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Immunoinflammatory and vascular inflammatory factors can be potential disease biomarkers of age-related hearing loss

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Abstract

Objectives: The relationship between age-related diseases and chronic inflammation associated with aging has recently been investigated. This study aimed to investigate how chronic inflammation is associated with age-related hearing loss (ARHL).

Methods: Twenty ARHL patients aged ≥65 years were prospectively enrolled from July 1 to 31 December 2015. Audiological tests and serological tests, such as C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), immunoglobulin G (IgG), interleukin 6 (IL-6), white blood cell (WBC) counts, neutrophil counts, lymphocyte counts, and platelet counts, were performed. The patients were divided into two groups: mild hearing loss group (n = 7) and moderate to profound hearing loss group (n = 13).

Results: Immunoinflammatory biomarkers, such as CRP, ESR, and IL-6, and vascular inflammatory biomarkers, such as neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio, were higher in the moderate to profound hearing loss group. IgG, WBC counts, and neutrophil counts were similar in both groups.

Conclusion: The present preliminary pilot study demonstrated that high levels of inflammatory biomarkers may be associated with ARHL. The results suggest a possible association between chronic inflammation and ARHL. Further well-designed studies of ARHL, based on a new perspective of chronic inflammation, should be performed.

Keywords

Presbycusis, age-related hearing loss, chronic inflammation, immunity, biomarker

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Introduction

As the lifespan of people is increasing; the incidence of senile diseases is also increasing. Presbycusis, or age-related hearing loss (ARHL), is an increase in the threshold of hearing that is associated with aging. Approximately 10% of the world's population is affected by ARHL, which correlates to approximately 30 million people in the United States.[1] In Korea, the incidence of ARHL in the capital and surrounding areas was 37.8% for ≥27 dB hearing level and 8.3% for ≥41 dB hearing level.[2]

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The association between age-related diseases and chronic inflammation associated with aging (i.e., inflammaging), has been recently investigated.[1,3–7] Inflammaging is the result of immunosenescence, which is aging of the immune system.[3,7] Chronic inflammation can also cause microvascular injury and atherogenesis.[6,8–10] Increases in the neutrophil-to-lymphocyte ratio (NLR) or the platelet-to-lymphocyte ratio (PLR) are associated with atherosclerosis in cardiovascular diseases and peripheral microvascular occlusion.[9,11,12]

In this study, we investigated the factors affecting ARHL with regard to chronic inflammation accompanied by aging. We evaluated the association between ARHL and immunoinflammatory factors such as C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), interleukin-6 (IL-6), immunoglobulin G (IgG), white blood cell (WBC) counts, and neutrophil counts as well as the association between ARHL and hematological vascular inflammatory factors such as NLR and PLR.

Materials and methods

Subjects

The study subjects were prospectively enrolled according to the criteria for ARHL, which were bilateral, and symmetric sensorineural hearing loss of 26 dB or more with weighted four-frequency average ([500 Hz + 1000 Hz × 2 + 2000 Hz × 2 + 4000 Hz]/6) in patients ≥65 years of age with no familial histories of hearing loss and no individual histories of head trauma, ototoxic drug use, chronic ear disease, noise exposure, or otologic surgery.

Patients who had familial histories of hearing loss or individual histories of chronic ear infection, otologic surgery, head trauma, ototoxic drug use, noise exposure, or sudden hearing loss were excluded from the study. In addition, patients with other chronic diseases, such as hypertension, hypercholesterolemia, heart disease, kidney disease, or diabetes, were excluded. Patients who were suspected of having acute inflammatory diseases, such as upper respiratory infections, were also excluded as acute inflammation could influence the immunoinflammatory values in blood tests.

This study was performed in accordance with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. The Institutional Review Board of Seoul Medical Center approved this study (IRB 2015-049). Written informed consent was obtained from each participant.

Methods

This study was cross-sectional. Pure tone audiometry, speech audiometry, and impedance audiometry were performed to evaluate the patients' hearing. CRP, ESR, IgG, IL-6, WBC counts, neutrophil counts, lymphocyte counts, and platelet counts were measured once on the same day of audiometry exam. The hearing thresholds of patients were calculated with weighted four-frequency average from both ears, respectively. The average of hearing thresholds from both ears was considered the patient's average hearing. Patients with ≥15 dB of threshold gap between air and bone conduction in the ipsilateral side and with ≥20 dB of average threshold gap in air conduction between both sides were excluded. Speech perception threshold in speech audiometry was checked to verify the reliability of thresholds in pure tone audiometry in all patients, and the thresholds in pure tone audiometry were reliable in all patients. In speech audiometry, the average of word recognition scores from both ears was considered the patient's average word recognition score. There was no abnormal tympanometric result in impedance audiometry in all patients.

