Noise-Induced Hearing Loss: An Update

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Section 1: Title: Noise-Induced Hearing Loss: An Update

Section 2: Background

Noise-induced hearing loss (NIHL) was first described under the umbrella of "acoustic trauma" in the 1930s, particularly in the setting of industrialization and the rise of modern warfare.[1-3] It has since been differentiated from acoustic trauma – which is defined as hearing loss caused by a single, brief exposure to a very loud sound – given its association with chronic, less intense noise exposure.[4] NIHL is defined as a permanent sensorineural hearing loss that develops gradually, initially involving higher hearing frequencies; it is mainly associated with damage to the cochlear hair cells in the context of a patient history of long-term exposure to dangerous levels of noise.[5] It is the second most common form of sensorineural hearing impairment, after presbycusis (age-related hearing loss),[6] affecting as many as 500 million individuals worldwide.[7] NIHL is the most common disability among US troops in the Middle East, and has an estimated total cost of more than $1.2 billion annually among the military population alone.[8] Additionally, it can greatly impact quality of life, affecting mental and physical health as well as overall productivity and social functioning.[9]

The auditory organ's response to noise is variable and can depend on the level, time and frequency of noise exposure of an individual, among other factors. In certain susceptible individuals, excessive noise exposure can lead to a loss of hearing sensitivity, termed a threshold shift, in which louder sounds are necessary to produce hearing at typical auditory frequencies. This threshold shift can be temporary (TTS), meaning it returns to

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baseline in the hours, days, or weeks following noise exposure (with the maximum limit of time being approximately 30 days post-exposure), or can be permanent (PTS).[10] TTS generally occurs in response to moderate sound exposure and presents symptomatically with elevated hearing thresholds in the 3 to 6 kHz frequencies, as well as tinnitus, loudness recruitment, muffled sounds, and diplacusis.[4] Histologically, it is correlated with buckling of the pillar bodies and uncoupling of the outer hair cell stereocilia from the tectorial membrane,[11] as well as spiral ganglion cell afferent terminal damage.[12] Excessive sound exposure, or re-exposure prior to recovery from TTS, can cause permanent threshold shifts in hearing (PTS). Histologically, PTS is characterized by a sequential degeneration of outer hair cells and nerve fibers that begins in the region of the cochlea that corresponds to the 4 kHz frequency, and progresses in a basilar direction. This translates into a permanent high-frequency hearing loss with the potential for associated tinnitus. Severe cases are characterized by loss of all sensory and neural elements in the basal end of the cochlea,[13] and will typically cause loss of all mid- to high-frequency hearing.

Both TTS and PTS are characteristically detected via pure-tone audiometry. This is an evaluation of auditory sensitivity and measures hearing thresholds at different sound frequencies ranging from 250 Hz to 8 kHz. In this method, a threshold is defined as "the lowest signal intensity at which multiple [sound] presentations are detected 50% of the time".[4] This is recorded in decibels of hearing loss (dB HL). The typical audiometric finding associated with NIHL is a notch (decreased hearing threshold) centered around 4 kHz with subsequent recovery at 8 kHz (Ref. Figure 1A); this notch can deepen and widen with increased severity of damage to the cochlear apparatus.[14] The recovery of hearing sensitivity at 8 kHz is common and distinguishes NIHL from presbycusis (Ref. Figure 1B). Severity of hearing loss can be categorized using the American Speech-Language-Hearing Association (ASHA) threshold-based classification system: normal hearing (0-15 dB HL), slight hearing loss (16-24 dB HL), mild (25-40 dB HL), moderate (41-55 dB HL), moderately severe (56-70 dB HL), severe (71-90 dB HL), or profound (>91 dB HL) (Ref Table 1[4]).

