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Original Article

# Sudden Sensorineural Hearing Loss Is Related to Endothelial Progenitor Cells and Lipoprotein-Associated Phospholipase A2

**Chao Dong[1], Dong Yang[1], Peng Zhang[1], Sitong Guo[1], Xin Li[2]**

[1]Department of Otolaryngology, General Hospital of Tianjin Medical University, Tianjin, China
[2]Department of Otolaryngology, Beijing Tsinghua Changgung Hospital, Tsinghua University, Beijing, China

ORCID IDs of the authors: C.D. 0000-0003-4329-6908, D.Y. 0000-0001-5919-1997, P.Z. 0000-0002-4300-1842, S.G. 0000-0002-7231-2615, X.L. 0000-0002-6627-3306.

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**BACKGROUND:** This study aimed to investigate the correlation between lipoprotein-associated phospholipase A2, endothelial progenitor cells, and sudden sensorineural hearing loss.

**METHODS:** The number of endothelial progenitor cells and lipoprotein-associated phospholipase A2 levels collected from peripheral blood samples were measured and compared between sudden sensorineural hearing loss group and control group.

**RESULTS:** The number of endothelial progenitor cells was reduced in sudden sensorineural hearing loss group compared to control group (38.88 ± 10.73 in sudden sensorineural hearing loss group vs. 77.14 ± 8.56 in control group, $P < .01$). The lipoprotein-associated phospholipase A2 level was markedly increased in sudden sensorineural hearing loss group compared to control group (244.94 ± 59.547 in sudden sensorineural hearing loss group vs. 189.00 ± 50.987 in control group, $P < .05$).

**CONCLUSION:** The number of endothelial progenitor cells was decreased and lipoprotein-associated phospholipase A2 levels were increased in sudden sensorineural hearing loss patients. Changes in the number of endothelial progenitor cells and lipoprotein-associated phospholipase A2 levels may be involved in the pathogenesis of sudden sensorineural hearing loss.

**KEYWORDS:** Sudden sensorineural hearing loss, lipoprotein-associated phospholipase A2, endothelial progenitor cells, hearing loss, pathogenesis

## INTRODUCTION

Sensorineural hearing loss (SNHL) is one of the leading causes of hearing loss worldwide.[1] In 2012, the World Health Organization reported that more than 360 million people suffer from disabling hearing loss globally.[2] Sensorineural hearing loss (sudden SNHL) is an enigmatic entity, with obscure pathophysiology and debatable efficacy of the treatment agents used.[3] It is commonly defined as SNHL of 30 dB or greater over at least 3 contiguous audiometric frequencies within a 72-hour period.[4] Sensorineural hearing loss has a multifactorial origin that is related to both genetic and environmental factors. Regarding the pathophysiology of SSNHL, several etiologies, such as viral infection, circulatory disorders, labyrinthine membrane rupture, and autoimmune processes, have been presented.[5] Vascular hemorrhage, thrombosis, or vasospasm may explain a decreased cochlear blood flow followed by hypoxia, reduced metabolic activity, and damage to cochlear hair cells.[6] Although numerous treatment modalities have been proposed for SSNHL in the past 80 years,[7] an ideal treatment for idiopathic SSNHL is still controversial due to spontaneous recovery in a great number of patients.[8]

Lipoprotein-associated phospholipase A2 (Lp-PLA2) is secreted by macrophages and is $Ca^{2+}$-independent, which belongs to group VII of the PLA2 superfamily. This enzyme is principally circulated in the blood in the form of a complex with low-density lipoprotein (LDL) and high-density lipoprotein (HDL).[9] Lipoprotein-associated phospholipase A2 is involved in the oxidative modification of LDL in the vascular wall, producing oxidized phospholipids, for example, oxidized non-esterified fatty acids and lysophosph

**Corresponding author**: Xin Li, e-mail: entlixintsinghua@sina.com
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atidylcholine, which promote atherosclerotic plaque development and vascular inflammation. Lipoprotein-associated phospholipase A2 was deemed as a biomarker for vascular dysfunction, as well as a potential target of treatment.[10] Circulatory endothelial progenitor cells (EPCs) are bone marrow-derived cells that contribute to vascular healing and remodeling under physiological and pathological conditions.[11] They can differentiate into ECs in vivo and in vitro, which is indicated by CD31, endothelial nitric oxide synthase, and E-selectin.[12] These cells potentially proliferate and differentiate into mature endothelial cells (ECs),[13] which may be involved in neovascularization of ischemic organs and endothelial repair.[11] Besides, cases who suffer coronary artery disease have a lower number of EPCs than healthy controls.[14] It was also reported that the number of EPCs decreases as the number of cardiovascular risk factors increase.[15] Yang et al[12] pointed out that vascular endothelial growth factor (VEGF) elicits specific chemotactic and permeable effects on the vascular ECs, which may mobilize EPCs into the peripheral circulation, targeting damaged sites and exerting a neoangiogenic effect.[12]

