Scientific Research Publishing

International Journal of Otolaryngology and Head & Neck Surgery, 2023, 12, 107-123
https://www.scirp.org/journal/ijohns
ISSN Online: 2168-5460
ISSN Print: 2168-5452

Hidden Hearing Loss: Causes, Current Knowledge, and Future Directions

Alexandra Jalkh[1,2]

[1]Department of Otolaryngology, Eye and Ear Hospital, Naccach-Dbayeh, Lebanon
[2]Department of Audiology, Escula de Formacio Superior SAERA, Castellon de la Plana, Spain
Email: alexandrajalkh@hotmail.com

How to cite this paper: Jalkh, A. (2023) Hidden Hearing Loss: Causes, Current Knowledge, and Future Directions. *International Journal of Otolaryngology and Head & Neck Surgery*, **12**, 107-123.
https://doi.org/10.4236/ijohns.2023.123012

Received: February 16, 2023
Accepted: May 14, 2023
Published: May 17, 2023

Abstract

Introduction: Hidden hearing loss (HHL) is a type of auditory disorder that affects the auditory neural processing and hearing sensitivity in subjects with normal hearing thresholds. Unlike central auditory processing disorders, HHL happens when the cochlea (the peripheral auditory organ) is affected. There are several known risk factors to HHL which includes noise exposure, ototoxic drugs, and peripheral neuropathies, and age. Recent studies have shed light on this type of hearing loss, its etiology, prevalence, and how it can affect the auditory acuity in humans. **Methods:** This paper covers the current research regarding HHL, its causes, the different mechanisms involved in this disorder, and the diagnosis and potential treatments related to it. We will delve deeply into different researches concerning HHL. 4 articles from 285 were selected focusing on normal hearing individuals with bad speech intelligibility were discussed in this paper. In addition, articles discussing the effects of noise exposure on hearing impaired individuals were not considered as this study solely aims to focus on normal hearing sensitivity individuals with HHL, resulting in 4 articles from 285. **Results:** Numerous literatures over the decades have suggested that HHL is due to the degeneration of cochlear ribbon synapses, or hair cells synapses without hair cell damage. Their association with HHL was noted several times through this study, whether we were studying the effect of noise exposure, of age, or of ototoxicity. In all cases, no significant hair cell damage was observed, and normal thresholds were recovered. However, a decline in the amplitude of Auditory Brainstem Response (ABR) peak I from auditory nerve (AN) responses in noise exposed subjects and a decline in compound action potential (CAP) was measured when certain drugs were applied to the round window of Guinea pigs. **Conclusion:** Most studies, have proven that cochlear synaptophysin is the major contributor to noise induced, age, and ototoxic related HHL. There are several au-

diometric tests that were used to help identify HHL including Puretone audiometry in background noise, ABR, CAP, Distortion Product Otoacoustic Emission (DPOAE).

Keywords

Hidden Hearing Loss, Speech Testing, Speech Intelligibility, Noise Induced Hearing Loss, Ototoxicity, Schwan's Cells Ablation

1. Introduction

Hearing loss is a common condition, but it can also be difficult to detect. This is especially true for HHL, a type of hearing loss that is not visible in the ear canal or eardrum and presents itself with normal hearing thresholds, but speech intelligibility is affected. While there are many reasons why this type of hearing loss occurs, including medical conditions, aging, and exposure to loud noises, there are things that can be done to protect an individual from it.

In a study conducted by Kohrman *et al.* (2020) [1], it is stated that the most common type of hearing loss is called sensorineural hearing loss (SNHL) and affects about 320 million people worldwide. This type of hearing loss is diagnosed by the presence of elevated audiometric thresholds ranging from mild to profound. It is caused by the degeneration of the cells responsible for the detection and transmission of acoustic sounds through the auditory circuit. These cells include the inner hair cells (IHCs) and outer hair cells (OHCs) as well as the spiral ganglion in the cochlea. However, unlike sensorineural hearing loss, HHL shows normal auditory thresholds yet has "significant perceptual difficulties including understanding speech in noisy backgrounds" (Berdawaj *et al.*, 2015) [2]. This has often been linked to "auditory processing disorder", which indicates a dysfunction in the peripheral auditory system also called "the cochlea". Recent studies have proven that this change can be related to several factors including noise, drugs, age, and peripheral neuropathy that can "alter the neural-evoked output of the AN independently of hair cells loss and changes in hearing thresholds" (Kohrman *et al.*, 2020) [1]. This type of hearing loss is known as HHL and often is not diagnosed by using standard audiological evaluations.

Numerous studies have highlighted that HHL can be caused by exposure to moderate noise. According to Hickox *et al.* (2017) [3], these studies have shown that long exposure to those moderate noises causes either a temporary threshold shift or a permanent threshold shift. In most cases of hearing sensitivity in a case of temporary threshold shift, it is usually recovered and back to normal within a few days or weeks without any outer or inner hair cells loss. However, even after thresholds have recovered back to normal yet "cochlear responses to suprathreshold sound levels are significantly altered" (Kohrman *et al.*, 2020) [1]. Recent studies also have suggested that the desynchrony also knowns as synaptic loss between the inner hair cells and the AN represent the main pathology even in

patients suffering from temporary threshold shifts following noise exposure. In addition, this synaptic loss is independent of the integrity of both inner hair cells and spiral ganglions. When the synapses are damaged, the nerve fibers start to degenerate, which causes HHL due to acute noise exposure.

