other because screening for hearing loss among school children has been proven to be a cost- effective strategy [63].

7.4 Introduction and intensification of educational programmes, public awareness and hearing- savvy legislation

Given the high rate of genetic causes of hearing loss in babies [14], developing countries need to focus more seriously on educational programmes in order to

create public awareness sufficient enough to transcend cultural practices and reduce the incidence of genetic sensorineural hearing loss [17]. Furthermore, the public needs to be made aware as much as possible about the deleterious effect of uncontrolled noise exposure both in the home and in the workplace [26]. Governments need to pass legislation for, develop and enforce standards for acceptable range of sound output emanated from toys and make it mandatory for toy manufacturers to issue appropriate warnings about the noise levels that their toys produce [27].

Health care providers need regular refresher courses on prevention of hearing loss in children through the rational use of ototoxic drugs like anti- malarials and aminoglycosides [11]. Primary health care providers should also be trained in primary ear care, as this has been proven to be cost-effective in the reduction of the incidence of chronic ear infections [5].

Policy makers, Health care workers and the public at large need to be made aware that minimal hearing loss is very common [125] and it has as deleterious consequences in children as do the other types of hearing loss [24, 126, 127]. Rather than focus primarily on bilateral hearing loss of higher degrees, health care professionals need to be constantly aware of the negative effects that minimal hearing loss has on the affected child, regardless of its type (i.e. unilateral, mild bilateral or high-frequency hearing loss), as described above.

8. Conclusion

In developing countries, hearing loss should be considered a public health priority for which concerted efforts must be made to prevent it by all means. Children who have hearing loss should be identified as early as possible and be enrolled into appropriate intervention services so that they can enjoy equal opportunities in life. The World Health Organization can contribute greatly in preventing and reducing hearing loss by helping to fund public health programmes and intervention services for hearing loss in developing countries, as well as lobbying developed countries to reduce the costs of hearing aids and cochlear implants.

Author details

Francis Msume Banda* and Britt Nakstad
Department of Paediatrics and Adolescent Health, Faculty of Medicine, University of Botswana, Gaborone, Botswana

*Address all correspondence to: fmbanda@yahoo.co.uk

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The auditory system is one of the finest structures in the human body. Although its anatomical structure is so small compared to other organs, without it, it would greatly affect a person's basic life. Hearing loss, also known as hearing impairment, is a partial or total inability to hear. When people communicate with others, listening is always the first step. That is why Helen Keller once said, "Blindness separates people from things; deafness separates people from people." To avoid the "epidemic" of hearing loss in the near future, it is necessary to promote early screening, change public attitudes toward noise, and wear hearing aids appropriately. Based on the contributions of many authors, whom I sincerely respect, this book incorporates updated developments as well as future perspectives in the ever-expanding field of hearing loss. This book can also serve as a reference for persons who are involved in this field whether they are clinicians, researchers, or patients.

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