Serum galectin-3 and α-1-acid glycoprotein levels in diagnosis and prognosis of idiopathic sudden sensorineural hearing loss

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Abstract. Idiopathic sudden sensorineural hearing loss (ISSNHL) is an otological emergency in which etiopathogenesis remains unclear. A number of disorders is considered as the cause; therefore, different treatment modalities are used without certainty of a cure. The present study aimed to analyse the potential correlation between serum α-1-acid glycoprotein (AGP) and galectin-3 levels with ISSNHL, and to investigate markers for guidance of treatment. A total of 55 patients with ISSNHL [29 (52.7%) female, 26 male, mean age, 46.76±17.68 years] and 47 healthy volunteers [25 (53.2%) female, 21 male, mean age, 43.95±12.96 years) were included in the study. The complete blood count, erythrocyte sedimentation rate, C-reactive protein, serum galectin-3 and AGP levels were evaluated. The audiological investigation included pure tone average and speech discrimination scores were also recorded before and after corticosteroid treatment. Serum AGP levels in the study group vs. the control group were 64.08±25.10 and 67.01±21.59 mg/dl (P=0.53), respectively. Galectin-3 levels were 16.80±4.55 in the study group and 15.15±3.74 ng/ml in the control group (P=0.05). Serum galectin-3 levels were significantly correlated with unresponsiveness to treatment (P<0.001). Galectin-3 is an important biomarker for patients with ISSNHL. Patients with high serum galectin-3 levels may be unresponsive to standard therapy.

Introduction

Idiopathic sudden sensorineural hearing loss (ISSNHL) is defined as sensorineural hearing loss of ≥30 dB, including at least three consecutive audiometric frequencies, started within 72 h, and is generally unilateral without any known aetiology (1). It affects 5-20 patients in 100,000 population (2). SSNHL is an otological emergency with unknown etiopathology. Infection, vascular pathology, blood disorders, ototoxic drugs and immune and metabolic disorders are common causes (3).

α-1-acid glycoprotein (AGP) is an acute-phase reactant that acts against inflammation in the body. AGP levels are also higher in acute inflammation, such as viral infections, which is hypothesized to be the cause of ISSNHL (4). AGP increases in response to systemic injuries, inflammation, infection or tissue damage (5). AGP has immunomodulatory activity and regulates neutrophil migration and superoxide generation (6).

Galectin-3 is considered to be a multifunctional oncogenic protein responsible for cell adhesion, angiogenesis, proliferation and apoptosis (7). It is also responsible for ischemia and vascular damage (8).

As the etiopathology of ISSNHL is unclear, its treatment is controversial. Systemic or intratympanic steroids, vasodilators or hyperbaric oxygen treatment can be used. Systemic corticosteroids are generally the first choice, although they have adverse effects (9). such as acne, weight gain, fatty liver, atherosclerosis, peptic ulcer, hypertension, diabetes mellitus, Cushingoid appearance, adrenal insufficiency, osteonecrosis, myopathy, impaired wound hearing, increased susceptibility to infections, atherosclerosis, osteoporosis, glaucoma, cataracts, pancreatitis, emotional lability, psychosis, pseudotumor cerebri can be seen (10).

The present study evaluated serum AGP and galectin-3 levels in patients with ISSNHL and aimed to investigate the correlation between these markers and severity of disease and response to treatment.

Materials and methods

Patient selection. Patients (29 female, 26 male; aged between 21 to 78) diagnosed with ISSNHL between January 2018 and January 2020 in Ufuk University Ridvan Ege Hospital, Ankara, Turkey were included in the present study. ISSNHL was defined as a unilateral hearing loss ≥30 dB for at least three consecutive frequencies occurring within three days. Patients were hospitalized and temporal bone magnetic resonance imaging was performed (data not shown). Disorders

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Table I. Laboratory findings of participants in the control and study groups.

Characteristic	Control group (n=47; mean ± SD)	Study group (n=55; mean ± SD)	P-value
White blood cell, $1x10^3/\mu l$	6.9±0.9	7.1±1.1	ns
Haemoglobin, g/dl	14.2±1.4	14.1±1.5	ns
Platelet, $10^3/\mu l$	232±35.2	245±46	ns
C-reactive protein, mg/dl	2.8±2.3	3.4±2.8	ns
E Erythrocyte sedimentation rate, mm/h	2.2±1.2	1.9±1	ns
α-1-acid glycoprotein, ng/ml	67.01±21.6	64.1±25.1	0.087
Galectin-3, ng/ml	15.2±3.7	16.80±4.6	0.050

Ns, non-significant; SD, standard deviation.

such as vestibular schwannoma, cerebrovascular disease and intracerebral malignancies were criteria for exclusion from the study. Patients with head trauma, a history of surgery, use of ototoxic drugs and chronic disease such as diabetes, hypertension, autoimmune or liver diseases, renal failure or cancer were also excluded. Zinc is essential in systemic inflammation because it is an anti-inflammatory and antioxidant element (11). Serum zinc levels were also measured and patients with low zinc levels (<10 μmol/l) were excluded.

