Original Article

Serum Leptin Levels in Patients with Idiopathic Sudden Sensorineural Hearing Loss

Ahmet Ural, Ahmet Alver, Abdülcemal Ümit Işık, Mehmet İmamoğlu
Department of Otorhinolaryngology, Karadeniz Technical University School of Medicine, Trabzon, Turkey (AU, AUI, MI)
Department of Biochemistry, Karadeniz Technical University School of Medicine, Trabzon, Turkey (AA)

OBJECTIVE: This study was performed to investigate whether serum leptin levels are altered in idiopathic sudden sensorineural hearing loss patients.

MATERIALS and METHODS: The study was performed between March 2010 and December 2011 in the otorhinolaryngology department of a tertiary referral center. A total of 33 idiopathic sudden sensorineural hearing loss patients and 38 healthy controls were compared in terms of demographic features (age, gender, and body mass index) and serum leptin levels. Serum leptin levels were assessed by enzyme-linked immunosorbent assay method, and statistical analysis was conducted via Mann-Whitney U- and student t-tests.

RESULTS: There was no significant difference between idiopathic sudden sensorineural hearing loss patients and the control group in terms of serum leptin levels (p=0.195), age (p=0.290), and body mass index (p=0.104). The patient and control groups displayed significant differences only with respect to gender distribution (p=0.002).

CONCLUSION: Our results indicated that serum leptin levels in idiopathic sudden sensorineural hearing loss patients were not different from controls. Any possible role of leptin in the pathophysiology of idiopathic sudden sensorineural hearing loss remains to be elucidated by further prospective, randomized, and controlled trials in larger series.

KEY WORDS: Idiopathic sudden sensorineural hearing loss, etiology, pathophysiology, leptin

INTRODUCTION
The term “idiopathic sudden sensorineural hearing loss” (ISSHL) is described as sensorineural hearing loss of 30 dB or more across at least three contiguous audiometric frequencies occurring within 3 or fewer days [1, 2]. The prevalence varies between 5-20 per 100,000, and the etiology can not be usually identified [3]. The three main theories postulated on the etiology of ISSHL are viral infection, vascular compromise, and rupture of cochlear membranes [1-4]. Even though ISSHL constitutes an emergency in terms of diagnosis and treatment, no consensus has been established on a standard protocol yet [2, 3].

The effects of proinflammatory cytokines on cochlear function have been investigated in recent studies [5-9]. Cytokines are supposed to contribute to the development of hearing loss by their effects, consistent with systemic inflammation and tissue damage through fluid hemostasis. The disturbance of the inflammatory cytokine balance in spiral ligaments may be one dimension of ISSHL pathophysiology [5]. Especially, interleukin-6 (IL-6) is supposed to have a role in ISSHL pathogenesis [6-9].

Leptin, a proinflammatory cytokine secreted mainly from adipocytes, is responsible for the regulation of energy metabolism and raises the sensation of satiety by acting on the hypothalamus [10]. Leptin is a member of the IL-6 cytokine subgroup, and its effects on body weight and energy metabolism are mediated by receptors in the central and peripheral nervous system [11].

Since the etiology and pathophysiology of ISSHL have not been fully elucidated yet, the efficacy of various therapeutic modalities still remains limited. Owing to their anti-inflammatory effects, steroids are often included in the treatment of ISSHL. But, targeted therapeutic outcomes have not been achieved promptly yet. If any association of IL-6 with ISSHL is to be established, new insights for the diagnosis and treatment of ISSHL can be mentioned. In other words, we think that an investigation of the role of IL-6...
subgroup cytokines may open new horizons in the development of new preventive and therapeutic strategies against cochlear damage. In such a circumstance, development of a specific anti-inflammatory treatment (eg, anti-IL-6 treatment) with minimal side effects and improved hearing outcomes is the main aim. As far as we know, this is the first study that deals with the relationship between leptin and ISSHL in the literature (PubMed).

