Original Article

Ischemia-modified albumin levels in patients with idiopathic sudden sensorineural hearing loss

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ABSTRACT

Objectives: This study aims to investigate whether serum levels of ischemia-modified albumin (IMA) are associated with idiopathic sudden sensorineural hearing loss (ISSNHL).

Patients and Methods: Between December 2015 and June 2017, a total of 17 patients (9 males, 8 females; mean age 49.4±18.0 years; range, 24 to 88 years) with ISSNHL and 24 age- and sex-matched healthy individuals (12 males, 12 females; mean age 44.5±13.3 years; range, 30 to 81 years) as the control group were included in the study. All patients underwent audiometric examination at the time of admission immediately before the beginning of the treatment and weekly after treatment initiation until one month using the Interacoustics AC40 audiometer. Serum IMA levels were evaluated using blood samples from the antecubital vein of both patient and control groups. The samples were centrifuged to separate the serum from the cells. Albumin cobalt binding test was used for IMA measurement.

Results: The mean IMA level was 0.374±0.081 absorbance units (ABSU) (range, 0.205 to 0.536) in the study group at the time of diagnosis, 0.358±0.051 ABSU (range, 0.297 to 0.466) in the post-treatment period, at least four weeks after onset, and 0.358±0.053 ABSU (range, 0.281 to 0.434) in the control group. There was no statistically significant difference between the patient and control groups. The IMA levels of the patients with ISSNHL in the post-treatment period were lower than the onset of illness, although this difference was not statically significant (0.440).

Conclusion: Our study results demonstrated that serum IMA levels in the patients with ISSNHL did not differ from the control group.

Keywords: Ischemia-modified albumin, idiopathic sudden sensorineural hearing loss.

Idiopathic sudden sensorineural hearing loss (ISSNHL) is defined as a decline in sensorineural hearing of ≥30 dB in three contiguous speech frequencies in less than a 72 hours period with no identifiable etiology. The incidence of ISSNHL ranges from 5 to 27/100,000 persons per year.[1,2] Although it may affect all ages, it is more commonly seen through the fifth and sixth decades of life.[3] The causes of sudden sensorineural hearing loss are obscure in most cases. Merely, in a limited number of cases, specific factors have been identified, while the remaining is considered ISSNHL. Viral, ischemic, vascular, hypoxic, and autoimmune pathologies

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have been hypothesized as etiologies.[4-7] In respect to vascular support, cochlea is a vulnerable organ, as it is an end-organ and its blood supply is maintained by only the labyrinthine artery. Dysfunctional microcirculation caused by vascular disorders, endothelial dysfunction, dysregulated hemostatic factors lead to cochlear injury and dysfunction secondary to anoxia or hypoxia. Although the relation between ISSNHL and cardiovascular diseases or stroke is not clear yet, some authors have suggested that sudden sensorineural hearing loss is associated with an increased risk of acute myocardial infarction and stroke due to common pathological mechanisms.[8,9]

Ischemia-modified albumin (IMA) is a marker of oxidative stress and tissue ischemia.[10,11] Structure of the N-terminal amino side of serum albumin is altered and disrupted by ischemia, oxidative stress, and hypoxia. The N-terminal location of the albumin molecules is bound to transitional metals such as nickel, copper, and cobalt.[11,12] The N terminus of albumin is changed from interaction between albumin and reactive oxygen species, weaken its binding capacity for metals due to this interaction and conclude the formation of IMA. The mechanism behind the alteration of serum albumin to IMA lies in the superoxide-radical injury due to hypoxia and/or ischemia.[10,13] Ischemia-modified albumin has been used as a diagnostic test for identifying myocardial ischemia. The elemental procedure of this test is based on measuring the binding capacity of serum albumin for cobalt which is reduced after oxidation.[10] An increased amount of IMA has been reported in various diseases which are associated with inflammation, ischemia, and oxidative stress such as acute coronary syndrome, cerebrovascular-ischemic stroke, peripheral vascular disease, systemic sclerosis, acute infections, malignancies, intrauterine disorders, nasal polyps, and obstructive sleep apnea.[14-16] Based on all these data, we believe that IMA formation occurs due to increased oxidative stress condition which affects many other organs, not only myocardium.

In the present study, we aimed to evaluate serum levels of IMA in patients with ISSNHL compared to healthy controls.