The control group (25 female, 22 male; aged between 26-65 ages) consisted of healthy volunteers without trauma, surgery, other chronic disease or drug users who had no otological complaints or ear pathologies between 18 and 65 years of age between January 2018 and December 2020 in Ufuk University, Ridvan Ege Hospital.

The local ethics committee of Ufuk University, Ankara, Turkey, approved the present study (approval no. 30042015-6). Written Informed consent was obtained from all patients and healthy volunteers.

Audiological examination. All participants underwent detailed otological and audiological examination. Audiological examinations were in an isolated, quiet chamber performed using the same clinical audiometer (Interacoustics AC-33 Clinical Audiometer; Assens).

Patient audiograms were divided into three groups: i) Downward sloping (falling curves) including sensorineural hearing loss at high frequencies; ii) 'U-shaped' or 'cookie bite', including sensorineural hearing loss in mid-frequencies and iii) all the frequencies >90 dB, defined as profound loss. Pure tone average (PTA) was calculated using the mean value of the frequencies of 250, 500, 1,000, 2,000, 3,000, 4,000, 6,000 and 8,000 Hz. Speech discrimination score (SDS) was measured by correctly identifying monosyllabic words from 50 selected words. PTA and SDS were calculated before and after treatment in the study group.

Hearing thresholds were recorded at the onset of disease and at 30 and 180 days of treatment. Improvement was defined as >10 dB improvement in PTA or 15% improvement in SDS. No recovery was described as <10 dB improvement in PTA (1). PTA improvement was calculated by subtracting the post-treatment PTA score from the pre-treatment PTA score of the same patient.

Treatment strategy. All patients were treated with prednisone (Precort-Liyo, Koçak Farma IlaC ve Kimya Sanayi A.S.) at a dose of 1 mg/kg/day (max dose, 60 mg) and the doses were gradually decreased (20 mg/3 days for 2 weeks.

Laboratory measurements. Blood samples (10 ml) were collected on the first day of hospitalization. Complete blood count, including white blood cell count, haemoglobin level, platelet count was measured with autoanalyzer (Abbott Cell-Dyn Ruby; Serial no. 54507BG; Abbott Diagnostics, Illinois, USA). Electrolyte and other biochemical parameters were analyzed with autoanalyzer (Abbott Architect c8000, Abbott Diagnostics). The Architect cSystems ICT (Integrated Chip Technology) is used for the quantitation of sodium, potassium and chloride in human serum. Erythrocyte sedimentation rate was analyzed with Cystat erythrocyte sedimentation rate analyzer (ESR 20-4-100). C-reactive protein level was measured with immunoturbidimetric assay (Abbott Architect c8000, Abbott Diagnostics).

Serum samples were obtained after blood samples were centrifuged at 2,500 g for 12 min in room temperature and stored at -80˚C. Serum galectin-3 levels were analysed with an autoanalyzer (Architect, G6-6005/R05, B5P03T, Abbott Pharmaceutical Co. Ltd.) using chemiluminescent microparticle immunoassay principles. The assay is based on two specific monoclonal antibodies 87B5 and M3/38. In the first step, galectin-3 in the sample and M3/38 anti-galectin-3 coated microparticles were combined. After washing, 87B5 anti-galectin-3 conjugate was added. Following another wash, pre-trigger and trigger solutions were added to result in chemiluminescent reaction. The amount of galectin-3 in the sample was detected by the Architect i System optics.

AGP levels were analysed using a QUANTIA A-1-AGP kit (Abbott Architect c 8000; Abbott Pharmaceutical Co. Ltd.). Intra-assay and inter-assay coefficient variation values were defined as 1.0 and 1.2%, respectively.

Statistical analysis. Data analysis was performed using IBM SPSS version 21.0 (IBM Corp.). The distribution of variables was determined using the Kolmogorov-Smirnov test. All data are presented as the mean ± standard deviation. Mann-Whitney and Kruskal-Wallis H tests were used to evaluate the differences between groups. The χ^2 test was used for categorical variables. The degree of association between continuous variables was

Table II. Pure tone average and speech discrimination score of the control and study groups.

Characteristic	Control group (n=47; mean ± SD)	Study group (n=55; mean ± SD)		P-value[a]
		Unaffected side (side without hearing loss)	Affected side (side with hearing loss)	
Pure tone average, dB	21.3±5.7	25.0±13.7	60.4±21.7	<0.001
Speech discrimination score, %	95.0±3.7	92.4±7.7	49.7±27.9	<0.001

[a]Control vs. affected side in the study group. SD, standard deviation.

