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REVIEW PAPER

Description of the characteristics, epidemiology, diagnosis, and risk factors of presbycusis disorder

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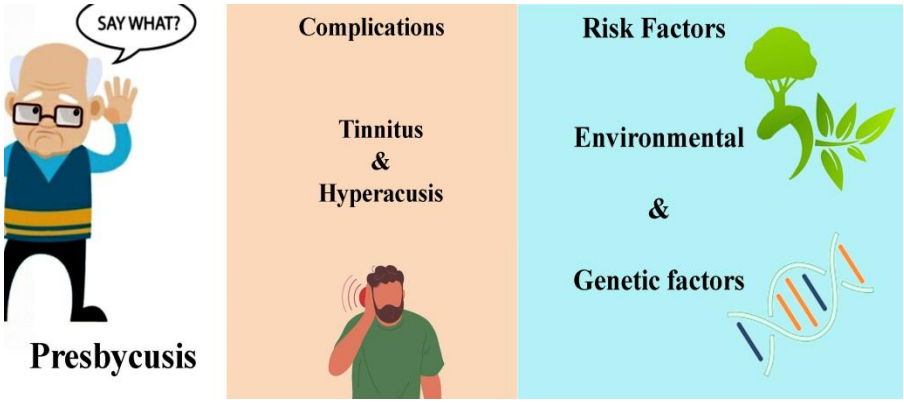
Highlights

- Presbycusis is one of the most common diseases associated with aging.
- Complications of presbycusis include perceptual disorders such as tinnitus and hyperacusis.
- Risk factors for presbycusis include environmental and genetic factors.

Graphical Abstract



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Abstract

Presbycusis is one of the most important and common diseases associated with aging. This disease is a symmetrical, irreversible and progressive bilateral disease of the cochlea. Complications of presbycusis include perceptual disorders such as tinnitus and hyperacusis. Methods for diagnosing this disease include signal-to-noise ratio, pure tone audiometry, and self-assessment. Many risk factors are involved in the development of presbycusis, which are divided into two categories: Environmental factors and genetic factors. Environmental risk factors include noise and external factors that influence lifestyle and diet. Individual health factors that are also involved in this disease include underlying diseases, ototoxic medications, and aging. Another group of risk factors involved in obesity are genetic factors. Genetic risk factors include abnormalities in genes involved in cochlear and mitochondrial genome function. The aim of this study was to describe the characteristics of presbycusis and the epidemiology, diagnostic methods, and risk factors for this disease.

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Introduction

Aging is a natural process that occurs due to progressive destructive changes in many organs of the body. These changes include DNA damage, decreased mitochondrial function, decreased intracellular water concentration, ionic changes, vascular insufficiency, and decreased cell membrane elasticity (1). Damage to certain organs automatically causes damage and dysfunction of other organs, for example, diabetes mellitus begins with exocrine pancreatic problems and is associated with many effects, including progressive atherosclerosis and polyneuropathy (2, 3). The aging process consists of three parts: biological degradation, external damage and internal damage. These factors can be overshadowed by age-related disease susceptibility. Age-related diseases are diseases that increase in frequency with age. These diseases include cardiovascular disease, osteoarthritis, cancer, Alzheimer's, cataracts, and presbycusis (4, 5).

Presbycusis, also known as Age-Related Hearing Loss, is one of the leading and most common age-related diseases worldwide. This disorder is a symmetrical, irreversible, and progressive bilateral disease of the cochlea that is seen in most people as they age. This complication is divided into three types: weak (low risk), moderate, and severe (high risk) (5). This disease is a type of sensorineural hearing disorder in which hearing loss occurs gradually; In this way, people first develop hearing loss at high frequencies, then hear sounds more slowly, and then have difficulty understanding words (6). Consequences of this disease include communication problems, early depression, withdrawal from society, anxiety, physical and mental functional disorders (7).

Hereditary presbycusis is usually moderate and its frequency is estimated at 30 to 70% (8). The disease is caused by age-related destructive changes in the cochlea of the inner ear and auditory canals. The cochlea has a complex structure that converts mechanical sound into electrical waves that the brain can perceive. The sound first enters the ear canal and strikes the eardrum; the resulting vibrations are transmitted to the middle ear bone, creating pressure on the cochlear oval window, which ultimately creates a fluid wave in the spiral structure. This fluid wave provides a sensitizing mechanism in the cochlear hair cells to initiate the potential action, which is eventually transmitted to the brainstem (9, 10).