PATIENTS AND METHODS

This study was conducted at Departments of Otorhinolaryngology of Health Sciences University, Umraniye Training and Research Hospital and Faculty of Medicine, Istanbul Medipol University between December 2015 and June 2017. A total of 17 patients (9 males, 8 females; mean age 49.4±18.0 years; range, 24 to 88 years) with ISSNHL and 24 age- and sex-matched healthy individuals (12 males, 12 females; mean age 44.5±13.3 years; range, 30 to 81 years) as the control group were included in the study. *Inclusion criteria were as follows:* ISSNHL defined as ≥30 dB hearing loss in no less than three consecutive frequencies in pure tone average (PTA) within 72 hours of disease onset. Those with no previous treatment, hearing loss without a recognizable cause, time elapsed between the awareness of disease and applying to clinic not after 24 hours were included in the study. *Exclusion criteria were as follows:* having a history of acoustic tumor, acute or chronic middle ear diseases, autoimmune diseases, otosclerosis, acoustic trauma history, Meniere's disease or rupture of the round window membrane, head or temporal area trauma, multiple sclerosis, infectious diseases or neurological disorders involving the auditory pathways, or use of ototoxic drugs. Patients with concurrent acute ischemic cardiovascular or cerebrovascular diseases were also excluded from the study. A written informed consent was obtained from each participant. The study protocol was approved by the Istanbul Medipol University Ethics Committee. The study was conducted in accordance with the principles of the Declaration of Helsinki.

All patients underwent a thorough otolaryngologic history taking and detailed physical examination. Audiometric evaluation was performed at the time of admission and repeated weekly after the initiation of the treatment for a month. Pure-tone thresholds were obtained for both air conduction and bone conduction at frequencies of 250, 500, 1,000, 2,000, 4,000, 8,000 Hz and at 250, 500, 1,000, 2,000, 4,000 Hz respectively. Hearing examination of the patients was performed using a clinical audiometer (AC 40, Interacoustics, Middelfart, Denmark). The PTA was quantified as an average

threshold measured at 250, 500, 1,000, 2,000, 4,000, and 8,000 Hz.

Methylprednisolone (Prednol; Mustafa Nevzat İlaç Sanayi, Istanbul, Turkey) was used for all patients, except one. It was administered at a dose of 1 mg/kg per oral for the first four days and, then, its dose was tapered daily. Systemic corticosteroids treatment was terminated at the minimum dose on Day 12. For one patient, due to other accompanying diseases such as previous gastrointestinal hemorrhage from ulcer disease and diabetes mellitus, intratympanic therapy was used. All patients were concomitantly administered an oral proton pump inhibitor. To one patient, an ear ventilation tube (inner diameter, 1.14 mm) was placed in the posterior-inferior quadrant of the tympanic membrane under local anesthesia. After the appropriate position was given to the patient and evenly warmed to the body temperature the dexamethasone (Onadron 1 mg/mL; I.E. Ulagay İlaç Sanayi, Istanbul, Turkey) insert five drops through the external auditory canal four times a day. The patient was examined daily to check whether the drug was applied correctly. The treatment continued for two weeks.

Measurement of serum IMA

To quantify serum IMA levels, venous blood samples were taken from the antecubital vein of both patient and control groups. The samples were placed into plain jelly biochemistry tubes and centrifuged at 4,000 rpm for 10 min to separate the serum from the cells. Then, sera were stored at -80°C until analysis. All specimens were transported under suitable conditions. The IMA measurement was performed using a calorimetric method described by Bar-Or et al.[13] This colorimetric assay measures complexes of dithiothreitol (DTT) with unbound cobalt. The test was performed initially by adding 50 µL 0.1% cobalt chloride to 200 µL serum and mixed, then, it was incubated for 10 min to allow albumin-cobalt binding. Next, 50 µL 1.5 mg/mL DTT compound was added to give way to reaction of free cobalt for two min. Then, the reaction was halted by adding 0.9% sodium chloride. The same method was applied to the sample blank. Meanwhile, water was used to prepare the sample blank, not DTT. The absorbance values (ABSU) were calculated at 470 nm in Shimadzu UV-1201 spectrophotometry (Shimadzu Corp., Kyoto, Japan). The IMA value was accepted as the difference between the sample and sample blank. The Intra-assay and inter-assay coefficient of variation, % values of the method were 3.20 and 3.91, respectively.