Age-related hearing loss, in almost all cases, causes a sensorineural hearing loss. The dysfunction is often referred to as presbycusis and is known to be the second most common health related problem among the elderly population. According to Salvi *et al.* (2018), [4] it affects approximately over 40% of patients from 70 years old or more. With age, speech perception in noisy environments is known to decrease even when subjects have normal hearing thresholds. One of the most common complaints among elderly patients, even if they believe to have normal hearing, is conversation in a restaurant, which in a noisy environment, is very hard. However, when conversation is carried out in a quiet environment, there are no difficulties at all, and they can understand everything. "Data obtained from carboplatin-treated chinchillas suggest that tone-in-noise thresholds are a sensitive and frequency dependent method of detecting damage to the IHC/type I system" (Salvi *et al.*, 2018) [4].

Ototoxic medications are known to cause hearing or a balance problem. This can happen when a patient is on a high dose of aminoglycoside antibiotics. For example, gentamicin is known to cause hearing loss among most patients who have taken it. When a drug is ototoxic, it causes damage to the inner and outer hair cells which are responsible for hearing, damage to them would therefore cause hearing loss. Inner hair cells are sensory receptors that transform sound vibration to electrical signals from the cochlear fluid which are then sent through the AN to the auditory brainstem and cortex. Outer hair cells are located near the basilar membrane, they act as an amplifier for low sounds that enter the cochlea with high sensitivity and accuracy. Moreover, exposure to ototoxic drugs can also "induce acute swelling of SGN terminal dendrites, similar to the morphology associated with excitotoxic damage of IHC synapses by noise exposure" (Ruel *et al.*, 2007) [5]. In addition, ototoxic drugs have been linked to CAP synapse loss in the inner hair cells, which in turn usually causes HHL. However, in this precise relationship, it is unclear exactly how the HHL and temporal processing are related, and if ototoxic drugs such as gentamicin can cause it. Not much information linking them has been delivered through studies over the years.

According to Kohrman *et al.* (2020) [1] and Kujawa and Liberman (2009) [6], the decline in synapses number was proportional to the decrease in audiometric responses at the basal regions of the cochlea, which are responsible for high frequencies. However, a damage to the synapses in the inner hair cells has been the only proposed mechanism of HHL, whether it is due to noise exposure, age, or ototoxicity. It is speculated that a damage in cochlear Schwann cells can be another cellular mechanism of HHL regardless of synaptic damage. It is hypnotized that a transient loss on Schwann cells results can be a characteristic of HHL, which is not correlated to hair cells synaptic loss but rather "with disrup-

tion of the first heminodes at the auditory nerve peripheral terminal" (Wan *et al.*, 2017) [7], which identifies a potential mechanism of HHL. In the cochlea, sensory hair cells and neurons are surrounded and myelinated by a type of glial-like cells called Schwann cells. These cells are essential in the peripheral nervous system as they are crucial for the growth, operation, and regeneration of peripheral nerves.

2. Objective

As mentioned before, HHL is very common and can be caused by several factors including noise exposure, age, ototoxicity. There are several audiometric tests that can help in identifying HHL. These include Puretone audiometry in background noise, ABR, CAP, DPOAE.

During an ABR testing, the amplitude of Wave I represents the presence of intact synapses. Therefore, damage to synapses between inner hair cells and AN fibers due to extended noise exposure causes a reduction in the wave I amplitude of the auditory brainstem in subjects with normal hearing thresholds which further indicates the presence of HHL. In a study conducted by Bramhall *et al.* (2017) [8], veterans and non-veterans, who were exposed to high noise levels due to the use of firearms, were compared to veterans and non-veterans with lower levels of noise exposures, both of which had normal hearing thresholds. ABR responses to a tone burst stimulus for the frequencies 1000 Hz, 3000 Hz, 4000 Hz, and 6000 Hz noted a smaller wave I amplitude in veterans and non-veterans that are exposed to high levels of noise compared to those who are exposed to low ones.

In a study performed by Salvi *et al.* (2018) [4], the performance of elderly patients was compared to younger patients with similar threshold in a quiet environment were tested again except in a noisy environment. Thresholds in noise for elderly subjects are expected to be worse than thresholds in noise for younger subjects, even though both groups had similar hearing thresholds in a quiet background. This highlights the significance of repeating measurements in broadband noise (BBN).

High doses of aminoglycoside antibiotics like gentamicin are known to cause a threshold shift since it damages inner and outer hair cells, which is why their use is largely restricted. In a study performed by Ishikawa *et al.* (2019) [9], the ototoxicity of various aminoglycoside drugs was tested for the effect of dosage of the aminoglycoside drug on outer hair cells, inner hair cells, synapses, and whether a reduction in dosage can still be a cause of HHL.

The consequences of removal of Schwann cells in the cochlea were also investigated. It is believed that severe loss of Schwann cells "causes rapid auditory nerve demyelination, which is followed by robust Schwann cell regeneration and axonal remyelination" (Mellado *et al.*, 2014) [10], which can in turn be a cause of HHL. This however is believed to differ from what was observed when studying the effects of noise exposure, aging, or ototoxicity, as it appears

without a decline in hair cells synapses. Instead, it correlates with "permanent disruptions of the first heminodes at the auditory nerve axon close to the IHCs" (Wan *et al.*, 2017) [7]. If correct, this study would unravel a new mechanism of HHL.

