Sex Differences in Hearing Loss

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Contributor: Chao-Hui Yang

The triad of noise-generated, drug-induced, and age-related hearing loss is the major cause of acquired sensorineural hearing loss (ASNHL) in modern society. Although these three forms of hearing loss display similar underlying mechanisms, detailed studies have revealed the presence of sex differences in the auditory system both in human and animal models of ASNHL. However, the sexual dimorphism of hearing varies among noise-induced hearing loss (NIHL), ototoxicity, and age-related hearing loss (ARHL).

Keywords: acquired sensorineural hearing loss ; noise trauma ; ototoxicity ; presbycusis ; estrogen ; cochlea ; sexual dimorphism

1. Introduction

Hearing loss is the predominant health issue in recent decades because it places psychological and socioeconomic burdens on the world. According to World Health Organization (WHO), almost 6.1% of the world's population has disabling hearing loss (about 432 million adults including 242 million males and 190 million females). Furthermore, it may rise to 630 million by 2030 and over 900 million by 2050 [1]. Acquired sensorineural hearing loss (ASNHL) is the most common type of hearing loss that includes noise-induced hearing loss (NIHL), ototoxicity, age-related hearing loss (ARHL), Meniere's disease, and autoimmune-related hearing loss, as well as others. Among these, noise, ototoxic drugs, and aging account for the major contributing causes of ASNHL in modern society. The triad of ASHNL represents the damage of the auditory pathway in response to acute, subchronic, and chronic environmental insults [2].

While the clinical features of noise, drug, and age-related hearing loss had been well understood, recent studies have demonstrated the sex differences of hearing severity in the triad of clinical ASNHL patients and explored the mechanisms underlying the sexual dimorphism in the animal models.

2. Clinical Aspects of Sex Differences in Acquired Sensorineural Hearing Loss

2.1. NIHL

NIHL accounted for at least 16% of all disabling hearing loss and has a demanding societal cost [3]. The pattern of an audiogram in NIHL usually presents a notch at 4 kHz with a spread to the frequencies of 3 kHz and 6 kHz [4][5]. After prolonged exposure to noise, the lower frequencies at 0.5, 1, or 2 kHz may also be involved [6]. Several reports have noted significant sexual dimorphism in NIHL. In Norway, a series of studies showed that women exhibited better hearing preservation after adjusting noise exposure and occupational factors [7][8]. In the latest cross-sectional study including 1140 males and 1140 females in China, males had a higher risk of high-frequency hearing loss compared to females in equivalent noise exposure and age [9]. The largest meta-analysis of occupational NIHL also demonstrated that male workers had higher odds of experiencing high-frequency NIHL than female workers [10]. Another aspect of gender difference in NIHL was described in Chung's study. They showed that males had a larger "ear effect" (right ear being more sensitive) in response to industrial noise exposure compared to females. In addition, females had better hearing than males after noise exposure in this study [11].

Apart from adults, NIHL in adolescents became a popular and crucial issue in recent years [12] but evidence of a sex difference in NIHL among adolescents is lacking. Several reports demonstrated the gender difference in their attitudes toward noise [13][14]. In 1997, Holmes et al. screened the hearing in 342 adolescents and 10.2% of males failed to pass at 6000 Hz in contrast to the 5% in females [15]. Males used firearms more frequently and a significant correlation was observed between failure at 6000 Hz and firearm use. Concerning the prevailing portable listening devices in recent decades, males had higher overall calculated exposure levels and chose higher levels of music in the quiet environment than females [14]. However, the hearing threshold at 4 kHz, which is most affected by noise, did not differ between males

and females aged 12–19 in the South Korean population [16]. Additional work with longitudinal follow-up is necessary to explore whether recreational music has a differential impact on the hearing between male and female adolescents.

2.2. Ototoxicity

Drug ototoxicity is another main cause of ASNHL in modern society. Abundant evidence has shown that ototoxic agents were mainly transported from the strial vessels or diffused via the round window into the cochlea after intratympanic administration or systemic use [17][18][19]. Various targeted sites of the inner ear including hair cells, supporting cells, spiral ganglion cells, and the auditory nerve can be injured according to the properties of the drugs. Among these, hair cells are consistently the predominant vulnerable site [20]. The well-known ototoxic agents include aminoglycosides, loop diuretics, platinum-based chemotherapies, nonsteroidal anti-inflammatory drugs (NSAIDS), and so on. Although various ototoxic drugs were found, the gendered difference was only discovered in part due to the lack of research until recent decades. Franconi et al. summarized the gender difference in drug responses from the pharmacokinetics to pharmacodynamics aspects. They concluded that females were more likely to experience adverse drug reactions including ototoxic effects [21] [22]. One cohort from Canada showed that the ototoxicity of an aminoglycoside antibiotic, amikacin, was associated with the female sex (females had a higher risk of ototoxicity than males) when treating patients with nontuberculous mycobacteria pulmonary disease [23]. In contrast, the ototoxicity risk of platinum-based chemotherapies such as cisplatin was higher in males [24][25][26][27]. The possible reason may attribute to the finding that some female cell lines are less sensitive to platinating agents than their male counterparts and may cause the phenotypic differences following cisplatin therapy [28]. However, some studies reported that platinum-based chemotherapies did not exhibit the gender difference in ototoxicity [29]. The sex difference of cisplatin ototoxicity still needs to be clarified due to the heterogeneous hearing results.