Statistical analysis

Statistical analysis was performed using the IBM SPSS version 20.0 software (IBM Corp., Armonk, NY, USA). Descriptive data were expressed in mean ± standard deviation (SD) or number and frequency. The normality of variables was examined using the Shapiro-Wilk and Kolmogorov-Smirnov tests. The chi-square test was utilized to check against qualitative variables. Quantitative variables with normal distribution were compared using the independent sample t-test, while non-normally distributed variables were compared using the Mann-Whitney U test.

Table 1. Baseline demographic and clinical characteristics of patients and healthy individuals

	ISSNHL group (n=17)			Control group (n=24)			
	n	Mean±SD	Range	n	Mean±SD	Range	*p*
Age (year)		49.4+18.0	24-88		44.5+13.3	30-81	0.321*
Gender							0.654**
Male	9			12			
Female	8			12			
SNHL side							
Right	7			-			
Left	10			-			

SD: Standard deviation; * Independent sample t-test; ** Chi-square test; ISSNHL: Idiopathic sudden sensorineural hearing loss; SNHL: Sensorineural hearing loss.

Table 2. Patients and control group IMA values

	ISSNHL group (n=17)	Control group (n=24)	
	Mean±SD	Mean±SD	*p**
Pre-treatment IMA (ABSU)	0.374±0.081	0.358±0.053	0.429
Post-treatment IMA (ABSU)	0.358±0.051	0.358±0.053	0.975
*p***		0.440*	

ISSNHL: Idiopathic sudden sensorineural hearing loss; SD: Standard deviation; IMA: Ischemia-modified albumin; ABSU: Absorbance units; * Independent samples t-test; ** Paired samples test.

Paired sample t-test was used to compare two dependent variables. A *p* value of <0.05 was considered statistically significant.

RESULTS

There was no significant difference in the age and sex of the patients and healthy controls (p=0.654 and p=0.321, respectively). Baseline demographic and clinical characteristics of both groups are shown in Table 1.

The mean IMA quantity was 0.374±0.081 ABSU (range, 0.205 to 0.536) in the patient group at the time of diagnosis and 0.358±0.053 ABSU (range, 0.281 to 0.434) in the control group. There was no statistically significant difference between the groups (p=0.429). The mean IMA amount of ISSNHL patients in the post-treatment period, at four weeks later onset, was 0.358±0.051 ABSU (range, 0.297 to 0.466). There was no statistically significant difference between the mean IMA levels in the post-treatment period of ISSNHL patients and healthy controls (p=0.975). In addition, although not statically significant, the IMA levels of patients at the time of diagnosis were higher than the control groups. In the post-treatment period, these levels were similar to the control group. Also, the IMA levels of patients with ISSNHL in the post-treatment period were lower than the disease onset, although this difference was not statically significant (p=0.440) (d=0.192). The IMA levels of both groups are presented in Table 2 and Figure 1.

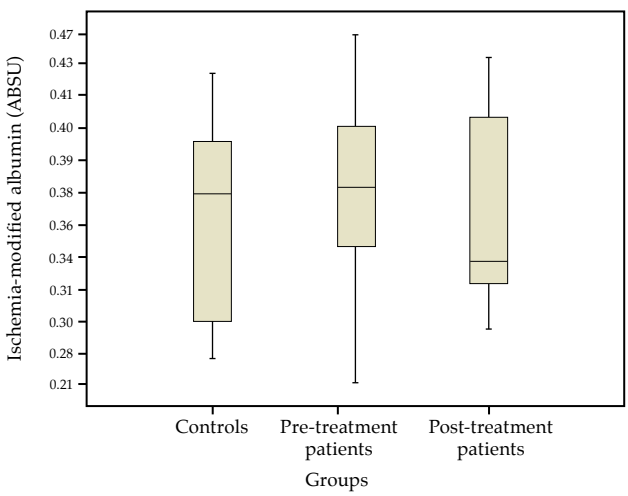

Figure 1. Serum ischemia-modified albumin levels of patient and control groups at the pre- and post-treatment period.

