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Coexistence of IL-6 -572C/G and ICAM-1 K469E Polymorphisms among Patients with Sudden Sensorineural Hearing Loss

Guangyong Tian,[1] Shanshan Zhang[1] and Jingya Yang[1]

[1]Department of Otolaryngology-Head and Neck Surgery, The Third Affiliated Hospital of Southern Medical University, Guangzhou, China

Sudden sensorineural hearing loss (SSNHL) is a multifactorial disease, and its etiology remains elusive. SSNHL is possibly caused by both the environmental factors and genetic alterations. Recently, several studies suggested that inflammation may be involved in the pathogenesis of SSNHL, and certain gene polymorphisms may have correlations with SSNHL. Interleukin 6 (IL-6) functions both as a pro-inflammatory cytokine and an anti-inflammatory factor. Intercellular adhesion molecule-1 (ICAM-1) is a member of the immunoglobulin family that is also involved in inflammation response. Importantly, the IL-6 gene promoter contains a single nucleotide polymorphism (SNP), -572C/G, and ICAM-1 gene contains a SNP (A/G) in the protein-coding region, Lys (AAG)/Glu (GAG) at codon 469, known as K469E polymorphism. However, there is no study about the ICAM-1 gene polymorphism among SSNHL patients. In this study, we explored the relationship between SSNHL with IL-6 -572C/G and ICAM-1 K469E polymorphisms. We conducted a case-control study including 75 SSNHL patients and 165 healthy controls and analyzed the distribution and odds ratios of IL-6 and ICAM-1 genotypes. The frequency of the G allele at IL-6 -572C/G polymorphism was significantly higher among SSNHL patients than that among healthy individuals. In multivariate analysis, the coexistence of IL-6 -572G allele (GG/CG) and E allele (EE/KE) of ICAM-1 K469E polymorphism was significantly associated with an increased SSNHL risk ($P < 0.001$). In conclusion, we propose that the combination of IL-6 -572C/G and ICAM-1 K469E polymorphisms have a synergistic effect on the onset of SSNHL.

Keywords: genetics; intercellular adhesion molecule-1; interleukin-6; polymorphism; sudden sensorineural hearing loss

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Introduction

Sudden sensorineural hearing loss (SSNHL) is a medical emergency defined as sudden onset with no identified cause, with the loss of hearing of ≥ 30 decibels (dB) in at least three contiguous frequencies. The pathogenesis of SSNHL is not fully understood. Possible etiologies include viral infection, vascular occlusion, autoimmune diseases, inner ear pathology, lipid metabolic disorder, and central nervous system anomalies (Chau et al. 2010). Notably, on the aspect of the special blood circulation of the inner ear, vascular impairment has recently been suggested as a final common pathway for idiopathic sudden hearing loss (Finger and Gostian 2006; Mösges et al. 2009). The internal auditory artery is a functional end artery with minimal collaterals, which supplies the cochlea and vestibular labyrinth, making the labyrinth particularly vulnerable to ischemia (Lee 2014). The onset of SSNHL is similar to that of myocardial infarction and cerebral stroke, both are majorly caused by atherosclerosis. Accumulating evidence indicates that atherosclerosis is a chronic vascular inflammatory disorder, and inflammatory reaction plays an essential role in the occurrence and progression of cardiovascular disease (Tuttolomondo et al. 2012; Alie et al. 2014; Liu et al. 2016). Previous studies provided imaging evidence for the involvement of inflammation in the inner ear of SSNHL patients by three-dimensional fluid-attenuated inversion recovery magnetic resonance imaging (3D-FLAIR MRI) (Berrettini et al. 2013). They found that hyper-intensity derived from 3D-FLAIR sequences provided three new radiologic indicators, including mild hemorrhage, acute inflammation, and breakdown of the blood labyrinth barrier. High signals on 3D-FLAIR in patients with affected inner ear have also been observed in another study (Yoshida et al. 2008). These signals are correlated with minor hemorrhage or increased vascular permeability, implying the involvement of inflammation.