Our study aimed to explore the potential relationship between hematological parameters and SSNHL and to analyze the potential implications of Lp-PLA2 and EPCs in SSNHL.

## METHODS

### Subjects and Inclusion Criteria

Clinical and audiometric data of 16 patients diagnosed as severe SSNHL from January 2018 to December 2019 at our hospital were collected and retrospectively analyzed. This study also recruited 14 healthy controls. The protocol was approved by the Ethic Committee of Tianjin Medical University General Hospital Hospital (No.: 20150911-05). Informed consent was obtained from each patient who participated in this study.

The medical records of patients were analyzed, including clinical data below: gender; age and date of birth; start date of hearing loss; concomitant symptoms (e.g., vertigo, tinnitus, ear fullness, and ear pain); presence of comorbidities, such as diabetes, hypertension, habits and thyroid changes; family history; use of medications; audiometric parameters; and imaging tests. Exclusion criteria were infection, trauma, magnetic resonance imaging-documented retrocochlear disease (e.g., schwannoma), perilymphatic fistula, barotrauma, exposure to ototoxic drugs, inner or middle ear malformation, and Meniere's disease. Moreover, patients with the following comorbidities were also excluded: autoimmune disease, venous or arterial thrombotic disease, liver and/or renal dysfunction, congestive heart failure, endocrine disorder, and hematological disease.

### MAIN POINTS

- An ideal treatment for idiopathic sudden sensorineural hearing loss (SSNHL) remains controversial and needs further investigation.
- The number of endothelial progenitor cells (EPCs) was found to be decreased and lipoprotein-associated phospholipase A2 (Lp-PLA2) levels were increased in SSNHL patients.
- Changes in the number of EPCs and Lp-PLA2 levels may be involved in the pathogenesis of SSNHL.

Besides, patients who took statins were not included because statins may influence circulatory levels of EPCs.[16] Medical history of each patient was taken, and audio-vestibular test was performed based on the literature.[17]

### Hematological Parameters

Venous blood samples were collected in the morning (7:00-9:00 AM) after a fasting period of 8-14 hours using an Ethylene Diamine Tetraacetic Acid (EDTA)-coated tube (final concentration, 0.5 mM). Blood (3 mL) was harvested from each case and gender- and age-matched control after the first 3 mL was disposed, to avoid contamination by circulatory ECs. Routine blood test, coagulation function test, liver function, and renal function test were performed to measure white blood cells (WBCs), red blood cells (RBCs), hemoglobulin, platelet, prothrombin time (PT), PT-international normalized ratio (PT-INR), activated partial thromboplastin time (APTT), thrombin time (TT), fibrinogen, D-dimer, total protein (TP), albumin, globulin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALKP), gamma-glutamyl transpeptidase (GGT), lactate dehydrogenase (LDH), glucose, urea, and creatinine.

For the quantification of circulatory EPCs, we harvested peripheral blood mononuclear cells (PBMCs) from venous blood samples according to the literature[18]. In brief, 3 mL of blood were taken and centrifugation (300 g) was performed at room temperature for 20 minutes. After washing inphosphate-buffered saline (PBS; pH adjusted to 7.2) for 3 times, the separated cells were resuspended in PBS (200 μL) supplemented with EDTA (2 mM) and bovine serum albumin (BSA; 0.5%). The cells were then labeled with fluorescein isothiocyanate (FITC)-conjugated CD34 monoclonal antibody (BD Biosciences, San Jose, Calif, USA) or a R-phycoerythrin-conjugated monoclonal CD133 antibody (provided by Miltenyi Biotec, Bergisch Gladbach, Germany) or both for 20 minutes at room temperature. CD133 and CD34 were used as cellular markers for the identification of circulatory EPCs. CD133 was mainly used to detect immature EPCs that can differentiate into EC, whereas CD34 can identify endothelial stem cells. Stained cells were washed with PBS/BSA, followed by flow cytometry (BD FACSCalibur; BD Biosciences). Two isotype controls of FITC-conjugated mouse immunoglobulin G antibodies and R-phycoerythrin were introduced for non-specific binding. Mononuclear cells were selected first by running on forward and side scatter, and signal noises from cellular debris, platelets, and cell aggregates were decreased by this way. Double-stained cells, $CD133^+$ cells, and $CD34^+$ cells were analyzed, which were expressed as number of positive cells. Cells were first gated based on CD133 and CD34 staining for dual-fluorescence determination. Endothelial progenitor cells were determined as gated cells, and the number of endothelial progenitor cells per $2 \times 10^6$ PBMCs was used for quantification.[18] From separated PBMCs, circulatory EPCs were determined using flow cytometry, which were further verified by double-labeling (using antibodies against CD133 and CD34).[19]

