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Pathophysiology of Age-Related Hearing Loss (Peripheral and Central)

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Age-related hearing loss (presbycusis) refers to bilaterally symmetrical hearing loss resulting from aging process. Presbycusis is a complex phenomenon characterized by audiometric threshold shift, deterioration in speech-understanding and speech-perception difficulties in noisy environments. Factors contributing to presbycusis include mitochondria DNA mutation, genetic disorders including *Ahl*, hypertension, diabetes, metabolic disease and other systemic diseases in the intrinsic aspects. Extrinsic factors include noise, ototoxic medication and diet. However, presbycusis may not be related to the intrinsic and extrinsic factors separately. Presbycusis affects not only the physical, cognitive and emotional activities of patients, but also their social functioning. As a result, patients' quality of life deteriorates, compounded by various symptoms including depression, social isolation and lower self-esteem. Presbycusis is classified into six categories, as based on results of audiometric tests and temporal bone pathology, established by Schuknecht (1993): sensory, neural, metabolic or strial, cochlear conductive, mixed and indeterminate types. Among these, metabolic presbycusis is the mainstay of presbycusis types. Age-related changes also develop in the central hearing system. Functional decline of the central auditory system, caused by aging, reduces speech-understanding in noisy background and increase temporal processing deficits in gap-detection measures. This study reviews the literature on the age-related hearing loss. **Korean J Audiol 2013;17:45-49**

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Age-related hearing loss (presbycusis) refers to bilaterally symmetrical hearing loss resulting from aging process.[1)] Presbycusis is a complex phenomenon characterized by audiometric threshold shift, deterioration in speech-understanding and speech-perception difficulties in noisy environment.[1,2)] According to ISO 7029:2000 (International Organization for Standardization), the over-60 age group loses hearing of 1dB on average per year. Hearing loss increases over time.[1)] Approximately 30% of the aged population, or 9 million elderly people, suffer from hearing loss.[3)] In the 2003 report by the Center for Disease Control (U.S.), presbycusis was the second most common illness next to arthritis in the aged people. Its morbidity has risen with the aging population. According to the reports of the National Statistical Office (Republic of Korea), the over-65 age population was 4.7 million in 2000, or 7.2% of the total population. This age group is expected to rise by more than 15% by 2020, as the pace of population-aging accelerates. The number of patients with presbycusis is expected to rise in South Korea accordingly. Factors contributing to presbycusis include mitochondria DNA mutation, genetic disorders such as *Ahl*, hypertension, diabetes, metabolic disease and other systemic diseases in the intrinsic aspects. Extrinsic factors include noise, ototoxic medication and diet. It is difficult to relate presbycusis to intrinsic and extrinsic factors separately.[1,4)] Presbycusis affects not only the physical, cognitive and emotional activities of patients, but also the social functioning. As a result, patients' quality of life deteriorates with various symptoms such as depression, social isolation and lowered self-esteem.[5)]

However, there is no clinical way to predict the onset of presbycusis in advance. There is neither medical prevention nor treatment that can restore hearing loss at this time.[6)]

Since conductive high-tone hearing loss occurs due to stiffness and laxity of eardrum and its attached ossicles in middle

ear by aging process, such hearing loss does not affect significantly on the hearing level.[7]

Presbycusis is commonly classified into four categories based on results of audiometric tests and temporal bone pathology as established by Schuknecht (1969): sensory, neural, metabolic or strial and cochlear conductive types. In 1993, mixed and indeterminate types were added for six categories.[2,8]

Sensory presbycusis stems from degenerating organ of Corti, which elicits hearing loss in the high-frequency range. This symmetrical hearing loss usually occurs in middle-age population. Sensory presbycusis is primarily caused by damaged outer hair cells, in 10 mm at the basal turn of the cochlear. Outer hair cell loss is the most prominent change in both human[2,8,9] and animal studies.[3,10,11] In an animal model of C57BL/6J mice, outer hair cell loss expanded from the basal turn to apex, while the progressive hearing loss began in the high-frequency range at six months of age.[4] According to the Schuknecht Classifications, the incidence of sensory presbycusis accounted for 5% of the total presbycusis cases. The incidence of sensory presbycusis was also not high in the study by Gates, et al., using a DPOAE study.[12]

Neural presbycusis shows a moderate downward slope of pure tone threshold toward high-frequency and a severe decrease in speech discrimination compared to pure tone threshold.[2] Based on histological data, the loss of 50% or more of 35500 cochlear neurons is used as the criteria for neural presbycusis. Otte, et al.[13] demonstrated that approximately 2100 neurons were lost every 10 years in human. The loss of 50% of afferent nerve results in decreased speech discrimination, and 90% of loss elicits a change in hearing threshold.[14,15]

