AGE-RELATED HEARING IMPAIRMENT (ARHI): A COMMON SENSORY DEFICIT IN THE ELDERLY

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[Perdita uditiva correlata all'età]

SUMMARY

This paper aims to give a broad overview of the scientific findings related to Age-related hearing impairment that is a complex disorder, with both environmental as well as genetic factors contributing to the impairment. The involvement of several environmental factors has been partially elucidated. A first step towards the identification of the genetic factors has been made, which will result in the identification of susceptibility genes, and will provide possible targets for the future treatment and/or prevention of ARHI.

Key words*:* Age related hearing loss, presbiacusis, tinnitus, deafness

RIASSUNTO

La perdita uditiva legata all'età anche nota come presbiacusia è una delle patologia complessa al cui sviluppo contribuiscono sia fattori ambientali sia genetici. Il ruolo dei fattori ambientali, l'importanza dei geni coinvolti, le attuali strategie terapeutiche e le potenziali prospettive terapeutiche e preventive future vengono trattate alla luce dei più recenti contributi scientifici.

Parole chiave: Perdita uditiva legata all'età, presbiacusia, tinnitus, sordità

Introduction

Age-related hearing impairment (ARHI) or presbycusis is the most common sensory deficit in the elderly and has become a severe social and health problem. Deafness is the fourth most common not infectious disease in the world after the arthritic and rheumatic diseases, cardiovascular and mental diseases. In Italy hearing loss is at fifth place among all disabling diseases of old age, with an incidence rate of 8.4%[(1)]. In 1999 The World Health Organization (WHO) has estimated that worldwide over 580 million people, older than 60 years old, are affected by ARHI. This number, as a result of lengthening of life expectancy, probably will increase with an estimate for 2020 of over one billion people (http://www.who.int/en/).

Several studies in scientific literature tried to define deafness incidence after 65 years of age with conflicting results (from 13% to 80%). However this in-homogeneity is explicable, because these studies were based on different defining criterias of hearing loss[(2-5)]. Considering only subjects with hearing loss equal or greater than 40 dB (average degree of deafness according to the Bureau International d'Audio-Phonologie) Cianfrone et al. estimated that in Italy 30% of the population older than 60 years has hearing problems[(6)]. It was agreed that this auditory dysfunction represents a physiological involution process which several factors can contribute. These factors, acting individually or together during lifetime, induce a cumulative damage of the auditory system characterized by reduced hearing sensitivity and speech understanding noisy environments, slowed central processing of acoustic information, and impaired localization of sound sources[(7,8)].

In its most typical form, ARHI is bilateral, symmetric, sensorineural, progressive and initially more pronounced in the high frequencies, but over time it also extend to medium-low frequencies becoming pantonal and disabling. Presbycusis sufferers first have a high tone hearing loss with reduced ability to perceive sounds of high pitch (doorbell, telephone ring), but during the years, show a progressive reduced intelligibility of voice messages particularly in noisy and/or reverberant listening situations, finally they usually lose the ability

to detect, identify, and localize sounds. Older adults frequently complain: "I can hear you, but I can't understand you". Verbal communication difficulties bring these patients to social isolation, depression, anxiety, social dissatisfaction that leads to a more or less rapid cognitive decline resulting in a 'dementia senile'[7-9]. Since there is not a specific medical or surgical therapy there is no way to reverse presbycusis, the only treatment are Hearing aids that do not restore hearing to normal but improve patient's ability to communicate especially when the impairment of verbal discrimination is low

Human age related hearing loss

Hearing loss is typically sensorineural bilateral symmetric and progressive, initially limited to high frequencies but over time also extended to the mid-low frequencies becoming pantonal. ARHI is caused by changes in peripheral (degeneration of hair cells, cochlear neurons and stria vascularis) and central auditory systems (consequent to peripheral modifications or changes in the neurobiologic activity underlying central processing of auditory informations). Consequences are reduced sensitivity, tuning sharpness, compression, and reduced signal-to-noise ratios, deficits in auditory discrimination, temporal processing, processing of degraded auditory signals or when embedded in competing acoustic signals. In presbycusis a very common symptom is tinnitus that constantly change frequency and intensity with negative psychological repercussions[8,9]. Usually tinnitus diminished or disappeared with hearing loss increasing[10].