Various components of the cochlea also have different functions in the homeostasis of inner ear and are also prone to age-related alterations. Internal and external hair cells with their stereocilia, which are enclosed by a tectorial membrane, are also susceptible to aging. On the other side of the organ of Corti, there is a neural network of afferent and efferent neuronal fibers, spiral ganglion, and the cochlear nucleus of the brainstem that show changes with age (3). Therefore, there are three types of cells in the cochlea: hair cells, spiral ganglion nerve cells, and stria vascularis cells, which the death of these cells in the ear result in presbycusis, and since hair cells are unable to reproduce, the process of loss hearing is a one-way, irreversible process; The result is a decrease in hearing power at high frequencies, a decrease in word differentiation, and a delay in the processing of auditory information (11). The aim of this study was to describe the characteristics, epidemiology, diagnosis, and risk factors of presbycusis.

Epidemiology of presbycusis

Assessing the prevalence and epidemiology of hearing loss is difficult because of the many different effects that lead to hearing loss, as well as different cultural, social, behavioral, psychological, and physiological aspects. In addition, these differences are due to the lack of standardization and different selection criteria that in themselves affect auditory function (12, 13). There are also difficulties in defining age timing that is directly related to the prevalence of presbycusis. Hearing loss can also begin at an early age but usually occurs in the ages of 60 and older. Over time, the hearing threshold range goes lower and lower. In previous epidemiological studies, it was said that the prevalence of this disease is in the frequency range of 500 Hz- 4 kHz and then 4-8 kHz. But today this frequency is known to be above 8 kHz. Two aging pathways under the influence of different hearing thresholds have been reported so far: 1- slower path with lower frequency up to 4 kHz and 2- faster path with higher frequency (6-8 kHz). The first path starts from the age of 30 to 36 and the second path involves the ages of 61 to 85 years. The disease is said to affect 11.2% of people aged 50-59, 24.7% of people aged

69-60, and about 63% of people over 70. According to the World Health Organization, it is estimated that by 2025, about 1.2 billion people over the age of 60 will be infected with the disease (14, 15).

Symptoms of presbycusis

As mentioned, in the presbycusis, the auditory nerve fibers of the efferent and afferents are destroyed and can cause perceptual disorders such as hyperacusis and tinnitus (16). Tinnitus is actually a conscious perception of sound that is felt from the head or ear without a sound source. Tinnitus is a complication that occurs in both children and adults but usually increases with age and the likelihood of developing presbycusis. It is also more common in men than women and may be unilateral or bilateral. People are usually unable to understand the exact source of the sound. Some feel it on the inside of the head and others on the outside (17). Regarding the role of gender with the rate of this complication and its prevalence, research has been done and the results were that tinnitus is higher in men or with a higher frequency than women, although at older ages, more complaints were observed by women with dizziness (18-20). Neri et al., assessed oxide stress markers in patients with tinnitus and found that the accumulation of oxidative markers including MDA and 4-HNE in the submandibular arteries of the elderly had higher symptoms of tinnitus (21).

Diagnostic methods

Diagnostic methods of presbycusis studies are often done through quantitative and qualitative characteristics. Signal to noise ratio (SNR), Pure-tone audiometry (PTA), and self-report have been methods of studying presbycusis disease to date (8). The mentioned diagnostic methods are described below and also the schematic of these methods are illustrated in Figure 1.

Pure-tone audiometry method

It is considered an index and gold standard in the diagnosis of presbycusis. This test shows a set of pure tone pulses at different intensities and frequencies, as well as partial analyzes of each person's hearing threshold at the measured frequencies separately from each ear and in the form of an audiogram. In this method, people are asked to press a button when hearing a sound to measure their ability to hear sound at different standard frequencies. It is said that this method, despite its sensitivity in hearing assessment, is not widely used and cannot be cost-effective. In addition, this test is not able to detect and understand background sounds. Lack of perception of surrounding sounds is one of the most common symptoms of presbycusis. Studies on the PTA method show that this test is not able to detect latent hearing impairment. As a result, no consensus has been reached on the diagnosis and evaluation of presbycusis by the PTA method (20, 21).

Signal to noise ratio method

Measures an individual's ability to direct and process sounds, usually in the form of triplet digits with different levels of background sounds. This test provides a speech reception threshold (SRT) for each person at a stage where they can understand 50% of the displayed three digits. The SNR test can be a good alternative to the PTA method in studies of presbycusis disease. This method can also be used to respond to large-scale genetic studies, which can be done over the phone or online without expensive equipment or trained staff (22).