Strial or metabolic presbycusis shows hearing loss across all frequency range in audiogram. Metabolic ARHL is caused by the atrophy of the stria vascularis: the loss of 30% or more of the tissue in the stria vascularis results in a decrease in hearing threshold.[16] The loss of strial tissue causes K^+ recycling disorder, resulting in a decrease in endolymphatic potential. The frequency range is therefore affected as a whole. One of six subjects in Schuknecht's temporal bones exhibited metabolic presbycusis. Mills cited metabolic type as the main cause of presbycusis.[2,17] It is known that high-frequency hearing loss is highly associated with the loss of endolymphatic potential, and that the degree of loss is a crucial factor.[18] Animal studies demonstrated degeneration of stria vascularis and decreased endolymphatic potential along with hearing loss in gerbil.[18-20] Also, severe degeneration of spiral ligament was observed in autosomal-dominant non-syndromic hearing loss (DFNA9) among genetic hearing loss.[21]

Cochlear conductive presbycusis is described as a degenerative change resulting from the stiffness in the basal area of the cochlear. It is said that this type of presbycusis is manifested by a low-frequency hearing loss, with unimpaired speech recognition. However cochlear conductive presbycusis has not been verified as yet.[2]

Mixed presbycusis refers to a combination of these types of hearing loss. It is characterized by a smooth down-slope hearing loss toward high-frequency and an abrupt increase in threshold at the high frequencies. Also loss of outer hair cells in 10 mm at the basal area of the cochlear is observed along with severe loss of cochlear neurons (50% or more) and stria vascularis (30% or more).[2] Low-tone hearing loss is stemmed from disorder of the stria vascularis, while high-tone hearing loss is caused by loss of outer hair cells.[2]

Indeterminate hearing loss refers no correlation between audiometric pattern and pathologic alterations in cochlea, although no abnormality is microscopically observed in the cochlear tissue.[2,9,22] The incidence of indeterminate hearing loss was as high as 25% of total cases in Schuknecht's study on temporal bones.[2] Indeterminate type appears to result from microstructural damage in the tip links of stereocilia and mechanoelectrical transduction channels and from the central hearing impairment, although the cochlear tissue shows no abnormalities under optical microscopy.[23]

Critics of Schuknecht's typology have claimed that most presbycusis types cannot be clearly classified by histopathological data and that the results are confused accordingly.[3] They have also pointed out the lack of data on the role of non-epithelial cells apart from outer hair cell in the cochlear and the change in the central hearing system apart from peripheral auditory system.[3] In addition, the atrophy or rupture of the cochlear tissue, which were described as changes in Reissner's membrane by aging process, has also been referred to as the cause of presbycusis.[24,25]

As seen, presbycusis may be caused by various medical disorders. Age-related vascular disorders are found in either cochlear or spiral ligaments, while metabolic diseases such as diabetes may also cause vascular changes.[4]

Changes in voltage-gated K-channel subunits Kv1.1 and Kv3.1 were observed in cochlear neurons in aging.[26] Glycine-evoked changes that affect hyperpolarizing action were found in cochlear nucleus in aged C57 mice and Fischer 344 rats.[27] Also, age-related changes in receptors of glutamate neurotransmitters, which are released upon depolarization in auditory neurons, have been found in the hearing nerves.[28] A study suggested that calcium-binding proteins such as parvalbumin, calretinin and calbindin, which increased with age in cochlear nucleus, led to degeneration of the cochlea.[29,30] Activity of glial fibrillary acid proteins, which maintain cellular func-

tion, is known to reduce cochlear nucleus during aging process in mice.[31] Age-related changes were observed in growth factors including insulin like growth factor-1, platelet-derived nerve growth factor, transforming growth factor-ß1, acidic fibroblast growth factor and brain-derived neurotrophic factor. Age-related down regulation of growth-associated protein-43 was discovered in cochlear nucleus.[32,33]

Effect of oxidative stress is one of the major causes of aging-related hearing loss. Antioxidant enzymes such as enzymes of glutathione metabolism, catalase and methionine sulfoxide reductase were found in the cochlear.[34] Presbycusis occurred in functional null mice related to glutathione peroxidase and glutathione S-transferase Mu 1.[35]

Age-related changes also develop in the central auditory system. Nearly 20% neuronal loss was discovered in vestibulocochlear nerve in rats, especially in the superior olivary complex.[36]

Age-related decrease in inhibitory effects of the medial olivary complex results in loss of contralateral suppression of DPOAE.[37,38] Functional decline of the central auditory system, caused by aging, reduces speech understanding in noisy environment and increase temporal processing deficits in the gap-detection measures.[39]

Age-related changes in the central nervous system result from the functional changes of neurotransmitters and synapses rather than loss of neurons. Additionally, age-related decline in concentration, memory and cognitive functions should also be considered as contributing factors in presbycusis.[3]

The cochlear nucleus is responsible for analysis of sound features, including frequency, sound intensity and temporal cue in the central hearing system, In C57 mice in which early presbycusis occurred, changes in sensitivity were found in the ventral cochlear nucleus. Also aging-related changes in coding intensity developed in the dorsal cochlear nucleus in addition to the loss of glycinergic inhibition in the ventral cochlear nucleus of Fischer 344 rats.[40]