### Hearing Evaluation

Before electronic otoscopy, examinations were performed to ensure the absence of ear cerumen and secretions, integrity of tympanic membranes, and patency of the external auditory canal. Pure tone audiometry was performed using a pure tone audiometer (MADSEN Itera, Copenhagen, Denmark), and air and bone conduction thresholds at 125, 500, 1000, 2000, 4000, and 8000 Hz were recorded in a

standard soundproof room with background noise below 30 dBSPL. Pure tone average (PTA) thresholds at frequencies of 0.5-1-2 kHz were calculated for each ear and were used to classify the degree of hearing loss as follows: profound, over 91 dB; severe, 71-91 dB; moderate, 41-71 dB; and mild, 21-41 dB. Hearing was assessed at the first visit. The audiograms were examined and hearing thresholds at 250, 500, 1000, 2000, 4000, and 8000 Hz were recorded.

### Statistical Analysis

Statistical Package for the Social Sciences 19.0 software (IBM SPSS Corp.; Armonk, NY, USA) was used to conduct the statistical analysis, and the results were expressed as mean ± standard deviation (SD). For comparisons between 2 groups, the Student's *t*-test was employed for normally distributed data, while non-parametric tests were used for continuous data not obeying normal distribution. Chi-square test or Fisher's exact test was used if appropriate. $P < .05$ was considered statistically significant.

## RESULTS

The hearing threshold was recorded at the frequencies of 250, 500, 1000, 2000, 4000, and 8000 Hz. The PTA in SSNHL group was >80 dB, and hearing thresholds of all patients in the SSNHL group were greater than 80 dBnHL. There were 14 participants in normal group, with PTA < 21 dB.

The clinical information of subjects with SSNHL and healthy controls is summarized in Table 1. The mean age of patients in SSNHL group and control group was 50.63 ± 14.91 and 49.71 ± 12.59 years old, respectively ($P > .05$). In SSNHL patients, hearing loss was at the left in 6 ears, at the right in 8 ears, and at both ears in 2 cases. Eight patients (50%) in the SSNHL group complained of tinnitus, while tinnitus was absent in the control group. The number of cases who had risk factors, for example, diabetes and hypertension, was similar in the 2 groups ($P > .05$). In addition, vestibular dysfunction was found in 2 patients in SSNHL group.

The results of routine blood test, coagulation function, liver function, and renal function showed that significant difference was not found in WBC, RBC, hemoglobin, platelet, PT-INR, APTT, TT, fibrinogen, D-dimer, TP, albumin, globulin, ALT, AST, ALKP, GGT, LDH, glucose, urea, and creatinine between the 2 groups (Tables 2-4). However, a significant difference was found in the number of EPCs and Lp-PLA2 levels (Table 5). In SSNHL group, the number of EPCs was 38.88 ± 10.73, which was significantly lower than that in the control group (77.14 ± 8.56, $P < .01$). In addition, compared with the control group, Lp-PLA2 levels were markedly elevated in the SSNHL group ($P < .05$).

**Table 1.** Clinical Characteristics of Cases in SSNHL Group and Control Group

| Parameters | SSNHL Group (n = 16) | Control Group (n = 14) | *P* |
|---|---|---|---|
| Age (years) | 50.63 ± 14.91 | 49.71 ± 12.59 | .859 |
| Sex (male/female) | 9/7 | 9/5 | .667 |
| Side of HL | 6L/8R/2B | NA | NA |
| Tinnitus | 50% | 0 | >.05 |
| Hypertension | 25% (4/16) | 29% (2/14) | .268 |
| Diabetes | 18.75% (3/16) | 21.43% (3/14) | >.05 |
| Vestibular | 12.5% (2/16) | 0 (1/14) | >.05 |

HL, hearing loss; NA, not available; SSNHL, sudden sensorineural hearing loss; L, left side; R, right side; B, both sides.

