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The Usefulness of Stress-related
Hormones as Predictors and Prognostic
Factors for Idiopathic Sudden
Sensorineural Hearing Loss

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Hormones as Predictors and Prognostic
Factors for Idiopathic Sudden
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A Masters Thesis

Submitted to the Department of Medicine
and the Graduate School of Yonsei University
in partial fulfillment of the
requirements for the degree of
Master of Medical Science

Hee Sung Chae

June 2020

This certifies that the masters thesis
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June 2020

감사의 글

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그리고 언제나 저의 학업에 있어 지원과 격려를 아끼지 않고 응원해주는 부모님, 같은 의학의 길을 걸으며 함께 고민해주고 진심어린 조언을 주는 누나에게도 깊은 감사드립니다.

지면으로 미처 언급하지 못했지만, 저를 아끼고 격려해주셨던 모든 분들께도 진심으로 감사하다는 말씀을 전합니다. 더욱 정진하며 꾸준히 겸손한 자세로 배우고 성장하여 이비인후과학 분야에서 꼭 필요한 존재가 되도록 노력하겠습니다. 감사합니다.

2020년 6월

채 희 성 드림

Table of contents

List of Figures	ii
List of Tables	iii
Abstract in English	iv
I. Introduction	1
II. Methods	5
A. Study participants	5
B. Treatment protocol	5
C. Evaluation of hearing level	6
D. Evaluation of psychological stress	7
E. Statistical analysis	8
III. Results	9
IV. Discussion	17
V. Conclusion	20
Reference	21
Index	27
Abstract in Korean	30

List of Figures

Figure 1. Treatment options and evaluation protocol.	6
Figure 2A. Results of average hearing level of affected ear and contralateral ear in 3 PTAs.	10
Figure 2B. Average hearing level by frequency in 1st and 3rd PTAs.	10
Figure 3. Positive correlation between 1st DHEAS level and average hearing level of 1st PTA.	12
Figure 4. Difference of hearing loss level in normal and elevated ACTH groups.	13
Figure 5. Positive correlation between the BDI score and the mean hearing thresholds of 3rd PTA.	15

List of Tables

Table 1. Demographic and clinical characteristics of patients.	9
Table 2. Correlation between the mean hearing threshold of 1st PTA and serum hormones level.	12
Table 3. Difference of hearing loss level in normal and elevated ACTH groups.	14
Table 4. Correlation between the mean hearing thresholds and score of stress questionnaires.	14
Table 5. Correlation between score of questionnaires and serum level of hormones.	16
Table 6. Difference of BDI and PSS scores in normal and elevated ACTH groups.	16

ABSTRACT

The Usefulness of Stress-related Hormones as Predictors and Prognostic Factors for Idiopathic Sudden Sensorineural Hearing Loss

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Previous studies have identified psychological factors as prognostic factors of idiopathic sudden sensorineural hearing loss (ISSNHL). Those studies suggested that serum levels of stress-related hormones [such as cortisol, growth hormone, prolactin, antidiuretic hormone (ADH), adrenocorticotrophic hormone (ACTH)] are elevated in patients with ISSNHL patients. However, little is known regarding their psychosocial measures and association with treatment response or therapeutic prognosis in ISSNHL. Therefore, we aimed to determine whether psychological factors of patients are associated with the severity of hearing loss treatment outcomes..

Psychological measures such as serum levels of stress-related hormonal (cortisol, ACTH, aldosterone, dehydroepiandrosterone sulfate[DHEAS]) and questionnaires (Beck Depression Inventory, Perceived Stress Scale) were used in

this study involving 15 patients diagnosed with ISSNHL.

Serum DHEAS level measured on day 1 showed a statistically significant correlation with the hearing threshold in the hearing test performed at the time of diagnosis ($p=0.037$, $R^2=0.293$). Serum ACTH level was measured on day 1, and patients were classified into normal and elevated groups based on a threshold of 1.5pg/mL; the normal group had better hearing thresholds in the first and second hearing test than the elevated group ($p=0.040$, 0.015, respectively). In the stress-related questionnaires, the BDI score showed a statistically significant correlation with the last hearing test ($p=0.015$, $R^2=0.376$).