3. Methods

An intensive analysis of existing literatures from 2005 to 2021, filled with findings from various researches was conducted to test the relationship between noise exposure, age, ototoxicity, Schwan cell ablation and HHL. The main database used for this review was PubMed using the keywords "hidden hearing loss, noise induced hidden hearing loss, age related hidden hearing loss, ototoxicity and hidden hearing loss, pathologies and causes of hidden hearing loss", and over twenty-five studies were preliminarily found. However, only articles based on evidence best practice procedures, achieving a good reliability and validity were selected and discussed in this review. The selection procedure is displayed in **Figure 1** below. In addition, articles discussing the effects of noise exposure on hearing impaired individuals were not considered as this study solely aims to focus on normal hearing sensitivity individuals with HHL, resulting in the detailed review of the results section of four different articles taken from the initial twenty-five.

4. Results

The aim of this literature review is to review the main causes of HHL and the appropriate tools to diagnose it based on its different causes which include noise exposure, age, ototoxicity, and Shawn cells ablation. In the following section, four main articles focusing on these different causes were explored in detail to show if a correlation between them and HHL is present or can be disproved, as well as investigate the best method to identify and diagnose this condition. A summary of the findings in each of the studies reviewed can be found in **Table 1**.

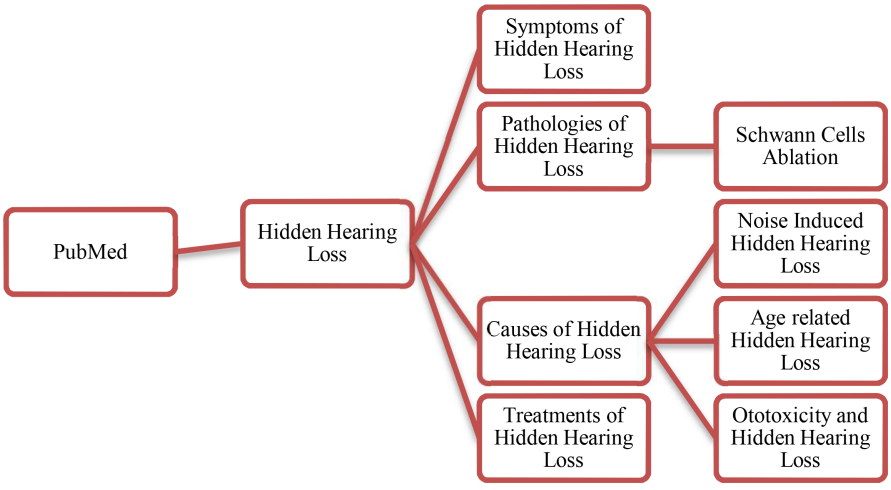

Figure 1. Literature selection procedure.

4.1. Detecting Noise Induced Hidden Hearing Loss in Subjects Using Puretone Audiometry and ABR

The study by Nam *et al.* (2021) [11] reviewed above was used in this paper to link and diagnose noise exposure to HHL using ABR and Puretone audiometry among other audiological evaluations.

In this study, audiological data of 15 patients (24 ears) with the following characteristics: noise exposure history, no history of neurotological disorders, normal Puretone audiometric and immittance results, present DPOAEs, and normal ABR wave I III and V were compared with 12 control subjects (24 ears) selected with the following criteria: no history of noise exposure, normal audiogram and no noise exposure.

In pure tone audiometry, no significant differences were observed between the control group and noise-exposed group for frequencies ranging from 250 to 8000 Hz. ABR was conducted using click stimuli at 90 dB SPL, the ABR amplitude of Wave I and Wave V as well as the interpeak interval between Wave I and Wave V did not show significant change between the noise exposed and the control groups when taking into consideration male subjects only.

The results of this study fail to link a history of noise exposure to HHL, which therefore disproves the theory that noise exposure can be a major effect and is correlated to HHL.

4.2. Detecting Age Related Hidden Hearing Loss Using Puretone Audiometry in Noisy Environment

The study by Salvi *et al.* (2018) [4] reviewed above was used in this paper to correlate age and HHL using and Puretone audiometry among other audiological evaluations.

To detect if age can be related to HHL, this study divided its cohort into two groups: a group of younger subjects with ages ranging between 19 - 24 and a group of older subjects with ages ranging between 54 - 71. All participants had a normal audiometric threshold of 25 dBHL in a quiet environment for frequencies ranging from 250 Hz to 8000 Hz.

Subjects were then tested in a noisy environment, using BBN in the background at 20 dBHL and then at 30 dBHL. At 20 dBHL, the threshold for young subjects stayed almost identical, while nearly all elderly subject's thresholds were above the mean threshold of normal subjects and outside normal range. In contrast, at 30 dBHL, young subjects experienced an increase in threshold from a mean of 20 dBHL to 30 dBHL. Elderly patients also experienced a greater shift in responses especially at high frequencies well above the mean threshold of younger subjects.

The results of this succeed in linking the age and environment of an individual to HHL, which therefore proves the theory that age can have a major effect and is correlated to HHL.

4.3. Detecting Hidden Hearing Loss Due to Dose Dependent Aminoglycoside Ototoxicity Using Animal Models

The study by Ishikawa *et al.* (2019) [9] reviewed above was used in this paper to investigate a possible correlation between ototoxicity and HHL using different doses of aminoglycoside. Aminoglycosides are a type of antibiotic, approved by the Food and Drug Administration (FDA), that are used to treat infections. A major side effect of these types of drugs is hearing impairment, it is believed that these antibiotics cause a permanent damage to sensory cells and neurons within the inner ear resulting in the hearing loss.