2.3. ARHL

ARHL or presbycusis usually represents developing high-frequency hearing impairment and frequently occurs with poor speech discrimination [30]. According to the WHO estimation, approximately one-third of people have disabling hearing loss after 65 years old and half of those are individuals over 85 years old in the United States [31]. Hearing loss in the elderly is often associated with countless negative impacts on life including communication obstacles, isolation, late-life depression, cognitive decline, and so on [32][33][34][35]. For decades, substantial cross-sectional and longitudinal human studies in various regions described that ARHL had a higher prevalence in males than females [36][37][38][39][40][41][42]. Pearson et al. proposed that the hearing threshold declined twice as fast in men than in women at almost any frequencies and men had an earlier onset of hearing decline [36]. Although it was considered that males might experience more noise exposure than females, their data still showed similar hearing outcomes after adjusting the noise and occupational factors [8]. Meanwhile, similar results were noted in another study that found that the thresholds at 0.25 kHz and 8 kHz increased gradually every year, and men had significantly higher increasing rates than women [43]. Concerning the hearing thresholds at different frequencies, elderly males had higher hearing thresholds than females at higher frequencies during aging in longitudinal [36] and large cohort [44] studies. These studies demonstrated that hearing loss is more profound in elderly males than females.

In recent years, a growing literature has shown that hearing loss is a risk factor for dementia [45]. The less perception from the peripheral auditory system decreases the transduction of sound to the central cortical area and also reduces the neural activities and signals' coding [32]. The treatment of hearing impairment could increase and maintain the cognitive reserve and prevent dementia as stated in the latest report of the Lancet Commission [35]. Although ARHL was identified as the most significant risk factor in dementia [46], the investigations of sex differences in the impact of ARHL on cognitive function were scarce. A study from Korea observed the association between hearing loss and cognitive impairment only in women aged 65 years and older [47], whereas recent research from a US national populational-based sample of adults aged 60 to 69 years old revealed that this association only appeared in males [48]. The discrepancy between the two studies may be due to the uncertain effect of gender differences in social networks [49][50][51]. While several factors could affect the sex differences in neurodegeneration [52], further studies to explore how ARHL affects cognition function in males and females would be helpful to determine whether hearing loss is a precocious sex-dependent indication of neurodegeneration.

2.4. Other Pathological Diseases Associated to ASNHL

Apart from NIHL, ototoxicity, and ARHL, Meniere's disease and autoimmune inner ear disease are also associated with ASNHL. Meniere's disease is characterized by fluctuating and progressive sensorineural hearing loss accompanied by episodic vertigo. Although the exact causes of Meniere's disease are not clear, endolymphatic hydrops are likely causative of this disease [53]. Several reports had revealed a slight female preponderance in Meniere's disease [54][55]. Those who had a lower estrogen level presented poor auditory function in postmenopausal patients with Meniere's disease [56].

Autoimmune inner ear disease features fluctuating bilateral progressive sensorineural hearing loss within weeks or months, likely due to a consequence of antibodies from various conditions such as viral infection, trauma, and vascular injury that damaged the inner ear [57]. In addition, autoimmune inner ear disease commonly occurs in females [58], similar to the female predominance in systemic autoimmune diseases [59].

3. Animal Investigations of Sex Differences in Acquired Sensorineural Hearing Loss

The sex differences in ASNHL were also evident in subsequent animal studies [60][61][62]. Sexual dimorphism in the auditory system was observed in many species for decades. Nonmammalian species including frogs, praying mantises, birds, and so on were described in detail [63][64][65]. However, only mammals are summarized here given the anatomical and physiological similarities with humans.

A series of studies in sex differences regarding the mammalian auditory system including mice, rats, chinchillas, rhesus monkeys, spotted hyena, and sheep were conducted [60][66][67][68][69][70]. Of these, several strains of mice such as CBA/CaJ and C57BL/6J mice were considered as useful models and were extensively applied in most types of hearing loss studies because the auditory circumstance and potentially interacting factors can be carefully controlled [71]. Auditory brainstem response (ABR) and otoacoustic emission (OAE) were typically used in animal models as the objective auditory measurements.