The patients were divided into two groups, a mild hearing loss group and a moderate to profound hearing loss group, based on 40 dB. CRP, ESR, IL-6, IgG, WBC counts, neutrophil counts, NLR, and PLR were compared between the two groups.

Statistical analysis

Although the significance of statistical analysis was low due to the small and unequal number of patients in the two groups, demographic characteristics and the values of blood tests were analyzed between the mild hearing loss group and the moderate to profound hearing loss group using the chi-squared test for sex, and non-parametric Mann-Whitney U test for age, mean hearing threshold, word recognition score, and the values of blood tests using IBM SPSS software, version 20 (IBM, Armonk, NY, USA).

Results

Twenty ARHL patients aged ≥65 years were prospectively enrolled from July 1 to 31 December 2015. Of the 20 patients with hearing loss, seven showed mild hearing loss, and 13 showed moderate to profound hearing loss. There were 11 males and 9 females, and the mean age was 74.0 ± 7.2 years. The mean hearing was 50.2 ± 17.1 dB in total, 33.5 ± 5.9 dB in the mild hearing loss group, and 59.2 ± 14.0 dB in the moderate to profound hearing loss group. The word recognition score was 85.1 ± 17.7% in total, 99.4 ± 1.5% in the mild hearing loss group, and 77.4 ± 17.7% in the moderate to profound hearing loss group (Table 1).

Table 1. Demographic characteristics of patients included in this study.

	Mild hearing loss group	Moderate to profound hearing loss group	*p*-value
Number of patients	7	13	
Sex (male:female)	4:3	7:6	.888
Age (years)	70.0 ± 3.1 (65–74)	76.2 ± 8.0 (66–90)	.115
Mean hearing threshold (dB hearing level)	33.5 ± 5.9 (25.4–40.0)	59.2 ± 14.0 (42.5–94.6)	<.001*
Word recognition score (%)	99.4 ± 1.5	77.4 ± 17.7	<.001*

*p-value < .05 was significant.

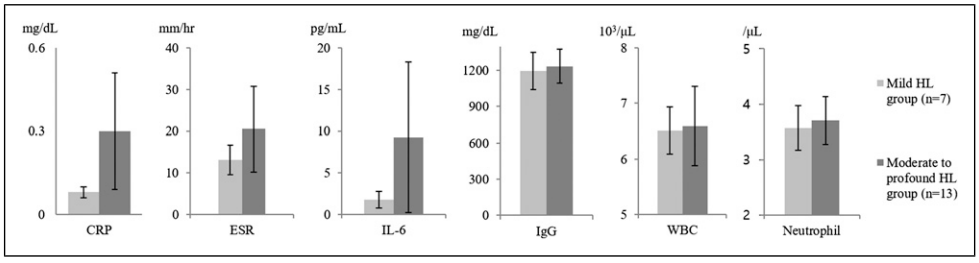

Figure 1. Immunoinflammatory biomarkers in the mild hearing loss and moderate to profound hearing loss groups. CRP, ESR, and IL-6 were higher in the moderate to profound hearing loss group than in the mild hearing loss group. CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; IL-6: interleukin-6; IgG: immunoglobulin G; WBC: white blood cell; HL: hearing loss.

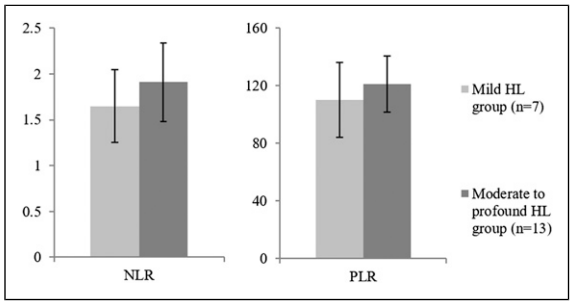

Figure 2. Vascular inflammatory biomarkers in the mild hearing loss and moderate to profound hearing loss groups. Both NLR and PLR were higher in the moderate to profound hearing loss group than in the mild hearing loss group. NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio; HL: hearing loss.

Hearing threshold and immunoinflammatory biomarkers

CRP (0.08 ± 0.04 mg/dL), ESR (13.1 ± 7.2 mm/h), and IL-6 (1.786 ± 2.04 pg/mL) of the mild hearing loss group were lower than in the moderate to profound hearing loss group (0.30 ± 0.42 mg/dL, 20.5 ± 20.5 mm/h, and 9.273 ± 18.11 pg/mL, respectively), but there was no statistical significance. IgG (1195.3 ± 311.8 mg/dL and 1235.4 ± 286.0 mg/dL, respectively), WBC counts (6.51 ± 0.85 10^3/μL and 6.59 ± 1.43 10^3/μL, respectively), and neutrophil counts (3.57 ± 0.96/μL and 3.70 ± 0.98/μL, respectively) were similar in both groups (Figure 1).