Table III. Correlations between galectin-3, α-1-acid glycoprotein levels and improvement in pure tone average scores in patients with idiopathic sudden sensorineural hearing loss.

Variable	r-value	P-value
Galectin, ng/ml	-0.350	0.010
α-1-acid glycoprotein, mg/dl	-0.142	0.301

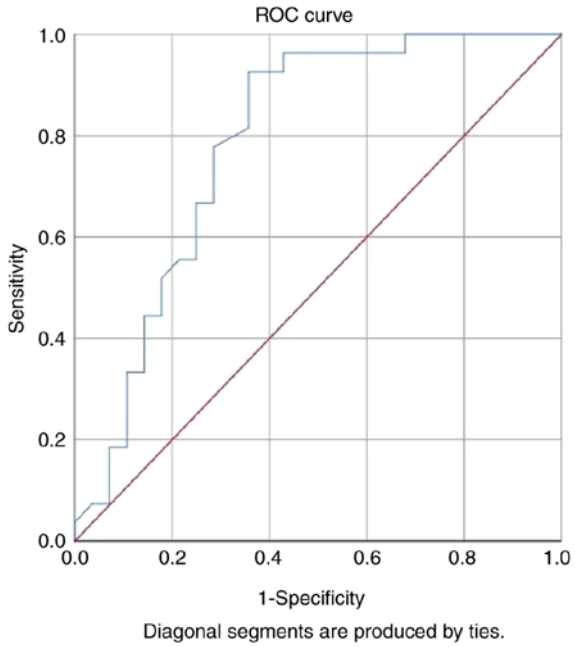

Figure 1. Receiver operating characteristic analysis of galectin-3.

calculated using Spearman's correlation coefficient. Receiver operating characteristic (ROC) curve analysis was used to determine the cut-off values for galectin. P<0.05 was considered to indicate a statistically significant difference. The effect size was calculated as 0.6 and the actual power was 0.90 using GPower 3.1 (G*Power version 3.1.9.6, Universitat Kiel).

Results

A total of 55 patients diagnosed with ISSNHL [29 (52.7%) female and 26 (47.3%) male] were included in the study group. The mean age of the study group was 46.76±17.68 years (range, 21-78 years; data not shown). The control group consisted of 47 volunteers [25 (53.2%) female and 22 (46.8%) male; mean age, 43.95±12.96 years (range, 26-65 years)]. There was no significant difference between the study and control groups regarding sex and age (P=0.96 and P=0.38, respectively).

The laboratory findings of the participants are shown in Table I. Galectin-3 levels were 16.80±4.55 ng/ml in the study group and 15.15±3.74 ng/ml in the control group (P=0.05).

Audiological tests were all performed in Ufuk University, Ridvan Ege Hospital. The audiological scores are shown in Table II. ISSNHL significantly increased PTA and decreased SDS. According to audiogram graphic configurations, 14 patients (25.5%) had a downward sloping audiogram. Of these, eight patients (57.1%) responded positively to medical treatment. U-shaped hearing loss was identified in 27 patients (49.1%), 12 (44.4%) of whom recovered following medical treatment. A total of 14 patients (25.5%) had profound hearing loss and only four (28.6%) recovered following medical treatment. In summary, out of 55 patients, 24 (43.6%) showed recovery, whereas 31 (56.4%) showed no improvement in hearing loss. There was no significant difference in response to treatment regarding the three different audiogram configurations (P=0.3). In addition, galectin-3 and AGP levels did not differ significantly between audiogram configurations (P=0.836 and P=0.402; respectively).

Serum galectin-3 levels were significantly correlated with PTA improvement in the study group (r=-0.35; P=0.010). There was no correlation between AGP and PTA score (P=0.301; Table III).

Based on ROC analysis, the cut-off level for galectin-3 for the prediction of treatment success was 14.95 ng/ml. Galectin-3 levels >14.95 ng/ml indicated poor improvement in PTA scores in patients with ISSNHL. The area under the ROC curve was 0.79 (P<0.001), with a sensitivity of 93% (95% CI, 0.77-0.98) and a specificity of 64% (95% CI, 0.46-0.79; Fig. 1).

Discussion

The present study showed that galectin-3 levels were elevated in patients with ISSNHL and that serum galectin-3 levels may help predict the prognosis of ISSNHL treatment. High galectin-3 levels were associated with poor improvement in PTA scores in patients with ISSNHL following treatment. By contrast, AGP levels showed no difference in patients with

ISSNHL compared with the control group and no association with PTA scores after treatment.