DISCUSSION

The present study investigated the relationship between the IMA levels of peripheral blood samples of patients with ISSNHL and healthy individuals. The causes of ISSNHL still remain unclear. The research on its etiology is limited by the difficulty of histopathologic exploration, as ISSNHL is not associated with mortality and cochlea tissue sample typically cannot be obtained at the time of the disease onset. To date, many different etiologic causes of ISSNHL have been proposed including viral, vascular, or inflammatory metabolic; however, little is known about its pathogenesis. Among all causes which have been proposed, the two most common pathways in the development of ISSNHL are viral and vascular-induced cochlear ischemia.[1]

The cochlea is vulnerable to ischemic attack due to lack of anastomosis.[6] Several studies have been carried on pathogenesis of ISSNHL with many focusing on oxidative stress, vascular disturbance, and ischemia. Rudack et al.[17] reported a relationship between

ISSNHL and vascular risk factors such as hyperfibrinogenemia and microembolisms, indicating that a local ischemic circumstance might play a pathophysiological role. Elevated plasma fibrinogen plays also a key role in cardiovascular diseases. It is postulated that it may play a role in the pathogenesis of sudden hearing loss, as well.[18] The study performed by Park et al.[19] provided data on the poor recovery rate in ISSNHL patients with hyperfibrinogenemia at the onset of the disorder. Hyperfibrinogenemia causes high viscosity and vascular reaction which, in turn, ends in vascular dysfunction.[20] There are also authors advocating hypercoagulation as a cause for ISSNHL and cardiovascular diseases.[21] Gul et al.[22] investigated oxidative imbalance in sudden hearing loss and found that total oxidant status levels were higher in patients suffering from ISSNHL than the healthy control group. Higher procalcitonin levels were detected in ISSNHL patients, compared to healthy individuals, as reported by Göde et al.[23] Kim et al.[24] also reported that vertebrobasilar loop was associated with a sudden sensorineural hearing loss in their study which provided more proof toward importance of ischemia as a potential cause for ISSNHL.

It is well-known that IMA values increase considerably with existing ischemia.[14] Ischemia-modified albumin is produced as a result of tissue hypoxia which is a known marker of oxidative stress and ischemia.[25] The IMA is accepted as the most sensitive biomarker in identification of myocardial ischemia where necrosis does not occur.[14] However, it is not an organ-specific ischemic marker. Recently, IMA has been investigated in several diseases. Ataş et al.[26] suggested that elevated levels of IMA in patients with vitiligo were a consequence of elevated oxidative stress. Similarly, Özdemir et al.[27] and Chandrashekar et al.[28] reported increased IMA levels in psoriasis patients. Li et al.[29] concluded that IMA could be used as reference for early diagnosis and prognosis in acute carbon monoxide poisoning. There are many studies on the association between hypothyroidism or hyperthyroidism and IMA levels, showing an increased oxidative stress status.[30,31] While majority of them demonstrate a significant correlation between IMA and thyroid hormones, Ersoy et al.[32] found no significant correlation. A study including patients with obstructive sleep apnea reported that serum amounts of IMA increased with the presence and severity of disease.[33] It was also reported that increased serum IMA levels might be regarded as a marker of increased tissue hypoxia in patients with acute leukemia.[34] In addition, in recent years, several studies have shown an interest to IMA levels and its possible correlation with diseases such as chronic obstructive pulmonary disease, acute rheumatic fever, and nasal polyposis.

To the best of our knowledge, no data is available in the literature on IMA levels in patients with ISSNHL. In our study, we found that there was no statistically significant difference for IMA levels between the patients and control group. Although the value of IMA in pre-treatment blood samples of patients higher than post-treatment values, this difference was not statistically significant. One explanation for this is that, as IMA has a short half-life, IMA levels might have decreased between the onset of the disease and the time of awareness of the disease by patients. The time between the onset of the disease and the awareness of the disease is unknown.

The main limitation of our study is its relatively small sample size. The lack of an evaluation for ischemic biomarkers or oxidative stress parameters and lack of data for serial IMA levels in the control group are the other limitations. Similar to our study, Einer et al.[7] evaluated the possible causal role of pathological hemostatic mechanisms in ISSNHL and they were unable to find any major impact on the pathogenesis of sudden deafness.

In conclusion, our study results demonstrated that serum IMA levels in the patients with ISSNHL did not differ from the control group. However, this is a preliminary study in which we were unable to obtain results clearly supporting the ischemic hypothesis of ISSNHL, although it does not completely reject it. Therefore, further large-scale, prospective studies are needed to confirm these findings.

Declaration of conflicting interests

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