By analyzing human temporal bones, Schuknecht and Gacek distinguished six distinct forms of ARHI, with different pathologic changes correlated with a different audiologic pattern[11]. According to this classification presbycusis can be divided into: Sensory presbycusis, Neural presbycusis, Strial presbycusis, Cochlear conductive presbycusis, Indeterminate presbycusis, Mixed presbycusis. Sensory presbycusis is defined by the atrophy of neurosensory and/or supporting cells of the basal turn of Corti's organ with secondary degeneration of neurons; audiometric curve shows bilateral sensorineural hearing loss for high frequencies, with a verbal ability discrimination usually preserved (Figure 1a).

Degenerative processes, that first affect outer hair cells and later internal hair cells, can be emphasized by the simultaneous presence of other etiopathogenetic factors such as damage from noise exposure, which elderly is particularly susceptible, or comorbidities like renal failure and/or cardiovascular disease. Neural presbycusis is characterized by a cochlear and central auditory path neuronal degeneration. The typical audiometric profile is a moderate hearing loss bilaterally, pantonal, more pronounced for high frequencies (Figure 1b) and usually with a significant reduction of word discrimination.

Even if neuronal loss can start at any age, neural damage clinically appears when neural units fall below the minimum level required for the acustic messages processing. The anatomical alteration of metabolic presbycusis is the stria vascular degeneration that probably change biochemical endolymph features. The corresponding clinical manifestation is a bilateral sensorineural, pantonal and flat, hearing loss with normal speech intelligibility (Figure 1c).

In 1991 Willot suggested that a high metabolic activity of the stria vascularis can produce an excess of oxidative processes and free radicals that, reacting with intracellular proteins, lipids and DNA, damage itself[12]. Actually the relationship between free radicals and aging is not already clear. The cochlear conductive or mechanical presbycusis is characterized by anatomical alterations of the basilar membrane and spiral ligament while Corti's organ and cochlear neurons are relatively normal. Clinically, hearing deficit is established by a slowly progressive bilateral sensorineural hearing loss for high frequencies with a speech discrimination compatible with hearing impairment (figure 1d).

Indeterminate presbycusis is not similar to any of the previous forms (figure 1e), while mixed presbycusis is the result of the combination of different types of presbycusis.

For example a sensory presbycusis associated with strial presbycusis is characterized by a pantonal flat hearing loss with a sharp drop of the higher frequencies (figure 1f).

Recently some authors, even if admit the importance of this etiopathogenetic classification, criticize its real clinical application because usually more than one type of inner ear lesion occur with age; infact "pure" forms of presbycusis are difficult to discriminate with common audiometric techniques and also presbycusis can be the result of physiological alterations and not histopathological lesions.

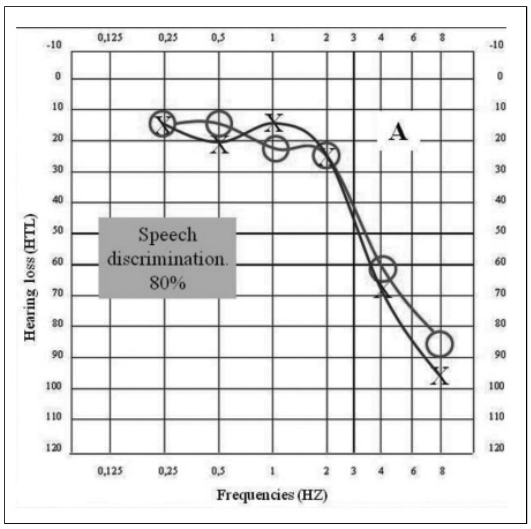

Fig. 1A: Types of Age related hearing loss and relative speech discrimination according to Schuknecht and Gacek classification. a) Sensory