Self-report method

In more complex cases and larger groups, self-reported assays have been very useful, and this method is very useful in collecting information on phenotypes in large populations. Self-report assessment includes simple questions such as the individual's ability to hear, the ability to hear in different situations, for example in an environment with background sounds, when using hearing aids or any diagnosis made by a physician in connection with age-related problems and symptoms related to hearing disorders such as tinnitus (8).

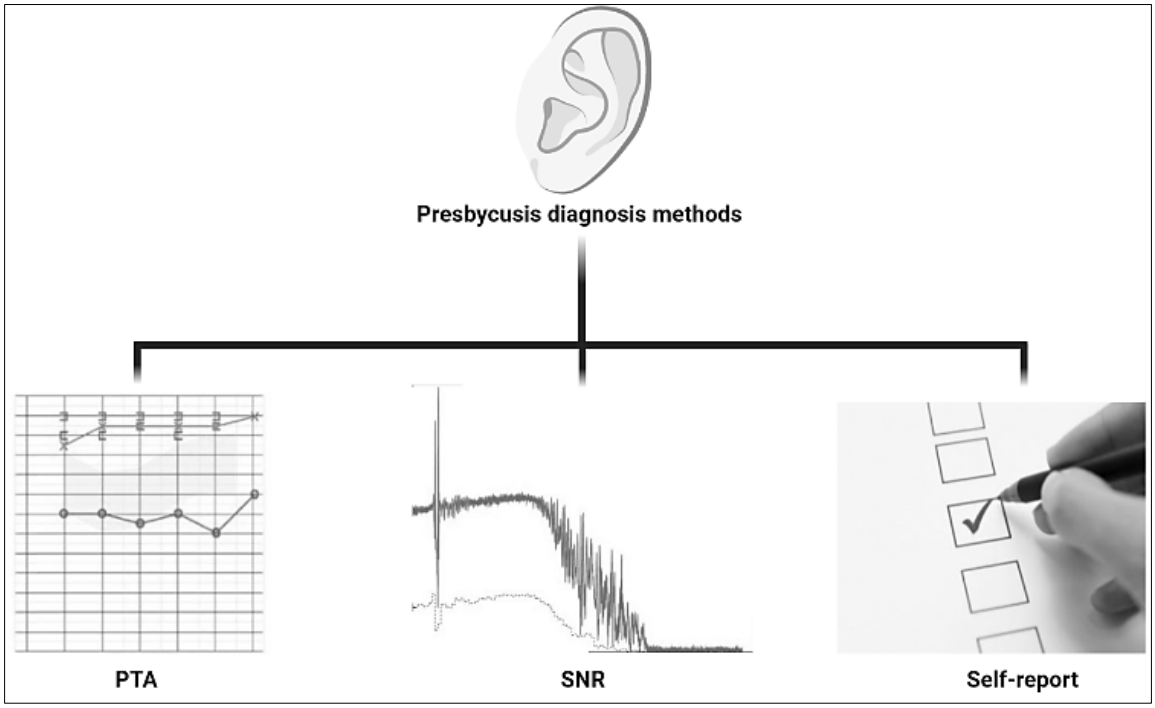

Figure 1. Diagnosis methods of presbycusis. The diagnosis of presbycusis could be performed by PTN, SNR, and self-report methods.

Risk factors for presbycusis

Many risk factors are involved in the development of presbycusis, which is classified into two categories: environmental factors (non-genetic) and genetic factors. Environmental factors are divided into two categories of external factors (such as noise and lifestyle) and individual health factors (such as age, use of ototoxic drugs, and underlying diseases). Genetic factors also include family history, sex, race, genes involved in ear structure and function, and mitochondrial-related genes (23). The risk factors of presbycusis are summarized in Figure 2.