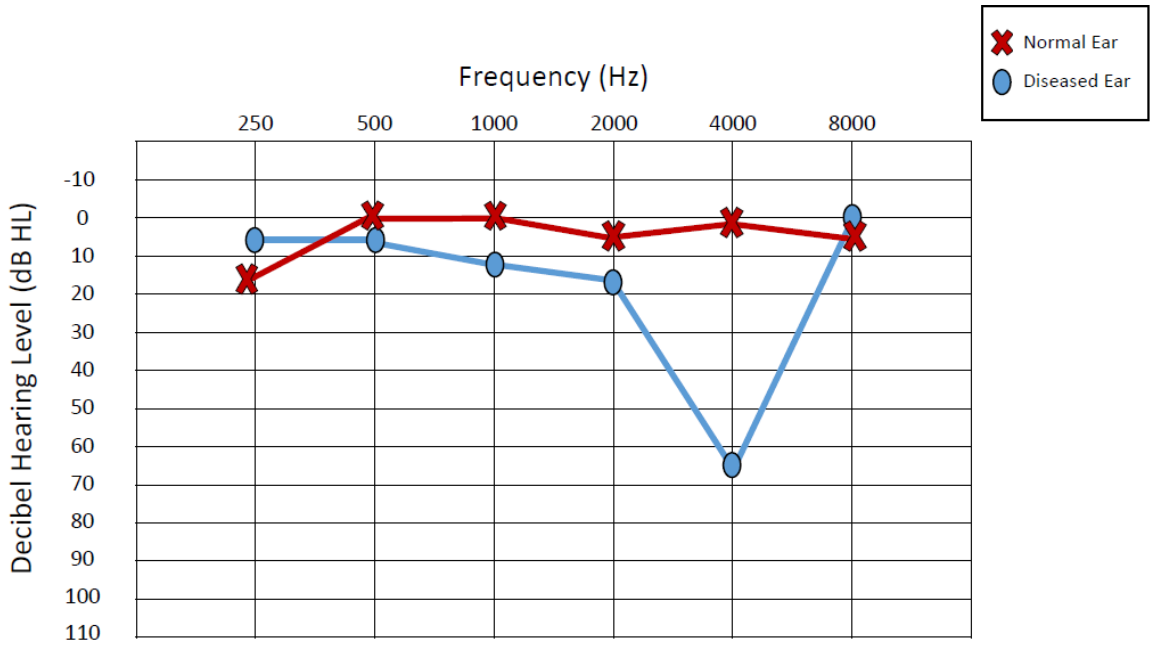

Figure 1A. Common audiogram findings of NIHL (blue) vs. normal hearing (red). Note the 4-kHz notch with subsequent return to normal hearing at 8-kHz in the affected ear.

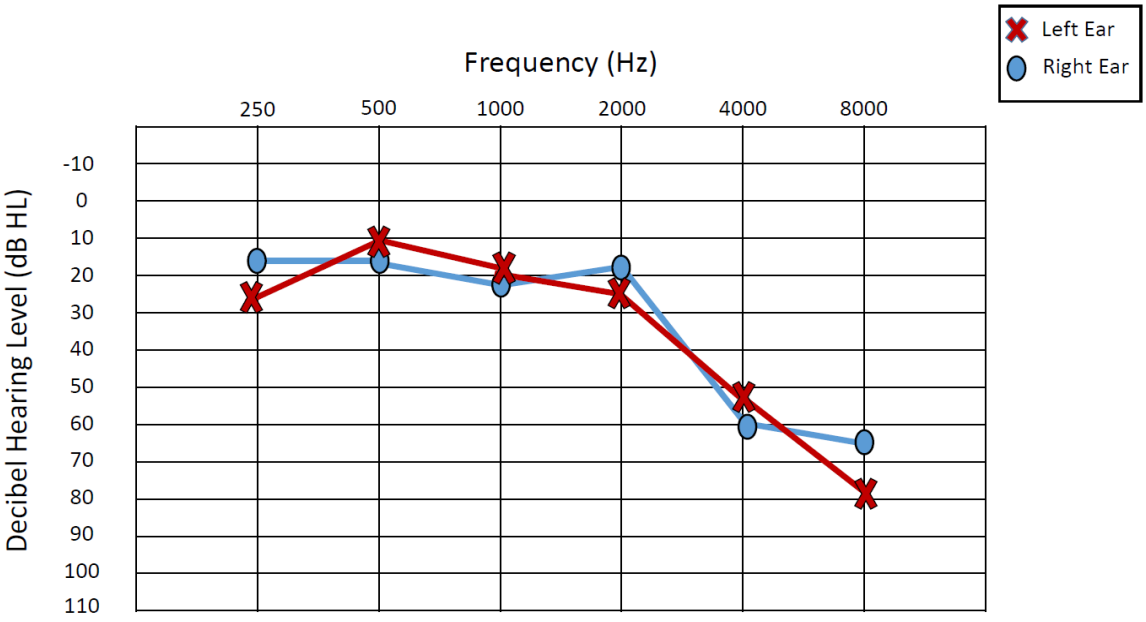

Figure 1B. Common audiogram findings of age-related hearing loss. Note the progressive decline in hearing level at higher frequencies. As compared to NIHL, there is no return to basal hearing at 8-kHz.