The superior olivary complex is responsible for various functions, including encoding temporal features of sound and localizing sound by receiving inputs from the cochlear nucleus on both sides.[41] The superior olivary complex is composed of three nuclei: medial superior olive, lateral superior olive and medical nucleus of trapezoid body. Binaural sound inputs are first processed in the lateral superior olive. The activity of glycine and gamma-amino butyric acid (GABA) decreased with increasing age in gerbils.[42] The medical nucleus of trapezoid body receives excitatory synaptic inputs. Activation of Kv3.1 potassium channel declined in this medical area as presbycusis occurred in C57BL6.[43] An increase in nitric oxide was observed in Djungarian dwarf hamster with age-related hearing loss.[44] Inhibitory GABA in olivary complex allows outer hair cells to maintain cellular activity, and in the inferior colliculus functions to localize sound. Loss of GABA-associated neuron was found in Fischer 344 with age-related hearing loss.[45,46]

Genetic factors are the most critical factors that influence age-related hearing loss among the complicate multiple-causes presbycusis. The Framingham cohort study showed heritability is greater in metabolic presbycusis.[47] The heritability of metabolic presbycusis was 53% between sister to sister and 36% between mother and daughter. Male twins showed heritability of 47% in a Swedish twin study. The heritability of 61% was reported in an American study.[48] Genes are responsible for forms of monogenic hearing loss which play a role in presbycusis. Presbycusis-related genes have been identified, including ten age-related hearing loss genes, mitochondrial DNA mutation and gene modifiers. Hearing loss-related genes including SNPs in KCNQ4, NAT2*6A polymorphism, grainyhead-like 2 gene, Glutamate receptor-7 gene and common' 4977-bp mitochondrial DNA deletion were identified through genome-wide association studies.[49]

Oxidative phosphorylation to generate ATP occurs in mitochondrial respiratory chain resulting in energy production in the body, but mitochondrial dysfunction induces hearing loss by affecting apoptosis, calcium imbalance and oxygen free radical. Mice with mutations of mitochondrial DNA showed early presbycusis and a neuronal loss in the dorsal cochlear nucleus and the posterior ventral cochlear nucleus.[50] MtDNA4834 was related to presbycusis in rodents and mtDNA4977 in human.

In mice model, 19 inbred strains exhibited presbycusis.[51-54] Of these, 10 strains had Ahl (age-related hearing loss) locus on chromosome 10.[55] Ahl that encodes cadherin-23 was found as a core gene in C57BL/6J mice. C57BL/6J mice were used as a key model for presbycusis, as they developed high-frequency hearing loss at six months of age, low-frequency hearing loss at 12 months and whole-frequency profound hearing loss at 15 months.[4] The progression of hearing loss was closely associated with histological changes in the cochlea. The loss of the dorsal cochlear neuron, which appears in some types of presbycusis, showed an association with the loss of peripheral outer hair cells in C57BL/6J.[56]

In addition to Ahl, Ahl 3 and Ahl-resistance alleles such as Ahl 2, Ahl 4 and Ahl 8 were also discovered. CBA/J mice have Ahl-resistant allele and have shown high-tone hearing loss developing at 12 months of age. The mice began to have the loss of outer hair cells at 18 months but did not exhibit abnormal findings of stria vascularis until 25 months of age. They

are therefore suitable as models for sensory and neural presbycusis.[57] CBA/CaJ mice are widely used as models for metabolic or strial presbycusis, as they develop hearing loss early with declined endocochlear potential.[4] DBA/2J mice developed hearing loss at two months of age by showing the loss of outer hair cells and cochlear ganglion. They have Ahl genes as well.[4] BALB/cJ mice, models for metabolic presbycusis, began to have progressive hearing loss at 19 months of age and a decrease in endocochlear potential. Fischer 344 albino rats developed a rapidly progressive hearing loss at 12 months of age with the loss of outer hair cells and the stria vascularis.[4,58]

As models for metabolic presbycusis, Mongolian gerbils share similar pathological characteristics as humans. The atrophy of stria vascularis and spinal ligaments and a decline of endocochlear potential were observed in the gerbils.[19,59] Chinchillas have aged-related hearing loss similar to humans but the long life span of 20 years poses a limitation for the presbycusis studies.

Conclusion

Presbycusis is the most common cause of hearing loss in the elderly population. Metabolic presbycusis is the mainstay of presbycusis types. Presbycusis develops and is exacerbated by various factors, including heredity, medical disease and environmental factors, showing various and complex clinical manifestations. There are still debates on which part of the inner ear is most affected by the aging process and which area is the most important for hearing. The prevention and treatment of presbycusis remain difficult. Further study is necessary in view of the rapidly aging population in Korea.

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