As a multifactorial disease, SSNHL is possibly caused

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Correspondence: Guangyong Tian, M.D., Department of Otolaryngology-Head and Neck Surgery, The Third Affiliated Hospital of Southern Medical University, No.183 Western Zhongshan Avenue, Tianhe District, Guangzhou 510630, China.

e-mail: whunversity_sp@126.com

by both the environmental factors and genetic alterations. Single Nucleotide Polymorphisms (SNPs) of inflammatory cytokines have recently been found in SSNHL. Interleukin 6 (IL-6) is an interleukin that functions both as a pro-inflammatory cytokine and an anti-inflammatory factor. IL-6 is predominantly secreted by T cells and macrophages, subsequently leads to inflammation in response to tissue damage and other immune conditions. Cadoni and colleagues (2015) demonstrated in a case-control study that the IL-6 levels were significantly elevated in SSNHL patients. Meanwhile, another group showed that the polymorphisms at the IL-1β -511, IL-1β -3953 and TNF-β -252 might play roles in SSNHL (Um et al. 2013). Similarly, the IL-1β -899C/T polymorphism was also reported to be associated with the susceptibility of SSNHL (Furuta et al. 2011). In addition, it was suggested that the polymorphisms at -1067GG (2G) of the matrix metalloproteinase-1 (MMP-1) gene promoter and Q576R of IL-4 receptor both increased the risk of SSNHL (Nam et al. 2011). Although these studies revealed the relationship between SSNHL and SNPs of some cytokines, the underlying mechanism of gene polymorphisms in the pathogenesis of SSNHL remains elusive. In our study, we further explored the roles of gene polymorphisms of certain inflammatory molecules in SSNHL.

Intercellular adhesion molecule-1 (ICAM-1, also named CD54) is a member of the immunoglobulin family and one of the adhesion molecules on cellular membrane. Adhesion molecules are important in establishing the complex network of cellular adhesion events between platelets, leucocytes and endothelial cells, which link the processes of hemostasis, thrombosis, and inflammation (Inwald et al. 2001; Sung et al. 2015). The ICAM-1 gene is located in human chromosome 19p13, and encodes the ICAM-1 protein of 532 amino acids. ICAM-1 has been proved to be a biomarker of inflammation and endothelial dysfunction. A previous study demonstrated that a higher plasma level of ICAM-1 was observed among patients with SSNHL (Quaranta et al. 2008). We thus aimed to explore the distribution of the ICAM-1 gene polymorphism in exon 6, Lys (AAG)/Glu (GAG) at codon 469, known as K469E polymorphism, among patients with SSNHL (Kitawaki et al. 2006). The K469E polymorphism is naturally present in humans (rs5498), without clearly identified physiological effects. Additionally, the correlation between ICAM-1 K469E polymorphism with tumorigenesis has been long suspected; however a recent meta-analysis study demonstrated little statistical significance (Cheng and Liang 2015).

IL-6 is characterized by pleiotropic functions in inflammation and the maturation of B cells (Kamimura et al. 2003). IL-6 promotes atherosclerosis by impairing vascular endothelial cells and contributing to endothelial activation (Papanicolaou et al. 1998). Elevated serum concentration of IL-6 has been reported in cardiovascular events and SSNHL (Hou et al. 2008; Hiramatsu et al. 2012). There is a polymorphism in the promoter region at position -572 of the IL-6 gene, which is C/G. This SNP in promoter region is highly possible to induce its expression abnormality, although need more experimental verification. A significant association between SSNHL and the IL-6 -572C/G polymorphism was found in Japanese patients (Hiramatsu et al. 2012). In addition, several previous studies indicated that IL-6 and ICAM-1 gene polymorphisms act synergistically in some diseases (Kitawaki et al. 2006; Lv et al. 2012). We postulated that the polymorphism of IL-6 -572C/G might have some association with SSNHL in a Chinese population. The aim of our study was to firstly investigate the distribution and possible synergistic effects of ICAM-1 K469E and IL-6 -572C/G polymorphisms on SSNHL.