**Table 2.** The Results of Routine Blood Test

| Parameters | Control Group (n = 14) | SSNHL Group (n = 16) | *P* |
|---|---|---|---|
| WBC | 5.7907 ± 1.54517 | 7.481 ± 2.40951 | .082 |
| RBC | 4.6986 ± 0.42995 | 4.7013 ± 0.50429 | .988 |
| Hemoglobulin | 142.29 ± 14.166 | 138.56 ± 20.884 | .578 |
| Platelet | 222.50 ± 44.838 | 245.94 ± 61.323 | .248 |

WBC, white blood cells; RBC, red blood cells; SSNHL, sudden sensorineural hearing loss.

**Table 3.** Results of Coagulation Test

| Parameters | Control Group (n = 14) | SSNHL Group (n = 16) | *P* |
|---|---|---|---|
| PT | 10.83 ± 0.779 | 10.96 ± 0.807 | .648 |
| PT-INR | 0.99 ± 0.072 | 1.00 ± 0.072 | .597 |
| APTT | 29.371 ± 3.0530 | 28.931 ± 3.0267 | .695 |
| TT | 19.364 ± 0.8473 | 19.563 ± 1.3475 | .639 |
| Fibrinogen | 2.8043 ± 0.36106 | 2.8550 ± 0.59110 | .783 |
| D-dimer | 423.21 ± 555.433 | 276.19 ± 139.953 | .314 |

PT, prothrombin time; PT-INR, prothrombin time-international normalized ratio; TT, thrombin time; APTT, activated partial thromboplastin time; SSNHL, sudden sensorineural hearing loss.

## DISCUSSION

In the present research, we analyzed 16 SSNHL patients who experienced a serious sudden deafness within 3 days. Pure tone average showed that hearing thresholds of patients in the SSNHL group were greater than 80 dB. In short term, SSNHL patients suffer from severe impairment of inner ear function. In recent years, several scholars

**Table 4.** Results of Liver Function and Renal Function Tests

| Parameters | Control Group (n = 14) | SSNHL Group (n = 16) | *P* |
|---|---|---|---|
| TP | 72.64 ± 5.583 | 73.25 ± 4.626 | .747 |
| Albumin | 42.21 ± 2.723 | 43.31 ± 2.983 | .304 |
| Globulin | 30.43 ± 3.837 | 29.94 ± 3.890 | .731 |
| ALT | 23.43 ± 11.386 | 26.31 ± 14.755 | .558 |
| AST | 24.57 ± 12.948 | 21.19 ± 9.586 | .419 |
| ALKP | 66.29 ± 13.909 | 69.13 ± 15.958 | .610 |
| GGT | 24.93 ± 15.041 | 34.31 ± 22.928 | .203 |
| LDH | 165.81 ± 28.247 | 159.46 ± 25.772 | .525 |
| Glucose | 4.600 ± 0.6279 | 4.764 ± 0.9842 | .677 |
| Urea | 5.079 ± 0.9625 | 4.994 ± 0.8629 | .801 |
| Creatinine | 63.57 ± 15.863 | 58.31 ± 11.377 | .301 |

TP, total protein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALKP, alkaline phosphatase; GGT, γ-glutamyl transpeptidase; LDH, lactate dehydrogenase; SSNHL, sudden sensorineural hearing loss.

**Table 5.** The Number of EPCs and Lp-PLA2 Levels in the 2 Groups

| Parameters | Control Group (n = 14) | SSNHL Group (n = 16) | *P* |
|---|---|---|---|
| EPCs | 77.14 ± 8.56 | 38.88 ± 10.73 | .000 |
| Lp-PLA2 | 189.00 ± 50.987 | 244.94 ± 59.547 | .011 |

EPCs, endothelial progenitor cells; Lp-PLA2, lipoprotein-associated phospholipase A2.