Deficit	ASHA Classification
0-15 dB HL	Normal hearing
16-24 dB HL	Slight hearing loss
25-40 dB HL	Mild hearing loss
41-55 dB HL	Moderate hearing loss
56-70 dB HL	Moderately severe hearing loss
71-90 dB HL	Severe hearing loss
>91 dB HL	Profound hearing loss

Table 1. ASHA Classification for severity of hearing loss, reported in decibels hearing level (db HL) with 0 dB HL being the standard for normal hearing.

Given the high prevalence and morbidity associated with NIHL, certain standards have been developed to guide acceptable levels of occupational noise exposure and to identify populations at risk of progressive hearing loss. The Occupational Safety and Health Administration (OSHA) has implemented a hearing conservation program that requires repeat monitoring of levels of workplace noise exposure, as well as the implementation of a yearly audiometric testing program in all settings where workers may be exposed to more than 85 dB of noise on average over an 8 hour period. Additionally, they have set a limit of permissible noise exposure in the workplace of 90 dB on average per 8 hour period or 95 dB on average per 4 hour period[15] (Ref. Table 2 for common examples of noise exposure levels[15-17]). Furthermore, the organization has formally defined a "standard threshold shift" (STS), a measure of significant hearing loss, as a 10 dB increase in hearing threshold averaged across 2, 3 and 4 kHz in the same ear as compared to the individual's baseline. Workers with two confirmed STS's within 30 days of one another can report their hearing loss as a work-related injury[10]; if an STS is discovered, employers are required to fit or refit the employee with adequate hearing protectors so as to minimize any further decline in hearing.

Noise Levels (dBA)	Common Examples
0 dBA	Lowest threshold of human hearing
10-20 dBA	Breathing, whispering
30-40dBA	Quiet rural areas, lowest limit of urban ambient sound
50-60 dBA	A normal conversation
70-80 dBA	People must speak loudly to be heard
90-100 dBA	People must shout to communicate with coworkers at an arms length away
>100 dBA	Jet take-off, motorcycle

Table 2. Common examples of levels of noise exposure.

Section 3: Recent Advances

Section 3.1: Mechanisms of Injury

Investigations of the mechanisms of NIHL have been extensively reported in the literature and thus an exhaustive discussion will not be attempted in this section. Instead, a few topics of interest have been selected to highlight the breadth of this field and the more recent work that is underway.

Histologic studies of NIHL have traditionally focused on cochlear inner and outer hair cell injury, which have been noted in animal models within a few hours of acoustic injury.[18] These specialized sensory cells are obvious areas of investigation, as the frequency-specific early changes in the audiometric findings of NIHL are likely related to specific injury to the base of the cochlea,[19] which is tonotopically organized to transmit high frequency sounds. Loss of these inner hair cells has also been hypothesized to result in subsequent degeneration of the spiral ganglion cells that innervate the hair cells and carry auditory signals to the cochlear nucleus. Oxidative stress and the generation of reactive oxygen species have been implicated as major mediators of hair cell injury immediately after noise exposure, and these are noted to persist for several days after significant exposures.[20] In addition, there is evidence of cochlear inflammation in response to both acute and chronic noise exposure, which is hypothesized to then induce a more central inflammatory response.[21,22]

Interestingly, recent evidence has suggested a different mechanism of NIHL involving injury to the cochlear synapse between inner hair cells and cochlear neurons, termed cochlear synaptopathy.[23] These early changes have been observed to occur without overt hair cell injury or changes in hearing thresholds, and stand in contrast to the prior

theory that the neural degeneration is secondary to cochlear injury. One postulated mechanism for this synaptopathy is glutamate excitotoxicity from chronic noise exposure resulting in dendritic injury and subsequent loss of neurons[24], although other pathways may also impact this interaction. Unfortunately, these early changes may be difficult to detect using the current standard audiometric battery, and the damage may be irreversible by the time hearing has been more severely impacted.[24] Further studies are needed to develop more sensitive tools to identify patients who are in these early stages of NIHL.