Materials and Methods

Patients and healthy controls

A total of 75 patients (39 males and 36 females, aged between 21 and 80 years old) were enrolled in this case-control study from June 2014 to June 2015. According to the clinical practice of SSNHL (Stachler et al. 2012), patients suffered from idiopathic hearing loss of at least 30 dB in three consecutive frequencies with the sudden onset within 3 days were included. Data on ototoxic mediation exposure, circulatory disease, clinical and family history were obtained via medical interview or self-reporting. Audiological examinations including ear microscopy, pure tone audiometry, tympanometry, auditory brainstem-evoked responses, and stapedial reflex were performed for all the patients. Retrocochlear disease was ruled out by MRI. Patients with a history of familiar deafness were excluded. We calculated the hearing levels by pure tone audiometry at frequencies of 0.25 kHz, 1 kHz, 2 kHz, 4 kHz, and 8 kHz. All the patients received an intravenous drip of dexamethasone with a gradual dosage reduction: 10 mg/d for the first week, followed by 2-mg taper every 2 days. Low molecular weight dextran and vitamin B complex were added to the treatment for 5 days. We retested hearing levels after 2 weeks of treatment. The healthy subjects (86 males and 79 females, aged between 22 and 79 years old) without a history of SSNHL were derived from the same region.

This study was approved by the Ethics Committee of the Third Affiliated Hospital of Southern Medical University. Signed informed consent forms were obtained from all the patients.

Blood samples and DNA extraction

Venous blood (2 ml) was collected from each participant into EDTA coated tubes. Genomic DNA was extracted from leukocytes separated from venous blood using DNA extraction kit (Sangon Biotech, Shanghai China), and quantified by a NanoDrop™ 2000 Spectrophotometer (Thermo Fisher Scientific, Pittsburgh, PA, USA).

Genotyping

Detection of SNPs (rs5498 and rs1800796) was performed by polymerase chain reaction (PCR), followed by restriction fragment length polymorphism (RFLP) analysis. The restriction enzyme-digested PCR products were analyzed by electrophoresis using 2% agarose gels. The restriction enzymes, length of PCR products, and sequences of primers were shown in Table 1. Following the general definition, we classified patients into different groups according to the heterozygous or homozygous of IL-6 -576 (CC/GG/CG) (Oana et al.

Table 1. Primers, restriction enzymes and product length for two SNPs.

Gene	rs no.	Primers	Restriction enzymes	Product length
ICAM1	rs5498	5'-AGGATGGCACTTTCCCACT-3' 5'-GGCTCACTCACAGAGCACAT-3'	BstUI	215 bp
IL6	rs1800796	5'-TGGAGACGCCTTGAAGTAAC-3' 5'-TTTAGCGTTCCAGTTAATTTGTAT-3'	BsrB1	140 bp

The primers, restriction enzymes and PCR products' information are provided in Table 1.

Table 2. Demographic and clinical features of SSNHL patients and controls.

Variables	Patients (n = 75)	Controls (n = 165)	P value
Age (years)	50.7 ± 16.7	46.4 ± 12.6	0.021*
Sex			
Female	36 (48%)	79 (47.9%)	0.986
Male	39 (52%)	86 (52.1%)	
Hypertension			
No	59 (78.7%)	149 (90.3%)	0.014*
Yes	16 (21.3%)	16 (9.7%)	
Diabetes			
No	68 (90.7%)	156 (94.5%)	0.264
Yes	7 (9.3%)	9 (5.5%)	
Dyslipidemia			
No	60 (80%)	144 (87.3%)	0.144
Yes	15 (20%)	21 (12.7%)	

The basic clinicopathological characteristics of all enrolled patients are listed.
*P < 0.05 by Spearman correlation test.

2014). Similarly, the ICAM-1 phenotypes were also defined as KK/EE/KE according to the heterozygotes or homozygotes as described by others (Chae et al. 2010; Liou et al. 2015).

Statistical analyses

Statistical analysis was performed using SPSS software version 19.0. The analyses of continuous variables between two groups were conducted with Student's *t* test or Mann-Whitney test. Chi-square test or Fisher's exact test was used to evaluate the frequency of alleles and genotypes between case and control groups. Logistic regression for odds ratio (OR) was assessed to test the risk of SSNHL in subjects with certain polymorphisms. $P < 0.05$ was considered statistically significant.

Results

Patients characteristics

This case-control study consisted of 165 healthy individuals and 75 SSNHL patients. Detailed information of all subjects is presented in Table 2. The mean age between control group and patient group was statistically different (50.7 vs. 46.4 years old, P = 0.021). However, age has little effect on gene polymorphism. There was no significant difference between SSNHL cases and controls on the aspects of sex, dyslipidemia, or diabetes. The prevalence of hypertension was significantly higher in SSNHL patients than in controls (21.3% vs. 9.7%, P = 0.014), indicating the possible common features of vascular-dysregulation in hypertension and SSNHL.