To test the relationship between ototoxicity and HHL, five aminoglycoside medications, three of which are still commonly used despite known ototoxicity, were selected and tested for ototoxicity on 45 Guinea pig models which included: Neomycin, gentamicin, paromomycin, apramycin and gentamicin C1a. Each of the 5 drugs antibacterial activity was compared and analyzed for three different aminoglycoside dosages: 60 mg/mL, 210 mg/mL, and 420 mg/mL to analyze long-term ototoxic effects on thresholds shift.

Threshold differences were noticed for all three concentrations of all five drugs starting within 60 to 90 minutes and then for days. CAP thresholds shift were observed on day 21 for 60, 210, & 420 mg/mL groups. It was also noted that higher frequencies (above 4 kHz) were more affected than lower ones which suggests changes in the basal region of the cochlea and a significant decrease in outer hair cells at the 420 mg/mL was observed compared to the 60 mg/mL.

The results of this prove that there is a dose dependent correlation between CAP and outer hair cells. Therefore proves the theory that aminoglycoside medications can have a major effect and is correlated to HHL.

4.4. Detecting Hidden Hearing Loss due to Schwann Cells Ablation Using Animal Models

The study by Mellado *et al.* (2014) [10] reviewed above was used in this paper to show how Schwann cells ablation can be related to HHL using ABR among other audiological evaluations on animal models.

To test the consequences of Schwann cells ablation and its causes on HHL, pathogen-free mice [12] from both genders were used.

When mice were injected with a tamoxifen from the postnatal age of 21 to 23 an ABR was performed at 1, 4, 8, and 16 weeks from injection time. Three differences were noted: A reduction in the Wave I amplitude, an increase in Wave I latency, and an increase in widths at all periods when stimulus was presented at 70 dB SPL.

These results suggest that Schwann cells ablation resulted in an impairment of the auditory system. Additionally, a change in APs and SPs was also noted after Schwann cells ablation. Through all periods of time the SP amplitude of DTA was not affected. However, a reduction in the AP of ABR peak 1 in DTA and an increase in the SP/AP ratio were noted.

4.5. Summary

Table 1. Summary of results.

Author	Participants	Factors	Results	Conclusion
Nam *et al.* (2021) [11]	15 patients (24 ears)	Noise Exposure	Pure tone audiometry from 250 Hz to 8 kHz: No significant threshold differences were observed between the control group and noise-exposed group. ABR at 90 dB SPL: Amplitude of Wave I, Wave V, and interpeak interval between Wave I and Wave V did not show a significant change between the noise exposure and the control groups.	Noise Exposure No significant differences were observed between the control and noise exposed group
Salvi *et al.* (2018) [4]	10 young patients (mean age of 20.09 years) 6 elderly patients (mean age of 62.66 years)	Age	Subjects were then tested in a noisy environment by using BBN at 20 dBHL and then at 30 dBHL 20 dBHL: • Young subjects threshold stayed almost identical. • Elderly subject's thresholds were above the mean threshold of normal subjects and outside normal range. • 30 dBHL: • Young subjects experienced an increase in threshold • Elderly patients also experienced a greater shift in responses especially at high frequencies above mean threshold of younger subjects.	Significant threshold shift was observed when presenting broadband background noise at 30 dBHL in both groups. Elderly patients were more affected especially at higher frequencies which explains poorer speech intelligibility compared to the control group.
Ishikawa *et al.* (2019) [9]	45 guinea pig models	Aminoglycoside (AG) induced ototoxicity	Five aminoglycoside medications were tested for dose dependent ototoxicity. Namely, neomycin, gentamicin, paromomycin, apramycin, gentamicin C1a. At three different dosages: 60 mg/mL, 210 mg/mL, and 420 mg/mL. Threshold differences were noticed for all three concentrations of all five drugs at different times ranging from minutes to days.	A direct correlation was observed between the different aminoglycosides dosages and threshold shifts especially at high frequencies. There is a deterioration in the integrity of the cochlear amplifiers, also known as the outer hair cells (OHCs) which could also explain poorer speech intelligibility.
Mellado *et al.* (2014) [10]	Pathogen-free mice from both Genders [12]	Schwann cells ablation	When mice were injected with a tamoxifen from P21 to P23, an ABR was performed at 1, 4, 8, and 16 weeks from injection time. Three differences were noted at all periods when stimulus was presented at 70 dB SPL: 1) Reduction in the Wave I amplitude 2) Increase in wave I latency 3) Increase in widths A reduction in the AP of ABR Peak 1 in DTA and increase in the SP/AP ratio was noted.	Schwann cells ablation resulted in an impairment of the auditory system.

4.6. Comparison of Results

Noise exposure was explored in two different ways in this section Nam *et al.* (2021) [11] introduced noise as a previous exposure within a patient's history, while Salvi *et al.* (2018) [4] used noise as an effect during testing. When subjects of all ages who were previously exposed to noise were tested for Puretone audiometry in a quiet environment, no significant changes were observed, while when young and elderly subjects were tested in a noisy environment (a BBN of 30 dB), a decrease in threshold was noted for both groups and a decrease in high frequency was noted for elderly subjects. Similarly, the research by Ishikawa *et al.* (2019) [9] studied different dosages of 5 aminoglycoside (AG) drugs and their effect on hearing. In this study, a threshold shift was also observed especially at higher frequencies. Both studies explain the difficulty in speech intelligibility since a hearing loss at high frequencies points to changes in the basal regions of the cochlea and therefore a loss of OHCs.