attempted to find out the pathogenesis of hearing loss by investigating the effects of blood and coagulation parameters on SSNHL, while opposite conclusions are often drawn. The results of routine blood test, liver function test, and renal function test demonstrated that significant differences were not found in WBC, RBC, hemoglobulin, platelet, TP, albumin, globulin, ALT, AST, ALKP, GGT, LDH, glucose, urea, and creatinine between the 2 groups. Besides, no significant differences were found in nutritional levels or renal and liver function parameters between the 2 groups. Mirvakili et al conducted a prospective case–control study, and it was found that none of the 3 examined parameters, including platelet count, mean platelet volume, and platelet distribution width, had a significant relationship with the occurrence of SSNHL. In contrast, hematological data of 348 and 31 SSNHL patients were analyzed in 2 studies, and platelet count values of SSNHL patients and healthy controls were reported to be significantly different.[3] In the current research, no significant difference in PLT levels was found between patients with hearing improvement and those without, which is consistent with Mirvakili et al's' findings. Similarly, there was no significant difference in parameters associated with blood coagulation function (PT, PT-INR, APTT, TT, fibrinogen, and D-dimer) between the 2 groups. In the present research, the coagulation function of patients with SSNHL was not noticeably affected, and the patients were not in the state of hypercoagulability.

It has been revealed that circulatory EPCs are elevated in cases of acute vascular damage, including vascular trauma, limb ischemia, and acute myocardial infarction and could be attenuated when there are cardiovascular risk factors.[12] Endothelial progenitor cells, derived from bone marrow, may differentiate into mature EC in peripheral circulation[20] and engage in neovascularization of ischemic organs and endothelial repair.[21,22] In the SSNHL group, the number of EPCs was 38.88 ± 10.73, which was significantly lower than that in the control group (77.14 ± 8.56, $P < .01$). In cases with SSHNL, the decreased number of EPCs may affect wound repair and angiogenesis. In our previous studies, the expression of VEGF in cochlea increased with the upper hearing threshold, further leading to increased number of EPCs in PBMCs in noise-induced hearing loss. After increasing the number of EPCs in peripheral blood samples, it was found that the function of cochlear was preserved compared with the control group. The degree of hearing loss after the number of EPCs was decreased was higher compared to the control group. As a result, the vascular endothelium of the inner ear was affected, leading to hearing loss, and the repair function of vascular endothelium was improved, which resulted in changes in inner ear microenvironment and redox reaction. The above-mentioned findings confirmed that EPCs are closely correlated with the level of hearing. This indicates that the repair of the cochlear vascular endothelium plays an important role in the process of hearing loss. In addition, it was observed that after hearing loss, the regeneration of blood vessels and the repair of endothelium were commenced.

In the present study, compared with the control group (189.00 ± 50.987), Lp-PLA2 levels were significantly elevated in the SSNHL group (244.94 ± 59.547)($P < .05$). The serum Lp-PLA2 level in SSNHL group was significantly different from that in the control group. Our findings revealed that the Lp-PLA2 level was positively correlated with SSNHL. Lipoprotein-associated phospholipase A2 inhibited cell viability and endothelium vasodilation and also induced the secretion of adhesion molecules, resulting in the downregulation of AMPK. Phosphorylation of AMPK can reverse the decline of cell viability induced by oxidized low-density lipoprotein, stimulate the secretion of NO, reduce the expression and secretion of EF-1, and decrease the increase of endothelial cell adhesion molecules induced by tumor necrosis factor. Eeukaryotic elongation factor-1 is a marker of vascular injury, which is related to the constriction of blood vessels, and it can not dilate vessels.[23] Lipoprotein-associated phospholipase A2 is deemed as a biomarker for vascular dysfunction and as a potential target of treatment.[10] It is believed that changes in Lp-PLA2 levels may provide evidence for cochlear perfusion. Besides, Lp-PLA2 may serve as an indicator for SSNHL.

In summary, the number of EPCs was decreased and Lp-PLA2 levels were increased in SSNHL patients. Changes in the number of EPCs and Lp-PLA2 levels may be involved in the pathogenesis of SSNHL. Further investigation on EPCs and Lp-PLA2 may be significant for the diagnosis and treatment of SSNHL.

### Limitations

First, the association between SSNHL and hematological parameters was lacking. Second, bias may be present due to retrospective nature of the study. Third, the sample size was relatively small. Thus, our findings remain to be further verified by large-sample well-designed prospective studies.

**Ethics Committee Approval:** Ethical committee approval was received from the Ethics Committee of Tianjin Medical University General Hospital Hospital (approval No: 20150911-05).

**Informed Consent:** Written informed consent was obtained from all participants who participated in this study.

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