Frequency of alleles and genotypes

Chi-square test revealed that the genotype distribution in case and control groups was consistent with Hardy-Weinberg equilibrium (Table 3). In detail, the E-allele frequency of ICAM-1 was higher in patients than in controls, although no significant difference on its genotype or allele frequency was observed between these two groups. For IL-6 -572C/G, the frequency of the G allele was significantly higher in subjects with SSNHL than in controls (P = 0.037). Meanwhile, the frequency of CG or GG genotype was also higher in cases than in controls, but did not reach statistical significance (P = 0.051).

Combination effects of IL-6 -572C/G and ICAM-1 K469E on SSNHL

Interestingly, the combination of G allele in IL-6 and E allele in ICAM-1, namely CG/GG and KE/EE genotypes, showed a higher prevalence in patients than in controls (P < 0.001, Table 4). Multiple logistic regression analysis was further used to assess the OR with adjustment of age, sex, hypertension, diabetes, and dyslipidemia in all the six models (Table 5). By combining different genotypes of both IL-6 and ICAM-1, multivariable analysis showed that the

Table 3. Prevalence of genotype and allele frequencies between groups.

Genotype	Patients (n = 75)	Controls (n = 165)	P value
ICAM-1 469K/E			
KK	33 (44%)	92 (55.8%)	
KE	30 (40%)	54 (32.7%)	0.229
EE	12 (16%)	19 (11.5%)	
Allele			
K	96 (64%)	238 (72.1%)	0.073
E	54 (36%)	92 (27.9%)	
IL-6 -572C/G			
CC	30 (40%)	94 (57%)	
CG	42 (56%)	66 (40%)	0.051
GG	3 (4%)	5 (3%)	
Allele			
C	102 (68%)	254 (77%)	0.037*
G	48 (32%)	76 (23%)	

Chi-square test revealed that the distribution of the genotype in case and control groups was almost consistent with Hardy-Weinberg equilibrium.
*P < 0.05 by Chi-square test.

Table 4. Combined distribution of IL-6 and ICAM-1 genotypes in patients and controls.

Genotype combination	Patients (n = 75)	controls (n = 165)	P value
CG/GG and KE/EE	33 (44.0%)	32 (19.4%)	< 0.001*
CG/GG and KK	13 (17.3%)	43 (26.1%)	0.138
CC and KE/EE	9 (12%)	41 (24.8%)	0.023*
CC and KK	20 (26.7%)	49 (29.7%)	0.631

The cohorts were grouped into four subgroups based on whether containing G allele in IL-6 and E allele in ICAM-1. Chi-square test showed the G allele and E allele were more frequent in SSNHL patients than normal controls.
*P < 0.05 by Chi-square test.

Table 5. Odds ratios for logistic regression models of polymorphisms with risk of SSNHL.

Model	Description	OR	CI (95%)	P value
Model 1	CG/GG	1.828	1.033-3.233	0.038*
Model 2	KE/EE	1.538	0.865-2.734	0.143
Model 3	CG/GG and KE/EE	3.122	1.662-5.866	< 0.001*
Model 4	CG/GG and KK	0.633	0.311-1.289	0.208
Model 5	CC and KE/EE	0.873	0.465-1.640	0.674
Model 6	CC and KK	0.432	0.195-0.956	0.038*

Multiple logistic regression was used to obtain odds ratios with adjustment of age, sex, hypertension, diabetes, and dyslipidemia in six models. The genotypes carrying G allele of IL-6 was considered as an independent variable in these logistic regression models. Multivariable analysis showed that the genotypes carrying G allele of IL-6 (model 1) were significantly associated with an increased risk of SSNHL (OR = 1.828, 95% CI: 1.033-3.233, P = 0.038). Interestingly, the IL-6 -572G and ICAM-1 K469E combination carriers (model 3) showed an increased risk of SSNHL (OR = 3.122, 95% CI: 1.662-5.866, P < 0.001) compared to those without G allele or E allele (model 6).
*P < 0.05 by Cox regression test.
OR, odds ratio; CI, confidence interval.