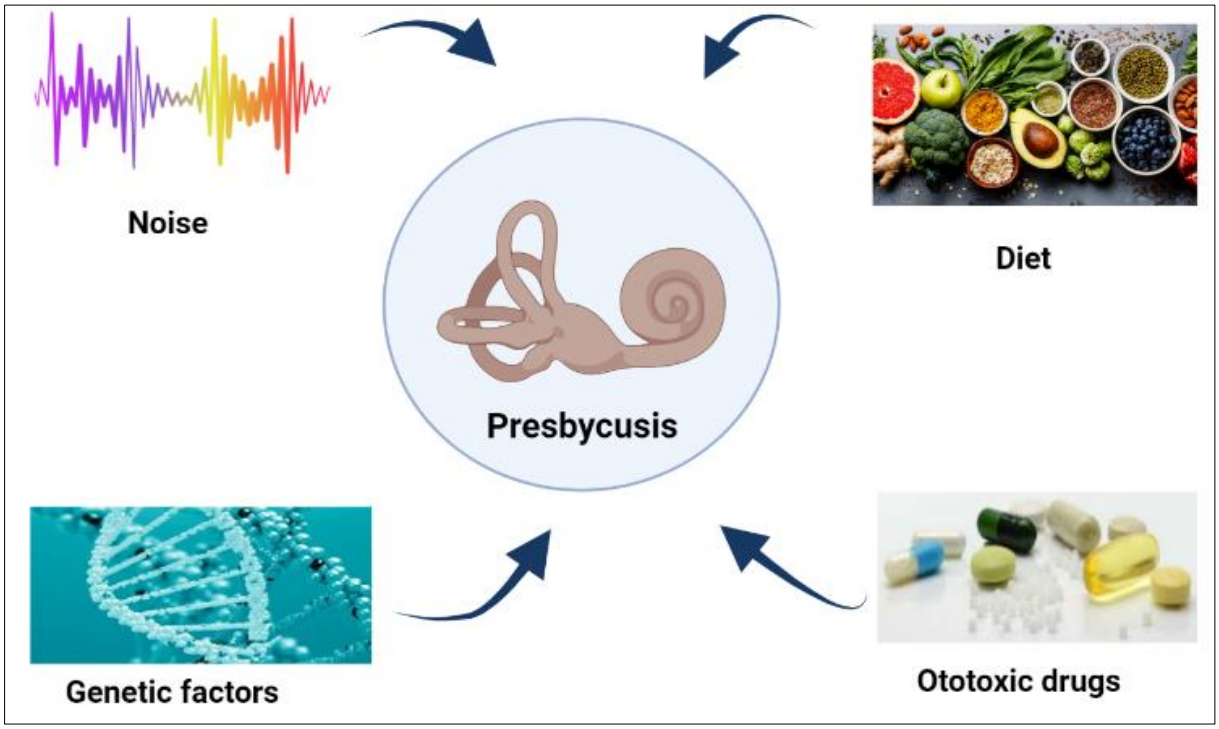

Figure 2. Risk factors of presbycusis. Some factors such as noise, diet, ototoxic drugs, and genetics could affect presbycusis risk.

Environmental risk factors

Influential external factors

Noise

Much research has been done on noise-related presbycusis, but little research has been done on the relationship between noise and the development of presbycusis. This type of presbycusis is often indicated by an increase in the hearing threshold in the range of 3,000 to 6,000 Hz, while presbycusis is seen in the frequency range of 4,000 to 8,000 Hz. This increase in the hearing threshold is also directly related to age (23). Recent studies in animal models have shown that exposure to noise makes the inner ear very vulnerable to the aging process, and this can lead to the onset or progression of hearing loss. Kujawa and Liberman performed experiments on CBA/CaJ mice, which are inherently good at hearing, and found that noise can cause nerve damage and thus exacerbate presbycusis, especially neurological presbycusis (24).

Lifestyle and diet

Nutrition has a vital role in the pathogenesis of hearing-related disorders. Excess fats, blood sugar, cholesterol, and carbohydrates are strongly associated with the development of presbycusis. Studies in animal models have shown that high levels of fat cause oxidative stress, mitochondrial damage, and apoptosis in the cochlear ganglion spiral (25). High levels of retinol and fat are associated with lower hearing. Diets high in cholesterol and carbohydrates are also clearly risk factors for hearing loss due to the potential for cardiovascular disease and diabetes, which can have a detrimental effect on cochlear blood flow (26). Oxidative stress caused by high blood sugar can also damage the cochlea. Studies have also been done on the effects of vitamins and their consumption and presbycusis, recent research has shown that vitamins with antioxidant properties may prevent cochlear damage by free radicals produced in the aging process (27). Since the inflammatory process also plays an important role in the aging of the cochlea, it can be said that consuming anti-inflammatory foods will also be effective in preventing aging. According to a study by Korean researchers, a diet rich in grains, nuts, fruits, seaweed, and vitamin A, which are anti-inflammatory foods, reduces the risk of hearing loss. These nutrients, along with vitamins A, C, and E, which are considered antioxidant vitamins, with their antioxidant properties that prevent the formation of free radicals, are effective in the prevention and even treatment of presbycusis. Vitamin A, which is naturally involved in the growth and development of the inner ear, contains compounds such as retinol, retinal, and carotenoids such as beta-carotene. Retinol, retinal, and retinoic acid are all active forms of vitamin A that are toxic in high concentrations. Also, depending on the amount of retinol in the body, carotenoids can be converted to vitamin A. Retinol and beta-carotene are both known to be active antioxidants responsible for inhibiting free radicals. These antioxidants are most effective when combined with nutrients (28, 29).