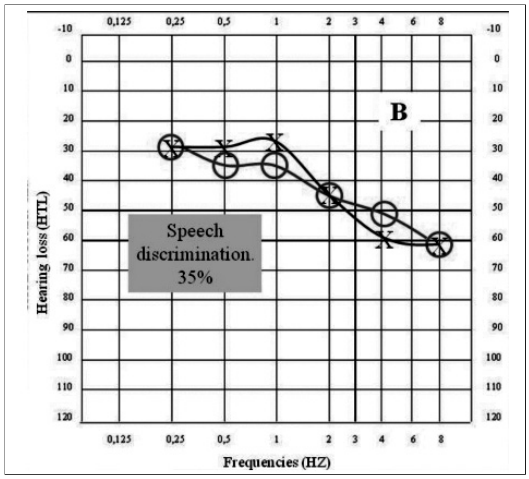

Fig. 1B: Neural

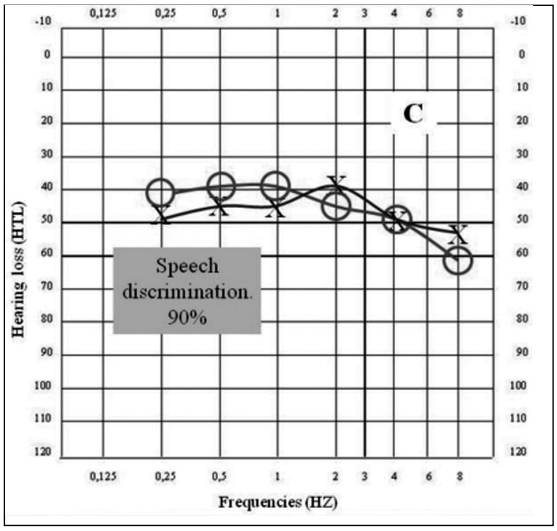

Fig. 1C: Strial

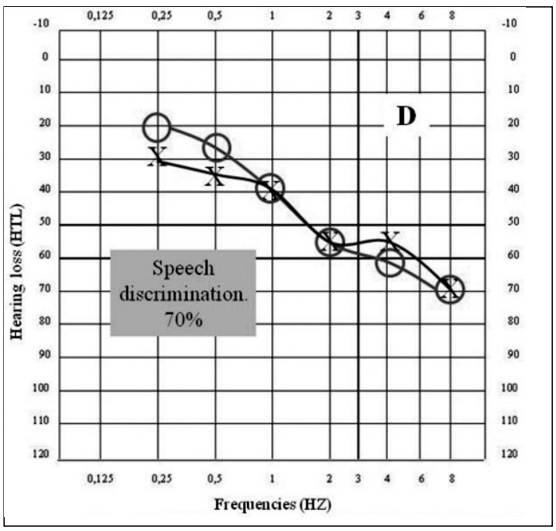

Fig. 1D: Cochlear

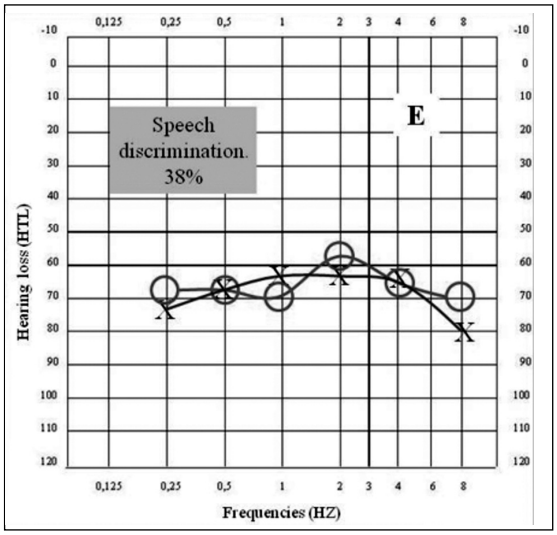

Fig. 1E: Indeterminate

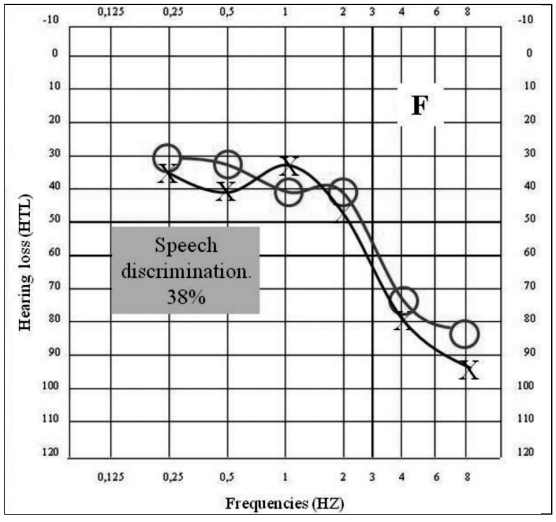

Fig. 1F: Mixed

Risk factors

Nowadays, presbycusis is defined as the inevitable process of physiological aging of the whole auditory system, a complex disorder caused by environmental and genetic factors even if is still not known how these factors contribute to the etiology of the disease, how they interact each other and what their individual contribution is.

This involution process begins early, since the age of 18-20 years, with a decrease in auditory sensibility, limited only to high frequencies and favored by factors closely related to the life such as acoustic pollution, ototoxic drugs treatment, high fat diets, etc.[13]

So the age of onset of this phenomenon and its clinical evolution are unpredictable because the biological causal mechanisms can act at any age.

Enviromental factors

Scientific community has identified many environmental factors that predispose and/or accelerate ARHI development. These factors, both isolated and concomitantly present, are responsible of a cumulative damage on one or more parts of the ear structures up to the cortical areas of the temporal lobe, that causes, with aging, a constant decline in hearing acuity.

Noise Exposure

Excessive noise exposure produces mechanical or metabolic cochlear damage with primary degeneration of the outer hair cells, and later also of the inner hair cells, probably induced by free radicals and reactive endogenous substances. Some subjects are more sensitive to noise due to a higher vulnerability of the hair cells[14,15].