MATERIALS and METHODS

Study Design

This study was approved by the local institutional review board (25.05.2009 / 474). Written informed consent was obtained from all participants. A total of 33 patients, admitted to the otorhinolaryngology department of our tertiary center for ISSHL between March 2010 and December 2011, constituted the study group. Patients with chronic systemic disease (hypertension, diabetes mellitus, thyroid disease) or body mass index >30 and cases <18 or >65 years of age were excluded from the study. ISSHL is defined as “idiopathic sudden sensorineural hearing loss of 30 dB or more that influences at least three consecutive audiometric frequencies within 3 or fewer days.” Patients who were admitted to the hospital within 3 weeks after the onset of complaints were included in the study. The control group consisted of 38 healthy people that applied to the hospital for a routine annual check-up program.

Outcome Parameters

Demographic parameters (age, gender, body mass index), as well as the serum leptin levels, were noted and compared in both groups. Body mass index (BMI) was calculated by division of body mass (kg) by the square of height (m$^2$). Body mass index <18.5 is regarded as thin, while BMI between 18.5 and 25 is termed normal; BMI between 25 and 30 is named overweight, and BMI >30 is accepted as obese.

Statistical Analysis

Statistical analysis was performed using the Statistical Package for Social Sciences 12.0 (SPSS Inc, Chicago, USA) program. Comparisons of variables were made with the Mann-Whitney U-test and student T-test. All differences associated with a probability of p<0.05 were considered statistically significant.

RESULTS

Data derived from the patient and control groups are demonstrated in Table 1. The idiopathic sudden sensorineural hearing loss patient group consisted of 8 females and 24 males with an average age of 43.42±12.75 (range: 23-65), while the control group was composed of 17 females and 21 males with an average age of 46.18±10.93 (range: 22-65).

No statistically significant difference between patients and controls with respect to age (p=0.290), BMI (p=0.104), and leptin levels (p=0.195) was found. On the other hand, gender distribution displayed a significant difference between groups (p=0.002).

DISCUSSION

Despite multiple reports of ISSHL over the years, there still is no accepted definition of the disease, its cause, and the appropriate treatment. Understanding the pathophysiology of ISSHL is crucial both to develop more cost-effective treatment modalities and to minimize side effects.

Over the years, many treatment protocols have been suggested in the literature, each one claiming various rates of success. One of the proposed causes of ISSHL is edema of the labyrinth, and thus, diuretics may play a role in these cases. The use of corticosteroids has been proposed in cases of ISSHL in the literature (PubMed).

Cochlear fibroblasts are able to secrete cytokines and participate in the regulation of local inflammation [14]. In vitro and in vivo studies have demonstrated that fibroblasts on the lateral cochlear wall can produce IL-6, IL-1b and TNF-α, which amplify the inflammation [15, 16]. Secondary inflammatory responses may lead to leukocyte infiltration, scar formation, and gliosis in the cochlea. In addition to degenerative changes, inflammatory changes, such as monocytic infiltration, have been observed in patients with sensorineural hearing secondary to acoustic trauma [12, 13].

In a recent publication, long-term levels of CRP were found to be associated with the incidence of hearing impairment in an aging population. Interestingly, this finding was independent of potential confounders, including age, sex, obesity, smoking, and alcohol use. On the other hand, levels of IL-6 and TNF-α did not exhibit such a relationship [17].

These reports support the involvement of proinflammatory cytokines in cochlear damage. If alterations of serum leptin levels in patients with ISSHL can be documented, some interpretations can be made in terms of pathophysiology. Such evidence may provide more valuable data on the association of proinflammatory cytokines with the pathophysiology of ISSHL.