According to a number of studies, vitamin B12 plays a very important role in improving cellular metabolism, myelin synthesis, and vascular function in the auditory system, and therefore people who have taken enough of this vitamin throughout their lives have better hearing and lower risk of presbycusis (23). Studies on cochlea have shown that calorie restriction reduces oxidative damage, increases the protective effect of antioxidants, increases expression in the sirtuin pathway, and increases the expression of heat shock proteins, which ultimately reduces cell death or apoptosis (30).

In terms of lifestyle, we can mention the consumption of cigarettes and alcoholic drinks. There have been many studies on the effects of smoking on the prevalence and incidence of presbycusis. Fransen et al. stated that smoking clearly increased the risk of developing high-frequency presbycusis, depending on the dose. Also, the specific effect of smoking and the possibility of cardiovascular disease, and the relationship between cardiovascular health and cochlear blood flow should not be overlooked. Studies by Dawes et al. have found that smokers and even non-smokers who are exposed to it are much more likely to develop presbycusis than those who are not. Smoking can cause oxidative damage to the inner ear due to the effect of nicotine on reduced blood flow to the cochlea. According to research in the UK, Europe and Japan, hearing loss has nothing to do

with alcohol consumption. Recent studies have reported that presbycusis caused by environmental factors occurs at a younger age than genetic presbycusis (23, 31, 32).

Individual health factors

Underlying diseases

Medical conditions and factors that affect people's health, including some disorders such as cardiovascular disease, diabetes mellitus, immune system dysfunction, metabolic disease, kidney failure, and bone density can affect presbycusis disease. Studies have shown that people with better cardiovascular health are less prone to cochlear damage and eventually hearing loss. According to statistics, women with a history of myocardial infarction are twice as likely to have cochlear damage. Cardiovascular disease may affect the microvascular system, which causes blood vessels to reach the cochlea. According to studies in human and animal models, the inner ear is very sensitive to hypoxia (lack of blood oxygen). Chronic cochlear hypoxia causes the accumulation of mtDNA mutations and decreases the electrical potential within the cochlea, resulting in mechanical or strial presbycusis (33).

Diabetes may affect auditory function by cellular changes in the central nervous system and metabolic changes caused by the accumulation of reactive oxygen species (ROS). According to studies between the two groups of people with diabetes mellitus and non-diabetics, the risk of hearing loss and its progression was higher in diabetics. Studies have also been performed on the role of the immune system in auditory function. Iwai et al. conducted experiments for premature aging in SAMP 1 mice suffering from hearing impairment and immunodeficiency and concluded that there was a link between immune function and presbycusis (23, 33, 34).

Ototoxic drugs

In a small number of studies, the association between ototoxic drugs, including aminoglycoside antibiotics, chemotherapy drugs, salicylates, cisplatin, and presbycusis, has been reported. These drugs affect the outer hair cells of the cochlea and cause high-frequency sensorineural hearing loss due to excessive ROS accumulation and cell death. High levels of salicylate may also cause hearing loss, while low levels of salicylates can improve hearing and have a protective effect against aminoglycosides and cisplatin in presbycusis. In a study of a group of men, people who took painkillers (such as acetaminophen, nonsteroidal anti-inflammatory drugs, aspirin) more than twice a week were more at risk of hearing loss than people who took them less than twice a week. A similar study in women found that those who took ibuprofen and acetaminophen less than twice a week had a lower risk of developing the disease. However, studies on the toxic effects of ototoxic drugs remain controversial (23, 33).