Exposure to Chemicals

Exposure to industrial chemicals (toluene, trichloroethylene, styrene and xylene) can produce ARHI especially if in combination with noise exposure, as demonstrated by Sliwinska-Kowalska et al. furthermore, Chang et al. reported that even at low doses chemical solvents might damage the inner ear[16,17].

Smoking and Alcohol

The effect of tobacco smoking on hearing loss is not clear. Some authors reported that smoking, reducing oxygen supply in the inner ear, may cause either cochlear damage and mitochondrial mutations, resulting in hearing loss; it's also universally accepted that alcohol abuse increases the risk of ARHI in heavy drinkers[18].

Ototoxic Medication

Ototoxic drugs can cause reversible or non-reversible hearing loss predominantly in the high frequencies, especially in older subjects with altered liver and renal functions that can induce toxic blood medication levels. Examples of frequently used ototoxic medication are aminoglycoside antibiotics, chemotherapeutics like cisplatin, salicylate and loop diuretics that usually cause a reversible sensorineural hearing loss strongly correlated to dose, timing and duration of therapy, but in presence of genetic mutations (i.e. A1555G mutation in the small ribosomal RNA gene) causes from severe to profound sensorineural hearing loss[19,20].

Medical Factors

The relationship between sensorineural hearing impairment and diabetes mellitus has been demonstrated probably determined by micro-angiopathic lesions in the inner ear[21].