The etiopathogenesis of ISSNHL remains unclear. Infection, vascular pathologies and systemic and metabolic disease have been reported to play a role in the etiopathogenesis of ISSNHL(2). The present analysis aimed to investigate inflammatory and vascular/ischemia biomarkers, namely galectin-3 and AGP, in ISSNHL and determine their potential predictive role for recovery after medical treatment.

The cochlea is vulnerable because few branches of the internal auditory artery support its vascularization. Therefore, hypoxia-induced vascular disorder can lead to cochlear damage and hearing loss (12). However, to the best of our knowledge, the association between sensorineural hearing loss and cardiovascular disorder has not been identified. A previous study investigated ISSNHL with ischemia-modified albumin (IMA) and found no significant relationship between ISSNHL and IMA levels (13).

Local ischemia serves a role in ISSNHL (14). Kim *et al* (15) found that vascular structures play an essential role in ISSNHL aetiology.

The present study used galectin-3 levels as indicators of ischemia and AGP values for inflammation. Only galectin-3 levels were increased in patients with ISSNHL and were also predictive of prognosis following treatment. When the association of serum galectin-3 levels with several types of ischemic disorder is considered (8), an ischemic aetiology may be considered as the etiopathogenesis of ISSNHL in patients with high galectin-3 levels and this may also explain the unresponsiveness of the patients to steroids. Patients with high galectin-3 levels may be evaluated for potential ischemic aetiology and anti-aggregant and anticoagulant therapy may be started to treat ISSNHL (8). Therefore, it would be a reasonable option to avoid the side effects of systemic corticosteroids and start anticoagulant therapy in patients with high galectin-3 levels.

AGP is an anti-inflammatory and immunoregulatory mediator that is synthesized in hepatocytes. It is hypothesized to be involved in the extravasation of leukocytes. AGP has anti-inflammatory effects against infection, inflammation, neoplasms and tissue damage (5). In addition, AGP is frequently investigated in blood especially in defining sepsis-associated mortality. Therefore, AGP is used to monitor the outcome of inflammation and infection (5). AGP can also be increased by drugs, such as phenobarbitone and rifampicin, burns and pregnancy (16). Thus, patients with chronic disease or drug use were excluded from the present study to search for a correlation with ISSNHL. Here, AGP was assessed as an inflammatory parameter; however, a significant association between this marker and ISSNHL was not found.

The galectin family consists of 14 members essential for binding proteins. The phosphorylation of galectin-3 is key for protein and carbohydrate interactions. Phosphorylated galectin-3 activates the mitogen-activated protein kinase pathway, thus affecting the anti-apoptotic process (17). Galectin-3 functions in cell proliferation, differentiation, adhesion, apoptosis and malignant transformation (18-22). Bertocchi *et al* (23) reported that serum galectin-3 levels serve a role in ischemic reperfusion injuries, particularly in the kidneys. A recent study also demonstrated that serum galectin-3 levels are associated with cardiovascular events, especially in patients with type 2 diabetes (24). Galectin-3 was chosen in the present study for these reasons and because of its broad range of actions, such as induction of oxidative stress, tissue damage and ischemia, which are believed to be the most common causes of ISSNHL (8,12).

Elevated galectin-3 levels are hypothesized to be related to atherosclerosis and morbidity associated with acute ischemic stroke (25-27).

The increased levels of galectin-3 in ISSNHL and its association with non-responsiveness to steroids should be studied further to determine the potential effect of an ischemic aetiology on ISSNHL and different treatment strategies may be planned according to the cause of ischemia.

To the best of our knowledge, the present study is the first to assess serum galectin-3 and AGP levels in patients with ISSNHL. However, the primary limitation of this study is the small sample size. More accurate results for galectin levels could be obtained with more participants. In addition, the ischemic aetiology of ISSNHL should be investigated in more detail to determine treatment strategy.

To the best of our knowledge, the present study is first to show galectin-3 levels are higher in patients with ISSNHL compared with those in healthy controls. In addition, the poor response of patients with high galectin-3 levels supports a potential ischemic cause. As AGP did not differ between the groups, anticoagulant therapy may be useful in patients with high levels of galectin-3. Further studies are needed to assess the role of galectin-3 levels in ISSNHL, particularly in selecting treatment strategies.

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Availability of data and materials

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

Authors' contributions

HA and TC confirm the authenticity of all the raw data. MMB wrote the manuscript and constructed figures. HA performed experiments and data analysis. HA and TC designed the study. TC collected data. MMB and HA performed the literature review and interpreted data. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

This study was approved by the local ethics committee of Ufuk University, Ankara (approval no. 30042015-6). Patients provided written informed consent to participate in the study.

Patients consent for publications

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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