Aging

The inner ear is much more vulnerable than the outer and middle ear. Studies have reported that with age, the destruction of spiral ganglion cells, the loss of nerve fibers in the spiral lamina, and the overgrowth of the elastic lamina from the internal auditory artery are achieved. Studies in mouse models have also shown progressive destruction of hair cells without damage to stria vascularis cells, destruction of spiral ganglion cells, and the Corti organ. Two of the obvious changes observed in the cochlea due to aging include a decrease in endocochlear potential (EP) and an increase in the action potential of auditory neurons. Recent studies have shown that metabolic obesity or destructive alterations in the lateral wall and stria vascularis are major causes of obesity. These changes reduce the expression of vital ion-transporting enzymes including Na^+, K^+ ATPase, and Na^+, Cl^-, K^+ co transporter, impair the function of foreign hair cells and reduce the quality of EP. EPs provide voltage to strengthen the cochlea, thus reducing its function, disrupting the cochlear amplifier, and weakening the auditory threshold (35).

Genetic risk factors

The hypothesis that presbycusis has a genetic background has been studied for many years. A number of studies have shown that hearing loss at high frequencies usually occurs in people over the age of 45 and in the absence of environmental risk factors. These studies were the beginning of proving the influence of genetics on presbycusis. Human studies on presbycusis have shown that family history has a significant effect on the disease. According to a Swedish researcher on 250 identical twins and 307 dissimilar twins, between the ages of 36 and 80, high-frequency presbycusis can be caused by both environmental and genetic factors. It has recently been estimated that 35 to 55% of people with presbycusis due to inner ear aging have a genetic background (36, 37). Studies on the heritability of presbycusis in humans show that the genetic background plays a 25 to 75% role in the pathogenesis of this disease. In the following, we will discuss the genetic factors and molecular mechanisms involved in the development of presbycusis.

History

Human research on presbycusis reveals a strong correlation between the disease and family history. Maternal family history of hearing loss in women showed a stronger association than paternal family history in men. The inheritance of presbycusis in the elderly is also estimated at 40 to 50% (23).

Gender

There is ample evidence that women have better hearing performance than men. In the US population between the ages of 20 and 69, men suffer more from hearing loss than women. In the Asian population, too, men are more at risk for hearing loss. By the age of 60, the rate of hearing loss in males is much higher than in females, but after that, the rate becomes almost the same. It is said that this is due to the protective function of estrogen and progesterone, which decreases after menopause (18). Estrogen is said to have strong antioxidant properties and neuroprotective effects. Menopause is also correlated with dysfunction of mitochondrial, synaptic dysfunction, neuroinflammation, cognitive impairment, and an elevated risk of age-related diseases. Alpha and beta estrogen receptors are located where electrical waves are transmitted (inner and outer hair cells, spiral ganglion) as well as where the homeostasis of inner ear is maintained (stria vascularis and spiral ligament). Although the exact role of estrogen is unclear, it appears to play a role in signal transmission and homeostasis of cochlear (3). In addition, women with Turner syndrome (45, X) are more likely to develop presbycusis than normal due to estrogen deficiency. At frequencies between 0.5 up to 8 kHz, the frequency of hearing loss in men is twice as high as in women. The onset of the disease occurs in men over the age of 30, but in women at older ages. The decreased hearing threshold at frequencies between 4 and 8 kHz in men, especially those over 50 years of age is much higher than in women. In contrast, the hearing threshold at frequencies of 6 to 12 kHz is faster in women than in men. As a result, it has been proven that the prevalence of presbycusis is higher in men than women (5, 35).

Race

According to studies conducted so far, black people are less prone to ear impairments than white people, which is about 60 to 70% less than people of the black race. According to recent research, it is caused by the presence of cochlear melanocytes, which have a protective function against presbycusis. Melanin produced in the cochlea plays a protective role against free radicals, regulating calcium homeostasis in stria vascularis, and metal chelators that are required in the natural auditory process (38).

Genes involved in cochlear structure and function

Many genes play a key role in presbycusis. However, the phenotypic expression of these genes can be controlled by exogenous and endogenous factors. Awareness of the factors that modulate gene expression may play a role in reducing cochlear pathogenesis and age-related hearing impairments by identifying and

determining genes in individuals prone to genetic damage (5, 39). Defects in the structure or development of sensory or supporting cells in the inner ear have been observed in many monogenic presbycusis. GRHL2, Grainyhead like Transcription Factor 2, is one of these genes, which is involved in inner ear neurotransmitters. GRHL2 is a transcription factor that is expressed in various epithelial tissues. It also has a special expression in the cochlear duct during embryonic development. Disruption of this gene produces a type of monogenic presbycusis (32, 36).