Section 3.2: Genetic Studies

Not all individuals who are exposed to significant levels of noise experience NIHL. Identifying groups at risk for NIHL has proven challenging in the human population due to several obstacles, including limited statistical power, wide variability in environmental noise exposure and exposure to other causes of hearing loss, and significant genetic heterogeneity. Existing human genetic studies have identified targets involving oxidative stress genes, potassium recycling genes, and heat shock proteins,[7,25] but these studies have been subject to the limitations discussed previously. As such, animal studies of NIHL have provided a more controlled setting to evaluate genetic components of hearing loss.

Recently, efforts have been made to characterize baseline hearing levels and susceptibility to significant noise exposure in various mouse strains. Auditory brainstem response (ABR) is an electrophysiologic technique used in both humans and animals to evaluate the auditory pathway. By presenting clicks or tones of varying frequencies and loudness and measuring the response along the neural pathway, a quantitative measure of hearing can be performed by observing the waveforms of the ABR. Myint et al. reported baseline hearing function and patterns of hearing loss after exposure to noise in a group of 100 inbred mice, and identified a group of mice that were resistant to NIHL, as well as numerous strains which were susceptible.[26]

Genome wide association studies (GWAS) have gained in popularity in identifying gene targets for many diseases in recent years. However, due to the complex, multifactorial nature of NIHL, there have not yet been large human population GWAS. Instead, GWAS was recently performed in mouse strains with varying susceptibilities to NIHL for the first time, and association analysis identified NADPH oxidase-3 (*Nox3*) as a potential target for investigation; this finding was validated when *Nox3* mutant mice demonstrated differences in hearing thresholds after exposure to noise.[27] A subsequent study analyzing an even larger number of mouse strains reported several intriguing novel candidate genes which had never previously been associated with hearing.[28] While targets identified in mouse model studies still require validation in the human population, these recent studies lay the foundation for a bright future in the understanding of the genomic landscape of noise induced hearing loss.

Section 3.3: Therapeutics

As mechanisms of NIHL are elucidated, pharmacologic interventions are being investigated to determine efficacy in preventing acute and long term injury. Given the role of oxidative stress in NIHL, agents with anti-oxidant effects such as N-acetyl cysteine (NAC) and glutathione have been

studied in both animal models as well as in clinical trials with promising results. There is evidence that administration of NAC may reduce TTS as well as provide a protective effect for the cochlear hair cells and cochlear nucleus.[29-31]

Steroids have long been used for their anti-inflammatory effects in cases of sudden sensorineural hearing loss, a category which includes NIHL. Steroids have been shown to have some benefit if administered early after onset,[32] although may lose their efficacy as time passes. Additionally, route of delivery of steroids has been investigated, as direct intratympanic instillation may impart greater protection than traditional systemic administration.[33]

Other less common agents have also been investigated, including but not limited to magnesium, calcium channel blockers, vitamin C and E, and Coenzyme Q10. Sakat et al. recently performed a thorough review of pharmacologic interventions for NIHL, and highlight the purported mechanisms by which each of these act.[34] Development of current therapeutics and identification of novel agents ultimately requires a fundamental understanding of the mechanisms by which acoustic trauma results in the observed deficits.

Section 4: Conclusion

NIHL is an increasingly common, yet preventable, form of hearing loss affecting a large segment of the population. It represents a large economic burden through both healthcare and disability costs and through lost productivity, and can have significant physical and mental health effects for affected individuals. Furthermore, the incidence of NIHL among adolescents and young adults is rapidly increasing, likely due to increased availability and use of personal listening devices.[35,36]

Significant advances have been made in understanding the physical and biochemical changes to the auditory apparatus in response to excessive noise exposure, as well as in discovering genetic susceptibility and potential treatments. However, more research is needed to fully understand the mechanisms and gene by environment interactions that cause NIHL, and to predict a specific damaging level of noise exposure for any individual patient. At this point in time, prevention is the only viable solution to this growing problem. Thus, it is important that internists become familiar with the current acceptable noise exposure standards as well as early diagnostic findings of NIHL, in order to educate patients and intervene at the earliest signs of a hearing deficit. Furthermore, we recommend a low threshold for audiometric testing or referral to an otolaryngologist in individuals who are exposed to dangerous levels of noise, particularly those above OSHA standards. With regards to NIHL, an ounce of prevention is truly worth a pound of cure.

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