During their study, both Nam *et al.* (2021) [11] and Mellado *et al.* (2014) [10] tried to identify HHL using ABR measurements. Just like before, when subjects who were previously exposed to noise were tested for ABR in a quiet environment, Amplitude of Wave I, Wave V, and interpeak interval between Wave I and Wave V did not show a significant change between both groups. However, when studying Schwann cells ablation, mice were injected with a tamoxifen and tested for ABR, a reduction in the Wave I amplitude, an increase in wave I latency, and an increase in widths at all periods when stimulus was presented at 70 dB SPL was observed. Wave I represent the distal portion of the AN, and a decreased amplitude, increased latency and width in this wave usually points to hearing loss. It also points to a loss of OHCs integrity which further explains the difficulty in speech intelligibility.

These four studies suggest that patient history, age, ototoxic drugs and the environment in which the audiological evaluation was performed all played a major role in identifying HHL, whether using Puretone audiometry or ABR, subjects case history should be studied in detail prior to testing, the age range should not be too broad and Puretone audiometry should not be only conducted in a quiet environment but rather in a noisy one.

5. Discussion

5.1. The Correlation between Noise Exposure and Hidden Hearing Loss

For decades, researchers believed that noise induced hearing loss (NIHL) caused damage to the outer and, however, recent studies have suggested that "the synapse between IHC and SGNs with low spontaneous firing rates and high thresholds are the most vulnerable" (Nam *et al.*, 2021) [11] to noise exposure. Sometimes, this dysfunctions in the synapses can be hidden and occur without any audiometric threshold shift. Animal studies and experiments were made concerning cochlear synaptopathy over the decades and were described as the most

likely mechanisms to cause HHL due to noise exposure. Similar studies were made concerning humans. The most likely and reliable diagnostic method of HHL in humans was ABR analysis. In an ABR, Wave I represents AN function. In animal models, when the synapses are affected, the amplitude of wave I would be affected. In animal models, the extent of the damage in the synapses is correlated to the amplitude of wave I. However, since human testing for HHL is not easy, measurements of Wave I are complicated in ABR recordings as several factors can affect the amplitude of Wave I. These include age, gender, type of stimulus, and recording method. According to the literature mentioned above, "the amplitudes were decreased with more extensive noise exposure history in females, but not in males, highlighting the significance of sex as a confounding factor" (Nam *et al*., 2021) [11] when testing for noise induced HHL, this is due to wave I amplitudes are smaller for male subjects than for females despite similar hearing thresholds which shows the importance of gender as a factor to take into consideration. Numerous similar studies tested patients with normal hearing thresholds and found no significant effects on ABR wave I due to noise exposure in both genders.

For example, in another study performed by Grinn *et al.* (2017) [13], participants were exposed to noise to investigate the presence of HHL. The subjects presented themselves with normal hearing thresholds prior to noise exposure and "there were no permanent changes in the participants' audiometric, electrophysiologic, or functional measures" (Nam *et al*., 2021) [11] which further proves that acute exposure to noise did not cause any changes in ABR waves. Another way suggested to diagnose HHL is the use of electrocochleography (ECoG), "since inter- and intra-subject variability may mask or exaggerate small differences in amplitude and the ratios of amplitudes of ABR wave I/wave V, the AP/SP values yielded by ECoG can be used instead" (Bramhall *et al*., 2017) [8]. However, big disadvantages in these studies would be due to lack of data on lifelong exposure to noise which is an important factor to take into consideration during testing. Researchers have found that the best solution to estimate a subject's noise exposure is by using questionnaires, which would be highly valuable for future testing.

Other disadvantages that many studies over the decades have failed to take into consideration prior to testing was their subject's speech perception in noisy environments. As we have mentioned before, word recognition in noisy environments despite normal thresholds has been a major symptom of HHL. "It has been suggested that poorer word recognition in noisy and difficult listening conditions might be related to cochlear synaptopathy. Studies have suggested that a test battery including electrophysiological and behavioral evaluations would be more reliable than a single test to identify the HHL caused by cochlear synaptopathy in subjects with normal hearing in conventional audiograms." (Liberman *et al*., 2016) [14] In most cases, pure tone audiometry and speech recognition are usually done in quiet environment, testing subject performance in noisy ones would be much more useful.

5.2. The Correlation between Age and Hidden Hearing Loss

The findings suggest that older individuals struggle more than younger individuals to detect tone in a noisy environment, especially at high frequencies. High frequencies are responsible for understanding speech therefore hearing impairment at high frequencies will affect speech understanding. This agrees with elderly patients' main complaint: "One interpretation of the tone-in-noise data from elderly with 'normal hearing' is that their IHC or high-thresholds type I fibers are damaged except near 1 kHz region." (Salvi *et al*., 2018) [4]. Usually, when performing Puretone audiometry, the testing is done under unrealistic conditions which include an extremely silent environment. A realistic environment would be communication and testing in a noisy background which would increase the intensity of hearing loss: "Aging subjects show declines in neural coding of the temporal features of sound that are likely important for speech perception in noise, and such deficits can also occur independently from increases in thresholds" (Marmel *et al*., 2013) [15].