Hearing threshold and vascular inflammatory biomarkers

NLR was 1.65 ± 0.80 in the mild hearing loss group, and 1.91 ± 0.86 in the moderate to profound hearing loss group. PLR was 110.23 ± 52.05 in the mild hearing loss group, and 121.43 ± 39.15 in the moderate to profound hearing loss group. Both NLR and PLR were higher in the moderate to profound hearing loss group than in the mild hearing loss group, but there was no statistical significance (Figure 2).

Discussion

ARHL is one of the three major chronic medical conditions in the older people, with cardiovascular disease and arthritis being the other two major conditions.[13,14] The mechanisms of ARHL are still poorly understood.[5,7] Prospective studies of ARHL are lacking because the establishment of the patient and control groups is difficult and factors, such as individual immunoinflammatory factors and genetic causes as well as environmental factors, have been suggested to affect ARHL.

Many age-related diseases have been recently investigated in regard to chronic inflammation.[1] IL-6 and CRP have been associated with the inflammatory status.[5] Previous cross-sectional cohort studies suggested that WBC, neutrophil, IL-6, and CRP levels were significantly associated with the hearing threshold.[5,7] High level of CRP in less than 60 years old was associated with the development of ARHL in another cohort study.[6] In another prospective

study, IgG levels were significantly associated with the hearing threshold.[15] High WBC counts, neutrophil counts, IL-6, CRP, and low IgG have been associated with the severity of ARHL. In contrast, in another prospective cohort study, CRP levels were not statistically associated with ARHL.[16]

Low IgG was associated with malnutrition and recurrent infections, involving poor access to medical care in sub-Saharan Africa, where malnutrition and recurrent infections were common, and low IgG was associated with ARHL.[15] In our study, there were almost no difference in IgG according to hearing. It seemed that the previously reported study reflected the specific environments of malnutrition and recurrent infections.

In addition to these factors, the values associated with chronic imflammation that were investigated in cardiovascular disease and then in sudden sensorineural hearing loss (SSNHL), were applied to the analysis of ARHL in this study. NLR and PLR values were significantly elevated in SSNHL and vestibular neuritis.[9,10,17] SSNHL and vestibular neuritis are associated with microcirculation which is reflected in NLR and PLR. Microvascular disturbance and chronic inflammation may induce ARHL. Platelet counts are important in atherosclerosis, and elevated PLR may reflect the vascular circulatory insufficiency in otologic diseases as well as in cardiovascular diseases.

As previously mentioned, WBC and neutrophil counts were associated with ARHL, but there have been no studies characterizing the association with vascular inflammatory biomarkers such as NLR and PLR with ARHL. NLR and PLR are important in the disease which shows acute phase symptoms of microcirculation insufficiency such as SSNHL and cardiovascular disease. However, ARHL is a chronic disease, and not acute phase, so the effect of NLR and PLR on ARHL is still unclear. Due to the small numbers of included patients and the insufficient study design, we could not definitively determine the significance of NLR and PLR in ARHL in this study, but we suggest that high NLR and PLR were associated with the severity of ARHL.

Furthermore, we planned to confirm previously reported immunoinflammatory biomarkers and newly introduced vascular inflammatory biomarkers affecting ARHL in a prospective study. Although the association between these biomarkers and ARHL was not statistically significant, our results were consistent with those reported previously suggesting that immunoinflammatory biomarkers were associated with ARHL. The number of included patients was small and the distribution of values was large, so statistical significance could not be reached despite a big difference in the reported values.

This study had several major limitations. First, as already mentioned, the number of patients included was small, the numbers of patients in two hearing loss groups were not similar, and there were no power analysis for the estimation of sample size and no statistical significance. Second, the patient groups with hearing loss could not be compared with the control group with normal hearing and the age-matched analysis could not be performed due to the small number of patients. Third, this study was cross-sectional, not longitudinal. Fourth, although ARHL is prominent at high frequencies, hearing thresholds at high frequencies, such as 6000 Hz or 8000 Hz, were not included in the weighted four-frequency average.

In spite of these limitations, this study suggested that chronic inflammation and immunoinflammatory and vascular inflammatory biomarkers related to chronic inflammation were associated with ARHL. ARHL is multifactorial, and many factors other than immunoinflammatory and vascular inflammatory biomarkers could influence ARHL, so controlling them in a study is difficult. Based on this preliminary pilot study, future well-designed studies should therefore include more patients to obtain significant results.