Cadherin23, also known as autocadherin, is another gene involved in the cochlear function that is specifically involved in the stereocilia function of hair cells. This gene contains 69 exons and encodes 3354 amino acids; It also has 27 extracellular domains, a membrane single pass domain, and a short cytoplasmic domain. Recent studies in animal and human models have shown an association between increased CDH23 methylation and presbycusis. Decreased gene yield and dysfunction of the inner ear hair cell were also observed. In peripheral blood samples of elderly women with presbycusis, the level of CDH23 methylation at the CpG site showed a clear association with presbycusis. These results were used to apply methylation patterns from blood samples as biomarkers in presbycusis (40). Also, found an association between single nucleotide polymorphisms (SNPs) of the KCNQ4 gene and presbycusis in two unrelated European populations. This gene encodes a protein that is expressed in cochlear hair cells and plays a key role in the potassium recovery of the inner ear. Defects in this gene produce a type of autosomal dominant progressive presbycusis (40).

GRM7, or metabotropic glutamate receptor, belongs to the mGluR III family, which is mainly expressed in the brain that develops during the formation of the hippocampus, cortex, and cerebellum. This receptor is located in the spiral ganglion cells of the inner ear and outer hair cells and is responsible for regulating the concentration and transport of glutamate at synapses between the hair cells and the auditory dendrites. Accumulation of glutamate in the inner ear causes oxidative stress and cell death. In many studies and populations, including the population of Europe and the United States, the link between this gene and presbycusis has been proven. Also, in the Chinese population, the association between the C mutant allele of the rs1485175 variety of the GRM7 gene was associated with a reduced risk of noise-dependent presbycusis (NIHL). As a result, the key role of glutamate and its transfer as a therapeutic target in aging can be mentioned (40, 41).

Mitochondrial related mutations

Mitochondria are recognized as a major factor in the development of presbycusis disease. This organelle is responsible for vital functions in the cell, including energy production, apoptosis, cell signaling, and calcium storage. Mitochondrial mutations, both points, and deletions, often increase with age, leading to cell aging in humans, monkeys, and rodents. In the cochlea, mitochondrial oxidation imbalances and point mutations and deletions are jointly involved in the development of presbycusis. Genetic studies of the human temporal bone in patients with presbycusis revealed mutations in mitochondrial genes encoding cytochrome oxidase and a 4977-bp deletion region in mitochondrial DNA. This deletion, also known as common deletion, is rarely seen in patients with presbycusis. Common deletion, also known as CD, is also known as a marker in aging. Common age-related deletions are also more common in the temporal bone with age. Markaryan et al. described three large deletions in the 5345, 5142, and 9682 bp regions in subunit III of the mitochondrial cytochrome c oxidase gene (42). Mutations in cochlear mtDNA in the elderly can lead to presbycusis. Some researchers have suggested that cochlear hypoxia can also cause the mutation.

Also, autopsy results from the temporal bone of people with presbycusis showed decreased expression of cytochrome c oxidase III, which is a major component in the electron transfer chain in mitochondrial aerobic metabolism, in spiral ganglion cells. Mutations in the cytochrome c oxidase subunit II gene in the spiral ganglion are also more common in patients with presbycusis in the control groups. In contrast, in mouse models, increased expression of mitochondrial catalase, which is responsible for reducing ROS, showed hair cell survival and delayed presbycusis (28, 43). UCP (Uncoupling protein) genes are very important transporter

proteins in the inner mitochondrial membrane that are responsible for the transport of anions and protons and regulators of temperature control and energy metabolism. There are more than five known types of UCP, the most well-known of which is UCP2. UCP mRNA transcripts are widely expressed in the spiral ganglion and cochlea in the inner ear of mice. This protein is also very important in enhancing antioxidant activity against the occurrence of presbycusis (44, 45).

Conclusion

Assessing the prevalence and epidemiology of presbycusis is difficult due to the effects of various factors. In addition, these differences are due to the lack of standardization and different selection criteria that in themselves affect auditory function. Hearing loss can also begin at an early age but usually occurs between the ages of 60 and older. Over time, the hearing threshold range goes lower and lower. As a result of deafness, it causes perceptual disorders such as tinnitus and hyperacusis, which can be very annoying. Understanding the genetic and non-genetic risk factors for presbycusis disease can provide the way for early diagnosis and treatment of the disease.

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