Some studies have shown that a decrease in ABR peak of wave I for elderly patients would agree with cochlear neuropathy and could prove the defects in temporal processing. Studies performed on mice have also shown a 50% decrease in ABR wave I peak amplitude which progresses over time. This decrease is consistent with the decrease in wave I amplitude due to IHCs synapses loss, which in turn contributes to age-related HHL.

According to several researches on human and animal subjects, it was proven that damage to the inner hair cells and type I neurons, which are responsible for transmitting and translating information from the ear to the brain, can cause hearing deficiency in noisy environments. This proves an efficient way to detect a person's hearing loss is by measuring tone detection thresholds in BBN rather than a quiet environment through different specific frequencies.

5.3. The Correlation between Ototoxicity and Hidden Hearing Loss

The studies also indicated a dose dependent toxicity in all five drugs. No hair cells loss or action potential threshold shifts were observed when the lowest dosage of the aminoglycoside drugs was applied to the round window. However, neomycin and aromomycin, unlike apramycin and gentamicin C1a, caused damage to the inner hair cells and synapses. When dosage was increased, a reduction in the mechanoelectrical transduction of inner hair cells was also observed. Recent studies have shown that Aminoglycosides are believed to "initially cause stereociliary damage, which will be followed by HC loss, mainly of OHCs in the basal (high frequency) region, which have been considered to date as the most vulnerable element of the inner ear to AG treatment" (Ishikawa *et al*. 2019) [9].

However, as mentioned previously, noise exposure can lead to hair cells degeneration even when normal thresholds are observed. "A reduction of up to 50% of the synapses between IHCs and cochlear neurons can occur. The same

primary loss of cochlear synapses occurs in the aging ear" (Viana *et al.*, 2015) [16] which is referred to as HHL. An interesting common aspect between the use of ototoxic drugs and HHL is established during this study. In both cases, inner hair cells synapses can be damaged while outer hair cells remain intact. this proves that inner hair cells are one of the most vulnerable elements for ototoxic medications in the inner ear. These observations in turn support the correlation between inner hair cells synapses, the amplitude of cochlear neural responses such as ABR, both of which can be influenced by noise exposure and age regardless of hearing threshold.

5.4. The Correlation between Schwann Cells and Hidden Hearing Loss

It was observed that the mice had a dramatic demyelination, it is assumed significant hearing impairment soon after the injection. That however would be solved during the next 4 months as during which the damaged nerve remyelinated. ABR threshold and DPOAEs which represent the function of inner and outer hair cells were not affected by this change. This shows that the mice had a normal threshold despite demyelination. However, based on the above results, mice suffering from Schwann cell ablation showed that the ABR wave I amplitude, which reflects the SGNs activity, was significantly reduced, and the latency and width, which represent the function of the AN, severely increased. When tested 4 months after injection, the effects did not reverse, even after remyelination of Schwann cells.

To further support the hypothesis that Schwann cells ablation can cause HHL even after remyelination, an analysis of the amplitude of SP/AP ratio, which is often used for the diagnosis of HHL, was performed. SP amplitude, if altered, would show the correlation between Schwann cells damage and hair cells function, was not affected within all timeframes. This proves that there is no link between the two. However, Wave I AP amplitude was reduced through all time points suggesting a neural dysfunction within the cochlea. Moreover, SP/AP ratio was also significantly reduced through all the time points. These results prove that there is no correlation between Schwann cells ablation damage and hair cells damage, but rather support the hypothesis that Schwann cells ablation results in a cochlear auditory neuropathy and HHL even after remyelination.

5.5. Diagnosis and Possible Treatments of Hidden Hearing Loss

As we already know, a major complaint of people affected by HHL is speech perception in a noisy environment despite normal audiometric thresholds. Through animal studies, it was proven that the amplitude of ABR Wave I is correlated with the function of synapses. Several studies on young subjects with normal hearing thresholds have found a link between difficulty in speech perception in noisy environments and changes in auditory evoked potentials (ABR Wave I amplitude) that are consistent with synaptic damage. A study based on veterans with normal auditory thresholds noted a correlation between a change

Wave I amplitude and noise exposure. However, another study detailed in this paper failed to find any link between the two.

More detailed research should have been done in this field as several factors could have affected the results. The above studies also concluded that synaptic damage could occur without any significant hair cells damage which is why a subject shows no hearing loss during Puretone audiometry. As we have seen from patient complaints, it is the reason why they have a difficulty understanding speech in noisy environments. Since current federal guidelines in the workplace are based on "the assumption that exposures producing no PTSs are benign" (Arenas *et al.*, 2014) [17], a change in these guidelines should be considered to prevent HHL.

Usually, hair cells in the cochlea cannot be replaced once damage. Although it is believed that some hearing impairments in sensorineural hearing loss might be treatable or even preventable. Multiple studies have stated that damaged hair cells and neurons can never be replaced. However, several animal studies have shown that a limited amount of hair cells could be regenerated via transdifferentiating other supporting cells. It has been demonstrated that the repair of cochlear synaptopathy due to an "extended therapeutic window in which the hair cell targets, as well as the spiral ganglions and their central axons, survive" Liberman (2017) [18] is even simpler. Several studies have shown that using neurotrophins "in the signaling pathways involved in neuronal development and maintenance, can elicit neurite extension from spiral ganglion cells even in the adult mammalian ear" (Wise *et al.*, 2005) [19]. Animal studies have shown that neurotrophin delivery can help in the treatment of noise induced synaptic damage by restoring ABR amplitudes. In conclusion these findings could lead to neurotrophin as a potential treatment for HHL by restoring cochlear synaptophysin.