CC and KK genotype (model 6) was statistically significant with a lowest OR (P = 0.038). Therefore, the CC and KK genotype should not be considered as a risk factor but as a protective factor for SSNHL (OR = 0.432, 95% CI: 0.195-0.956). In contrast, the genotypes carrying G allele of IL-6 (CG/GG, model 1) were significantly associated with an increased risk of SSNHL (OR = 1.828, 95% CI: 1.033-3.233, P = 0.038). Futhermore, the combination of the IL-6 -572G allele with the ICAM-1 469E allele (model 3) showed the highest risk of SSNHL (OR = 3.122, 95% CI: 1.662-5.866, P < 0.001), especially when compared with subjects carrying CC and KK alleles (model 6).

Discussion

The results of this study revealed a positive association between SSNHL and IL-6 (rs1800796) polymorphism. In this study, the patients carrying G allele at IL-6 -572 showed a higher risk of SSNHL compared to those with only C allele. Thus, the IL-6 -572 genotypes carrying G allele might confer susceptibility to the development of SSNHL. On the other hand, no significant difference was observed between cases and controls on the aspect of ICAM-1 K469E genotype. Although the E-allele presented an increased frequency in patients, it was not significantly associated (P = 0.073). Furthermore, we evaluated the combined effects of IL-6 -572C/G and ICAM-1 K469E in the development of SSNHL. Our results suggested that IL-6 and ICAM-1 gene polymorphisms may act synergistically to raise the risk of SSNHL.

The most studied polymorphic site of IL-6 gene is IL-6 -174C/G. However, genetic polymorphisms vary with ethnicity, and the polymorphism of -174C/G is rare in Chinese population (Pan et al. 2011; Gao et al. 2014). We, therefore, investigated the potential association between IL-6 -572C/G polymorphism and SSNHL. Our results were consistent with a previous study which indicated that IL-6 -572C/G polymorphism might influence the susceptibility to SSNHL in Japanese patients (Hiramatsu et al. 2012). The gene encoding ICAM-1 is located on chromosome 19p13.2. Its polymorphic site K469E has been suggested to affect the function of ICAM-1 molecule (Iwao et al. 2004) and influence the risk of inflammatory and autoimmune diseases (Cournu-Rebeix et al. 2003; Lv et al. 2012). Although our study failed to show the independent significant association between ICAM-1 K469E polymorphism and SSNHL, a synergistic effect was indicated between ICAM-1 K469E and IL-6 -572C/G in patients with SSNHL.

There may exist a reciprocal interaction between ICAM-1 and IL-6. By working on experimental animals, Researchers found that the IL-6/IL-6R could induce the augmentation of ICAM-1 in leukocyte recruitment (Romano et al. 1997). Briefly, exposure of IL-6 promoted endothelial cell activation. Consequently, the expression of ICAM-1 on the surface of activated endothelial cell was increased. After adding the IL-6 antibody or IL-6R antibody into conditional medium, the effect of IL-6 on ICAM-1 was blocked (Romano et al. 1997). Similarly, it was reported that ICAM-1 could induce the expression of IL-6 by signal-regulated kinase and p38 mitogen-activated protein kinase pathways (Lee et al. 2000). The interplay between IL-6 and ICAM-1 amplifies inflammation, which shows a negative effect on lipid metabolism and microvascular perfusion, resulting in ischemia. The I/R (ischemia/reperfusion) injury, in turn, increases the expression of Interleukins, generates oxygen free radicals and promotes neutrophil infiltration, which can significantly contribute to microvascular perfusion failures (Bächle et al. 2011; Moreira et al. 2015). In addition, a study in albino guinea pigs revealed that ischemia for 30 min or longer would induce irreversible damage to cochlea (Tsuji et al. 2002). Thus, the synergistic effect of IL-6 -572C/G and ICAM-1 K469E polymorphisms may function by regulating the blood circulation of inner ear whose impairment could lead to a sudden hearing loss. Future study with a larger sample size is needed to confirm our results and to improve understanding of the combined effect of IL-6 -572C/G and ICAM-1 K469E polymorphisms in the pathogenesis of SSNHL.

In conclusion, the IL-6 -572C/G polymorphism is significantly associated with SSNHL prevalence, and there is a combined effect of the IL-6 -572G allele and the ICAM-1 469E allele on the susceptibility of SSNHL.

Conflict of Interest

The authors declare no conflict of interest.

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