Many studies have looked for a possible association between CVD and ARHI, particullary in the Framingham cohort was found a clear correlation between low-frequency hearing loss and cardiovascular events and risk factors[22]. Renal failure causes high frequencies hearing loss through different mechanisms (chronic dialysis, uraemic neuropathy, electrolyte imbalance etc..)[23]. Head trauma can produce hearing loss through the lesion of the cochlea or inner ear hemorrhage[24,25].It's known that Immune System can have a role in ARHI development, according to Iwai et al. study, a pathogen-induced infections may induce a dysfunction of the immune system followed by a decline in hearing capacity (Autoimmune hearing loss)[26].

Diet

To date the role of diet in presbycusis is not clear with different and not univocal results among different studies, but It has been suggested that a poor nutritional status has an effect on ARHI[27,28].

Hormones

The clinical evidences of a strong correlation between human hormones levels and hearing loss are supported by Hederstierna et al. and Hultcrantz et al. which revealed that estrogenous therapy in menopausal women reduce ARHI development

while progestin have a negative effect[29-31].

Socioeconomic Status

Lower social class and a low level of education are correlated with hearing impairment probably secondary to risk factors prevalent in lower socioeconomic classes lifestyle (smoking, heavy drinking, exposure to occupational noise)[32].

Genetic factors

Even if little is known about the genes involved in ARHI, it is expected that many genes will participate in the etiology of ARHI. In the last years scientific research has focused its attention on the relationship between presbycusis and genetic substrate, with new possible future therapeutic strategies. Due to the significant similarities of the auditory system between mice and humans, mice are very useful as a model for human hearing loss. Erway et al through a research conducted on "inbread" mouse, have identified a recessive gene located on chromosome 10, called AHL1 (Age Hearing Loss-1), associated with the degeneration of Corti's organ, vascular stria, spiral ligament and Corti's spiral ganglion(33). A second locus AHL2 responsible for this disease was identified on chromosome 5 and third AHL3 on chromosome 17[34,35].

The close correlation between the human auditory system and animal (mice) and the identification of genes responsible for presbycusis, have justified new genetic studies of association and linkage, conducted on family groups and samples of populations, without encouraging results to date. Fischel-Ghodsian et al demonstrated, in patients with ARHI, a highly significant increase in mitochondrial mutations in auditory tissue[36]. The mitochondrial alterations that occur most frequently in humans are the mtDNA 4977 deletion and the cytochrome oxidase mitochondrial gene mutation. These changes can induce a cellular metabolic alterations resulting in increased oxygen free radicals (ROS), cellular damage and apoptosis of inner, outer hair cells and first neuron[37].

In the future the study of genetic factors of hearing loss probably will explain the relationship between genetic damage and presbycusis, identifying specific genetic mutations associated with this disease. The integration of the data concerning genetic background and environmental risk factors will verify each individual hearing susceptibility. This will make possible a "drug-genomic" therapeutic approach or genetic engineering approaches.

Treatment strategy

Actually the only intervention available for subjects with ARHI is a hearing aid that can improve the hearing ability but in a limited number of affected individuals due to the limited efficacy in improving speech understanding, especially in noisy environments. Possible pharmacological strategies are antioxidants and growth factors[38].

Anyway pharmacological substances can be used with systemic or local therapy. But while systemic therapy requires high doses of the drug potentially toxic, on the other side local therapy is invasive and potentially harmful for the cochlea. In the future, this problem can be solved by new and safer administration routes. A better understanding of the molecular and cellular processes taking place in the inner ear are necessary for possible future therapies. One of the possible future strategies is gene therapy. This is confirmed by the introduction of Math1, a gene that induces, in mice, regrowth of hair cells with the recovery of hearing abilities[39].

Another treatment strategy under development is the implantation of stem cells supported by Ito et al who had evidenced that neural stem cells survive when grafted into newborn rat cochleae adopting the morphologies and positions of hair cells and by Rivolta et al who by murine embryonic cells had generated inner ear progenitor cells subsequently differentiated into hair cells[40,41].