5.6. What Affects Hidden Hearing Loss and How Can It be Treated

In this review, I have attempted to provide a deep study of HHL by identifying the major causes using several studies, and clarifying that mechanisms, other than synaptopathy, can be a contributor to HHL. Potential treatments were also discussed in this paper.

These findings are crucial to take into consideration when for future research concerning HHL since if not done correctly, it will impact the diagnosis and potential treatment. For example, as mentioned above, a reduction in ABR wave I amplitude does not always indicate synaptic damage, it can be due to other pathologies such as a dysfunction affecting Schwann cells. Another example observed is that if subjects' background is not properly considered, it can affect results tremendously. More detailed research on diagnostic tools of HHL should be made to identify what cochlear components are affected, synapses, hair cells or Schwann cells, and then treat them.

In cases of HHL, most people, especially medical legal cases, tend to be dismissed as they couldn't find any obvious hearing impairments, but we as audi-

ologists must think outside the box and administer extra testing to explore the possibility of HHL. Two examples of tests that could be done are: speech in noise at 5 dB SNR, normally a person would do 72% or better, less than that would indicate the presence of an underlying problem. Another test that can be done would be QuickSin to test for any asymmetry between the ears in terms of signal to noise ratio (SNR) loss. It is therefore necessary that we implement additional tastings to identify HHL.

It is also believed that untreated HHL can lead to earlier developed age-related hearing loss and in some cases tinnitus. This shows a correlation between them and therefore managing correctly HHL would help decrease the risk of developing other hearing pathologies especially in the elderly population.

6. Conclusions

In conclusion, the study above has failed to find a link between noise exposure and HHL. Moreover, studies have found small to no correlation between noise exposure and a diminished wave I amplitude in ABR measurements while using suprathreshold click stimuli. No significant difference was observed between subjects who were exposed to acute noise and the control group in the literature mentioned above. However, several studies have found the opposite and that noise exposure and the ABR amplitude of Wave I are correlated. This proves how studies concerning HHL due to noise exposure are very misleading due to the inaccuracy of lifetime noise exposure, age, gender, or other underlying pathologies in humans, all things that can affect this type of study. Therefore, future research should include more detailed evaluations of noise exposure history, and other electrophysiological methods such as ECoG or neuroimaging to try and identify HHL from noise exposure.

Several studies over the years have proven that a normal noise-free audiogram is not always the best way to detect certain types of pathologies. HHL usually presents itself with normal Puretone threshold but at difficulty in understanding speech. The above research concluded that an efficient way to detect age related HHL is by performing Puretone audiometry in a noisy environment by using BBN rather than a quiet one.

In addition, it was deduced that HHL can be caused by neomycin, gentamicin and paromomycin but not apramycin or gentamicin C1a at different concentrations where no significant outer hair cells damage was recorded, however inner hair cells were one of the most vulnerable elements when tested after the use of ototoxic drugs. The research in turn also suggests regardless of a reduced gentamicin dosage, HHL is still a possible side-effect. This may eventually develop to hearing loss later in life as we have seen previously in age related and noise induced hearing loss. However, this literature also showed that there is safer aminoglycoside, such as apramycin and gentamicin C1a that can be potentially used for future clinical treatments.

HHL is a type of auditory disorder that affects the auditory neural processing

and hearing sensitivity in subjects with normal hearing thresholds. They are often diagnosed by abnormal ABR Wave I amplitudes and latencies. This makes HHL hard to detect using normal audiometry testing. Subjects suffering from HHL have difficulty in speech understanding in a noisy environment. Studies have focused on HHL caused by synaptic due to noise exposure, ototoxicity, and aging. This had made most studies explore possible treatments to repair hair cells synaptic loss.

However, the results of this experiment have opened a new possible pathology that causes HHL which arises from cochlear Schwann cells rather than synaptic loss. Some subjects who suffer demyelinating pathologies, for example, Charcot-Marie-Tooth disease (CMT) and Guillain-Barré (GBS), suffer from an auditory impairment due to reduced ABR Wave I amplitudes and increased width and latencies. The following studies suggested a new mechanism that can be affected by HHL. In the coming years, the prevalence of HHL related to pathologies such as CMT and GBS which causes Schwann cells ablation is likely to increase. In conclusion, the following study revealed that this research may have clinical implications in diagnosing and treating HHL.

It was concluded that the major causes of HHL which include noise exposure, age and ototoxicity causes damage in cochlear synapses. However, this is not the only mechanism involved, a damage in Schwann cells can also contribute to it. Understanding these mechanisms is crucial for the possibility of future treatments because currently available ones such as hearing aids and cochlear implants focus on an abnormal auditory threshold, which is not the case in a subject suffering from HHL.

Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

References

[1] Kohrman, D., Wan, G., Cassinotti, L. and Corfas, G. (2020) Hidden Hearing Loss: A Disorder with Multiple Etiologies and Mechanisms. *Cold Spring Harbor Perspectives in Medicine*, **10**, a035493. https://doi.org/10.1101/cshperspect.a035493

[2] Bharadwaj, H.M., Masud, S., Mehraei, G., Verhulst, S. and Shinn-Cunningham, B.G. (2015) Individual Differences Reveal Correlates of Hidden Hearing Deficits. *The Journal of Neuroscience*: *The Official Journal of the Society for Neuroscience*, **35**, 2161-2172. https://doi.org/10.1523/JNEUROSCI.3915-14.2015

[3] Hickox, A.E., Larsen, E., Heinz, M.G., Shinobu, L. and Whitton, J.P. (2017) Translational Issues in Cochlear Synaptopathy. *Hearing Research*, **349**, 164-171. https://doi.org/10.1016/j.heares.2016.12.010

[4] Salvi, R., Ding, D., Jiang, H., Chen, G.D., Greco, A., Manohar, S., Sun, W. and Ralli, M. (2018) Hidden Age-Related Hearing Loss and Hearing Disorders: Current Knowledge and Future Directions. *Hearing, Balance and Communication*, **16**, 74-82. https://doi.org/10.1080/21695717.2018.1442282

[5] Ruel, J., *et al.* (2007) Physiology, Pharmacology and Plasticity at the Inner Hair Cell

Synaptic Complex. *Hearing Research*, **227**, 19-27.
https://doi.org/10.1016/j.heares.2006.08.017

[6] Kujawa, S.G. and Liberman, M.C. (2009) Adding Insult to Injury: Cochlear Nerve Degeneration after "Temporary" Noise-Induced Hearing Loss. *The Journal of Neuroscience*: *The Official Journal of the Society for Neuroscience*, **29**, 14077-14085.
https://doi.org/10.1523/JNEUROSCI.2845-09.2009

[7] Wan, G. and Corfas, G. (2017) Transient Auditory Nerve Demyelination as a New Mechanism for Hidden Hearing Loss. *Nature Communications*, **8**, Article No. 14487. https://doi.org/10.1038/ncomms14487

[8] Bramhall, N.F., Konrad-Martin, D., McMillan, G.P. and Griest, S.E. (2017) Auditory Brainstem Response Altered in Humans with Noise Exposure Despite Normal Outer Hair Cell Function. *Ear and Hearing*, **38**, e1-e12.
https://doi.org/10.1097/AUD.0000000000000370

[9] Ishikawa, M., *et al.* (2019) Lower Ototoxicity and Absence of Hidden Hearing Loss Point to Gentamicin C1a and Apramycin as Promising Antibiotics for Clinical Use. *Scientific Reports*, **9**, Article No. 2410. https://doi.org/10.1038/s41598-019-38634-3

[10] Mellado, L.M.M., *et al.* (2014) Spontaneous Regeneration of Cochlear Supporting Cells after Neonatal Ablation Ensures Hearing in the Adult Mouse. *Proceedings of the National Academy of Sciences of the United States of America*, **111**, 16919-16924.
https://doi.org/10.1073/pnas.1408064111

[11] Nam, G.S., Kim, J.Y., Hong, S.A., Kim, S.G. and Son, E.J. (2021) Limitation of Conventional Audiometry in Identifying Hidden Hearing Loss in Acute Noise Exposure. *Yonsei Medical Journal*, **62**, 615-621.
https://doi.org/10.3349/ymj.2021.62.7.615

[12] Traka, M., *et al.* (2010) A Genetic Mouse Model of Adult-Onset, Pervasive Central Nervous System Demyelination with Robust Remyelination. *Brain*: *A Journal of Neurology*, **133**, 3017-3029. https://doi.org/10.1093/brain/awq247

[13] Grinn, S.K., Wiseman, K.B., Baker, J.A. and Le Prell, C.G. (2017) Hidden Hearing Loss? No Effect of Common Recreational Noise Exposure on Cochlear Nerve Response Amplitude in Humans. *Frontiers in Neuroscience*, **11**, Article 465.
https://doi.org/10.3389/fnins.2017.00465

[14] Liberman, M.C., Epstein, M.J., Cleveland, S.S., Wang, H. and Maison, S.F. (2016) Toward a Differential Diagnosis of Hidden Hearing Loss in Humans. *PLOS ONE*, **11**, e0162726. https://doi.org/10.1371/journal.pone.0162726

[15] Marmel, F., *et al.* (2013) Subcortical Neural Synchrony and Absolute Thresholds Predict Frequency Discrimination Independently. *Journal of the Association for Research in Otolaryngology*, **14**, 757-766.
https://doi.org/10.1007/s10162-013-0402-3

[16] Viana, L.M., *et al.* (2015) Cochlear Neuropathy in Human Presbycusis: Confocal Analysis of Hidden Hearing Loss in Post-Mortem Tissue. *Hearing Research*, **327**, 78-88. https://doi.org/10.1016/j.heares.2015.04.014

[17] Arenas, J.P. and Suter, A.H. (2014) Comparison of Occupational Noise Legislation in the Americas: An Overview and Analysis. *Noise & Health*, **16**, 306-319.
https://doi.org/10.4103/1463-1741.140511

[18] Liberman, M.C. (2017) Noise-Induced and Age-Related Hearing Loss: New Perspectives and Potential Therapies. *F*1000*Research*, **6**, Article 927.
https://doi.org/10.12688/f1000research.11310.1

[19] Wise, A.K., Richardson, R., Hardman, J., Clark, G. and O'leary, S. (2005) Resprout-

ing and Survival of Guinea Pig Cochlear Neurons in Response to the Administration of the Neurotrophins Brain-Derived Neurotrophic Factor and Neurotrophin-3. *The Journal of Comparative Neurology*, **487**, 147-165.
https://doi.org/10.1002/cne.20563