Since the global population is aging, patients with ARHL are increasing. As with other age-related diseases, clinical and experimental studies of ARHL should be performed based on the new perspective of chronic inflammation. The accumulation of results from these studies may therefore suggest avenues to help prevent and treat ARHL.

Conclusion

The present preliminary pilot study demonstrated that high levels of inflammatory biomarkers may be associated with ARHL, suggesting an association between chronic inflammation and ARHL. Further well-designed studies of ARHL, based on a new perspective of chronic inflammation, should be performed to confirm a significant association.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical approval

This study was approved by the Institutional Review Board of Seoul Medical Center (IRB 2015-049).

Informed consent

Written informed consent was obtained from each participant.

Data availability

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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References

1. Watson N, Ding B, Zhu X, et al. Chronic inflammation - inflammaging - in the ageing cochlea: a novel target for future presbycusis therapy. *Ageing Res Rev* 2017; 40: 142–148.
2. Kim HN, Kim SG, Lee HK, et al. Incidence of presbycusis of Korean populations in Seoul, Kyunggi and Kangwon provinces. *J Korean Med Sci* 2000; 15(5): 580–584.
3. Capri M, Monti D, Salvioli S, et al. Complexity of anti-immunosenescence strategies in humans. *Artif Organs* 2006; 30(10): 730–742.
4. Larbi A, Franceschi C, Mazzatti D, et al. Aging of the immune system as a prognostic factor for human longevity. *Physiology (Bethesda)* 2008; 23: 64–74.
5. Verschuur CA, Dowell A, Syddall HE, et al. Markers of inflammatory status are associated with hearing threshold in older people: findings from the Hertfordshire ageing study. *Age Ageing* 2012; 41(1): 92–97.
6. Nash SD, Cruickshanks KJ, Zhan W, et al. Long-term assessment of systemic inflammation and the cumulative incidence of age-related hearing impairment in the epidemiology of hearing loss study. *J Gerontol A Biol Sci Med Sci* 2014; 69(2): 207–214.
7. Verschuur C, Agyemang-Prempeh A and Newman TA. Inflammation is associated with a worsening of presbycusis: evidence from the MRC national study of hearing. *Int J Audiol* 2014; 53(7): 469–475.
8. Hoffman M, Blum A, Baruch R, et al. Leukocytes and coronary heart disease. *Atherosclerosis* 2004; 172(1): 1–6.
9. Seo YJ, Jeong JH, Choi JY, et al. Neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio: novel markers for diagnosis and prognosis in patients with idiopathic sudden sensorineural hearing loss. *Dis Markers* 2014; 2014: 702807–702816.
10. Seo YJ, Park YA, Bong JP, et al. Predictive value of neutrophil to lymphocyte ratio in first-time and recurrent idiopathic sudden sensorineural hearing loss. *Auris Nasus Larynx* 2015; 42(6): 438–442.
11. Papa A, Emdin M, Passino C, et al. Predictive value of elevated neutrophil-lymphocyte ratio on cardiac mortality in patients with stable coronary artery disease. *Clin Chim Acta* 2008; 395(1–2): 27–31.
12. Gary T, Pichler M, Belaj K, et al. Platelet-to-lymphocyte ratio: a novel marker for critical limb ischemia in peripheral arterial occlusive disease patients. *PLoS One* 2013; 8(7): e67688.
13. Frisina RD, Ding B, Zhu X, et al. Age-related hearing loss: prevention of threshold declines, cell loss and apoptosis in spiral ganglion neurons. *Aging (Albany NY)* 2016; 8(9): 2081–2099.
14. Halonen J, Hinton AS, Frisina RD, et al. Long-term treatment with aldosterone slows the progression of age-related hearing loss. *Hear Res* 2016; 336: 63–71.
15. Lasisi AO, Fehintola FA, Yusuf OB, et al. Correlation between serum immunoglobulin G and hearing threshold among elderly subjects with age-related hearing loss. *ORL J Otorhinolaryngol Relat Spec* 2011; 73(2): 88–92.
16. Simpson AN, Matthews LJ and Dubno JR. Lipid and C-reactive protein levels as risk factors for hearing loss in older adults. *Otolaryngol Head Neck Surg* 2013; 148(4): 664–670.
17. Chung JH, Lim J, Jeong JH, et al. The significance of neutrophil to lymphocyte ratio and platelet to lymphocyte ratio in vestibular neuritis. *Laryngoscope* 2015; 125(7): E257–E261.