References

1) Arpini A. *L'incidenza della sordità nella popolazione adulta in Italia*. Audiometrie 1980; 24:*3*.
2) Desai M, Pratt LA, Lentzner H et al. *Trends in vision and hearing amongst older Americans*. Aging Trends 2001; 2: *1–8*.
3) Cruickshanks KJ, Wiley TL, Tweed TS et al. *Prevalence of hearing loss in older adults in Beaver Dam, Wisconsin*. The Epidemiology of Hearing Loss Study. Am J Epidemiol 1998b;148: *879–886*.
4) Pearson JD, Morrell CH, Gordon-Salant S et al. *Gender differences in a longitudinal study of age-associated hearing loss*. J Acoust Soc Am 1995; 97: *1196–1205*.
5) Davis AC. *The prevalence of hearing impairment and reported hearing disability among adults in Great Britain*. Int J Epidemiol 1989; 18: *911-917*.
6) Cianfrone G, Turchetta R, Maiolo A et al. *La sordità prelinguale: epidemiologia, tipologia, rilevazione*. Atti del Workshop "Il bambino che non parla". Milano. Ed. CRS Amplifon. 1998.

7) Gates GA, Mills JH. Presbycusis. Lancet 2005; 366: *1111–1120*.
8) Dalton DS, Cruickshanks KJ, Klein BE et al. The impact of hearing loss on quality of life in older adults. Gerontologist 2003; 43: *661-668*.
9) Heine C, Browning CJ. *Communication and psychosocial consequences of sensory loss in older adults: overview and rehabilitation directions*. Disabil Rehabil 2002; 24: *763–773*.
10) Martines M, Bentivegna D, Martines E et al. *Characteristics of tinnitus with or without hearing loss: Clinical observations in Sicilian tinnitus patients*. Auris Nasus Larynx 2010; 37: *685-693*.
11) Schuknecht HF, Gacek MR. *Cochlear pathology in presbyacusis*. Ann Otol Rhinol Laringol 1993; 102: 1-16.
12) Willot JF. *Central physiological correlates of ageing and presbyacusis in mice*. Acta Otolaryng. 1991; 476: *153-156*.
13) Van Eyken E, Van Camp G, Van Laer L. *The complexity of age-related hearing impairment: contributing environmental and genetic factors*. Audiol Neurootol 2007; 12(6): *345-58*.
14) Emmerich E, Richter F, Reinhold U et al. *Effects of industrial noise exposure on distortion product otoacoustic emissions (DPOAEs) and hair cell loss of the cochlea – Long-term experiments in awake guinea pigs*. Hear Res 2000; 148: *9–17*.
15) Kujawa SG, Liberman MC. *Acceleration of agerelated hearing loss by early noise exposure: evidence of a misspent youth*. J Neurosci 2006; 26: *2115–2123*.
16) Sliwinska-Kowalska M, Zamyslowska-Szmytke E, Szymczak W et al. *Effects of coexposure to noise and mixture of organic solvents on hearing in dockyard workers*. J Occup Environ Med 2004; 46: *30–38*.
17) Chang SJ, Chen CJ, Lien CH et al. *Hearing loss in workers exposed to toluene and noise*. Environ Health Perspect 2006; 114: *1283–1286*.
18) Itoh A, Nakashima T, Arao H et al. *Smoking and drinking habits as risk factors for hearing loss in the elderly: epidemiological study of subjects undergoing routine health checks in Aichi, Japan*. Public Health 2001; 115: *192–196*.
19) Rybak LP. Hearing: *the effect of chemicals*. Otolaryngol Head Neck Surg 1992; 106: *677–686*.
20) Selimoglu E. *Aminoglycoside-induced ototoxicity*. Curr Pharm Des 2007; 13: *119–126*.
21) Kurien M, Thomas K, Bhanu TS. *Hearing threshold in patients with diabetes mellitus*. J Laryngol 1989; 103: *164–168*.