There are sundry sexual facets that contribute to the roles of this dimorphism: genetic factors, anatomical differences, occupation type, employment status, and so on. Some studies reported that males possess a slightly longer cochlear length but this finding still lacked clinical data and pathophysiological evidence [72][73]. From the molecular aspects to the clinical presentations, the disparities of sex and sex-related hormones are of interest to scientists and clinicians. Therefore, studying the sexual dimorphism in animal models of the auditory system may help us develop treatments for hearing impairment based on different genders.

3.1. NIHL

Although several animal studies have reported the sex difference in NIHL, the results varied in different species or strains. Milon et al. demonstrated that after exposure to 2 h of octave-band noise, female B6CBAF1/J mice had a significantly lower compound threshold shift and reduced permanent threshold shift compared to control male mice. However, no significant difference in hair cell counts and inner hair cell synapse counts between the two groups was noted [60]. Another study found that after exposure to 100 dB SPL broadband noise, there was no difference in the ABR threshold but a significant effect on the frequency–sex interaction in CBA/CaJ mice was noted. In addition, females had more excitatory synapses of immunolabeling in the ventral cochlear nucleus at the lower frequency and less at the higher frequency [74]. This result was consistent with McFadden et al. who emphasized that female chinchillas had less low-frequency hearing loss than males but exhibited greater hearing loss at 16 kHz. Meanwhile, less hair cell loss in female chinchillas was noted [69][75]. However, in Willott's study, female C57BL/6J mice lost more outer hair cells than ovariectomized female or male mice after exposure to nightly moderately intense augmented acoustic environments [76]. This opposite result may be attributed to the specific characteristic of C57BL/6J mice regarding elevated ABR thresholds of higher frequencies at 3 months of age and this trait may induce the interaction of ARHL and NIHL [62].

3.2. Ototoxicity

Sex differences in ototoxicity are also a widely discussed topic. Various animal models were examined for further investigation due to inconsistent human observational studies as mentioned above. One study provided direct evidence that the female cisplatin group had more deteriorated OAE values than the male cisplatin group among the Wistar albino rats. Although ABR values did not show a significant difference, the female cisplatin group had more apoptotic spiral ganglion neurons [77]. One recent study reported that inconsistent hearing thresholds after cisplatin injection were observed in different strains of mice [78]. For example, the CBA/CaJ mice revealed no significant sex difference; the female C57BL/6J mice had higher threshold shifts than the males at 4 kHz and 16 kHz. In contrast, in BALB/cJ mice, males had higher threshold shifts than the females at 4 k, 8 k, and 12 kHz. Interestingly, no significant difference in hair cell counts between male and female mice was observed in this study. There are two possible reasons for the heterogeneous results. First, there may be different susceptibilities to ototoxicity in these strains. Second, the different aging rates in these strains induced by ARHL may interfere with the degree of ototoxicities. Thus, the clear mechanism still needs to be investigated.

Regarding aminoglycosides, one animal study demonstrated that male Long–Evans rats had poor OAE values compared to female rats after treatment with kanamycin [79]. In the same manner, another study found that female guinea pigs that received gentamicin had better ABR performance than both the males with the same dosage treatment and the lower dosage male controls [80]. The diverse results between clinical and animal studies may be due to different animal species and drug pharmacodynamics.

3.3. ARHL

To understand the mechanism of sexual dimorphism in presbycusis, various animal models were conducted. CBA/CaJ mice experience progressive high-frequency hearing loss first and then gradually experience low-frequency loss. In addition, CBA/CaJ mice do not develop premature hearing loss, thus they are a suitable animal model for evaluating aging hearing [81][82]. When mice are growing older, the trend of dropped sex hormone levels mimics the trends for humans. One study reported that middle-aged and elderly male CBA mice had decreased OAE levels which indicated the outer hair cell dysfunction, while female mice levels only declined after menopause [61]. Another study examined both CBA/J and CBA/CaJ mice for the onset of ARHL and found that male mice had significantly poorer high-frequency thresholds than the females but not in C57BL/6J mice [76][82]. Subsequently, the *Ahl* gene was proposed as the reason to explain the trait of C57BL/6J mice in having a different result compared to CBA mice [76][83]. Overall, the structural cochlear changes including in spiral ganglion cell counts or strial capillary density in these animal models provided evidence of sex differences in auditory organs during aging [76][84][85].

4. Conclusions

Sex differences are important in the studies of translational neuroscience. Although the mechanisms underlying the triad of ASNHL may be similar, we need to consider sexual dimorphism during the interpretation of results in clinical and basic hearing research. From a clinical perspective, females exhibited better hearing than males during noise exposure and aging, while animal investigations only demonstrated better hearing in females in ARHL. In the current era of translation research and personalized medicine, future basic and clinical investigations to elucidate the sex differences in the cochlea are essential to help to develop personalized therapeutic strategies against ASNHL.

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