The primary role of leptin, an adipocyte-derived hormone, is to regulate body weight and energy expenditure, and the circulating

<table>
<thead>
<tr>
<th>Group</th>
<th>Age</th>
<th>Gender</th>
<th>BMI</th>
<th>Serum leptin level</th>
</tr>
</thead>
<tbody>
<tr>
<td>ISSHL</td>
<td>43.42±12.75</td>
<td>8 (25%)</td>
<td>24 (75%)</td>
<td>26.12±5.68</td>
</tr>
<tr>
<td>Control</td>
<td>46.18±10.93</td>
<td>17 (44.7%)</td>
<td>21 (55.3%)</td>
<td>28.04±6.12</td>
</tr>
<tr>
<td>p</td>
<td>0.290</td>
<td>0.002*</td>
<td>0.104</td>
<td>0.195</td>
</tr>
</tbody>
</table>

SSNHL: sudden sensorineural hearing loss; BMI: body mass index; *: Statistically significant
concentration of leptin is positively correlated with body fat mass. Leptin, a member of the IL-6 family of cytokines, induces a complex response in order to control body weight and energy expenditure via interactions with specific receptors located in the central nervous system and in peripheral tissues. Leptin receptors have been identified in bone of the otic labyrinth and the cochleovestibular nerve in guinea pig, and these receptors are affected by hormone-induced anorexia. This finding reminds us of the involvement of leptin receptors and adipose metabolism in hearing impairments.

Interleukin-6 is synthesized by monocytes, macrophages, and T-lymphocytes, and it has a chemotactic effect on T lymphocytes. Interleukin-6 production in spiral ganglion neurons may also be due to cellular stresses, including noise overstimulation, because overstimulation of hair cells induces secondary degeneration in spiral ganglion. Interleukin-6 is an intracellular signaling molecule via paracrine or autocrine manner. One of the roles of IL-6 is its anti-oxidative stress effect, upregulating several anti-apoptotic genes, including the bcl family, or cell survival signals. Another role is regulating inflammation, including immune responses. The loss of IL-6 production suppresses macrophage recruitment and decreases local inflammation but increases apoptosis in injured cells. Suppression of cytokine-mediated inflammation with fewer side effects using non-steroid anti-inflammatory agents and specific inhibitors of each cytokine is possible.

In Takayasu arteritis patients, IL-6 levels are higher and have been correlated with the activity and severity of the disease, as well as the degree of sensorineural hearing loss. IL-6 levels are higher than normal in the serum of patients with Takayasu arteritis during the active phase, and their serum concentrations are positively correlated with disease activity, including sensorineural hearing loss. Similarly, IL-6 levels are decreased in proportion to the reduction of disease activity and hearing loss.

Muckle-Wells syndrome is a rare autosomal disease characterized by chronic recurrent urticaria, arthralgia, and deafness. Sensorineural hearing loss becomes more evident during the flares of urticaria, and elevated serum levels of IL-6 are observed during these attack periods of the disease. This finding is noteworthy, since it reminds us of the possible role of IL-6 in the pathophysiology of sensorineural hearing loss.

Interleukin-6 antagonists that serve as suppressors of acute inflammation can be considered a “double-edged sword.” In the setting of a central nervous system injury, blockage of IL-6 had a positive effect at the level of the spinal cord, but they displayed an adverse impact in an experimental cerebral ischemia model.

Our results showed that serum leptin levels were not different in patients than in control subjects. Therefore, we did not come across any finding that supports the possible role of leptin in ISSHL pathophysiology. However, we think that an investigation of cytokines (especially those in the IL-6 family) may provide valuable clues for the development of new diagnostic and therapeutic strategies against ISSHL.

The limitations of our study include the small sample size and the difference between patient and control groups in terms of gender distribution. In addition, the patient may be unaware of any co-existing disease or metabolic problem that can affect leptin levels. It must be kept in mind that local cochlear cytokine levels may be altered without significant changes in serum values. The average BMIs of both the study and control groups is relevant with the “overweight” category, and this circumstance may influence serum leptin levels. Further trials must be targeted on an investigation of leptin and other IL-6 cytokins in local cochlear microcirculation.

Our results indicated that serum leptin levels in ISSHL were not different from controls. Any possible role of leptin in the pathophysiology of ISSHL remains to be elucidated by further prospective, randomized, and controlled trials in larger series.

Informed Consent: Written informed consent has been obtained from all participants.

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