22) Gates GA, Cobb JL, D'Agostino RB et al. *The relation of hearing in the elderly to the presence of cardiovascular disease and cardiovascular risk factors*. Arch Otolaryngol Head Neck Surg 1993; 119: *156–161*.
23) Antonelli AR, Bonfioli F, Garrubba V et al. *Audiological findings in elderly patients with chronic renal failure*. Acta Otolaryngol Suppl 1990; 476: *54–68*.
24) Danielidis V, Tsimpiris N, Balatsouras DG et al. *Short-term pathophysiologic changes and histopathologic findings of the auditory pathway after closed head injury, using a rabbit model*. Audiol Neurootol 2007; 12: *145–154*.
25) Fitzgerald DC. *Head trauma: hearing loss and dizziness*. J Trauma 1996; 40: *488–496*.
26) Iwai H, Lee S, Inaba M et al. *Correlation between accelerated presbycusis and decreased immune functions*. Exp Gerontol 2003; 38: *319–325*.
27) Houston DK, Johnson MA, Nozza RJ et al. *Agerelated hearing loss, vitamin B-12, and folate in elderly women*. Am J Clin Nutr 1999; 69: *564–571*.
28) Seidman MD. *Effects of dietary restriction and antioxidants on presbyacusis*. Laryngoscope 2000; 110: *727–738*.
29) Hederstierna C, Hultcrantz M, Collins A et al. *Hearing in women at menopause. Prevalence of hearing loss, audiometric configuration and relation to hormone replacement therapy*. Acta Otolaryngol 2007; 127: *149–155*.
30) Hultcrantz M, Simonoska R, Stenberg AE. *Estrogen and hearing: a summary of recent investigations*. Acta Otolaryngol 2006; 126: *10–14*.
31) Guimaraes P, Frisina ST, Mapes F et al. *Progestin negatively affects hearing in aged women*. Proc Natl Acad Sci USA 2006; 103: *14246–14249*.
32) Poortinga W. *The prevalence and clustering of four major lifestyle risk factors in an English adult population*. Prev Med 2007; 44: *124–128*.
33) Erway LC, Willott JF, Archer JR et al. *Genetics of age-related hearing loss in mice*. Inbred and F1 hybrid strains. Hear Res 1993; 65: *125–132*.
34) Johnson KR, Zheng QY. Ahl2, *a second locus affecting age-related hearing loss in mice*. Genomics 2002; 80: *461–464*.
35) Nemoto M, Morita Y, Mishima Y et al. *Ahl3, a third locus on mouse chromosome 17 affecting age-related hearing loss*. Biochem Biophys Res Commun 2004; 324: *1283–1288*.
36) Fischel-Ghodsian N, Bykhovskaya Y, Taylor K et al. *Temporal bone analysis of patients with presbycusis reveals high frequency of mitochondrial mutations*. Hear Res 1997; 110: *147–154*.
37) Longuet M, Riva C, Magnam J et al. *Implication de l'apoptose mitochondriale dans la degenerescence neurale de la cohlée dans un modèle murin CD1 de presbyacousie*. Rev. Laryngol. Otol. Rhinol. 2005; 126: *67-74*.
38) Lefebvre PP, Staecker H, Van de Water T et al. *Pharmacologic treatment of inner ear: from basic science to the patient*. Acta Otorhinolaryngol Belg 2002; 56: *45–49*.
39) Izumikawa M, Minoda R, Kawamoto K et al. *Auditory hair cell replacement and hearing improvement by Atoh1 gene therapy in deaf mammals*. Nat Med 2005; 11: *271–276*.
40) Ito J, Kojima K, Kawaguchi S. Survival of neural stem cells in the cochlea. Acta Otolaryngol 2001; 121: 140–142.
41) Rivolta MN, Li H, Heller S. *Generation of inner ear cell types from embryonic stem cells*. Methods Mol Biol 2006; 330: *71–92*.

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