We demonstrated the possible role of stress-related hormones in the pathogenesis of ISSNHL and suggest that depressive stress response can be a strong predictor of treatment response in patients with ISSNHL. However, the impact of response to stress on the inner ear and endolymph homeostasis remains unknown. Further investigation is necessary to identify the mechanism of interaction between stress and hearing ability in the inner ear.

Key words : Idiopathic sudden sensorineural hearing loss, ISSNHL, Stress, Hormone, HPA axis, Questionnaire

I . Introduction

Idiopathic sudden sensorineural hearing loss (ISSNHL) is a rapid hearing loss of above 30 decibels(dB) at least three contiguous audiometric frequencies occurring over 72hours¹. The global incidence of ISSNHL is known as to be 5-20 out of every 100,000 individuals². The true incidence of ISSNHL may be higher than these estimates because affected individuals who recover quickly do not seek medical care³. Although individuals of all ages can be affected, the peak incidence occurs in those in between the fifth and sixth decades of life. ISSNHL occurs with equal incidence in men and women^{4,5}. Nearly all cases are unilateral; less than 2% of patients have bilateral involvement and typically bilateral involvement is sequential⁶. Tinnitus has been reported in 70% of patients with ISSNHL. Vertigo is also present in 50% of patients⁷.

To date, many approaches have been attempted to treat ISSNHL; however, none have proven consistently successful. One reason is the ambiguous pathogenesis of the disease. The etiology of ISSNHL remains a mystery despite an extensive work-up. The differential diagnosis in patients with ISSNHL is broad and could be divided into neoplastic, vascular, traumatic, infectious, metabolic, neurologic, immunologic, toxic, cochlear, and other causes. About 1-15% of patients with an acoustic neuroma will present with sudden sensorineural hearing loss as the initial symptom⁸. Circulatory disorders including vascular and hematologic diseases such as leukemia, sickle cell anemia, macroglobulinemia, and polycythemia are considered possible causes of ISSNHL⁹. Trauma to the

inner ear whether physical, acoustic or barotrauma, can cause sudden deafness secondary to a perilymphatic fistula or cochlear membrane breaks¹⁰. Other important considerations in patients with ISSNHL are infectious causes. Although any pathogen could be suspected, some pathogens are implicated more than others because of their known pathologic effect on the inner ear such as syphilis, mumps, measles, herpes zoster, and adenovirus. Meningitis is well recognized cause of ISSNHL with possible spread of the pathogen into the inner ear and/or internal auditory canal causing neuritis of the cochlear nerve, septic emboli to the vertebrobasilar system or central auditory pathway dysfunction^{11,12,13}. In addition, autoimmune diseases, metabolic diseases (diabetes and thyroid diseases), and neurologic disorder (multiple sclerosis) can cause ISSNHL¹⁴. Because the causes are so diverse that it cannot be identified, cause of sudden sensorineural hearing loss is often considered "idiopathic". However, without a clear understanding of the etiology and pathogenesis of ISSNHL, devising new and effective treatments is difficult.

Patients with ISSNHL usually recover within 2 weeks without treatment, and the natural recovery rate is 47–63%, including partial recovery⁹. Recovery rates of patients with mild hearing loss, hearing loss over 50 dB and loss in the 90 dB region are 70%, 30%, and 10%, respectively¹⁵. Several studies have reported prognostic factors of ISSNHL, including age, the presence or absence of vertigo, type and severity of hearing loss, shape of audiogram, and time from symptom development to initiation of treatment^{14,16}. A previous study performed by Seo *et al.* also predicted the recurrence of sudden hearing loss through analysis of

neutrophil-lymphocyte ratio(NLR) and platelet levels and revealed that NLR levels were higher in patients with severe sudden hearing loss^{17,18}. Psychological factors are also considered to be a prognostic factor of ISSNHL^{19,20,21}. An emotional disorder may alter the neurovascular mechanism via an autonomic nervous system response. There would be vascular contractions, viscosity alterations and eventual congestion, anoxia, increase in capillary permeability and local metabolic impairment, resulting ISSNHL²².

Stress is commonly defined as a state of real or perceived threat to homeostasis that may challenge an organism's well-being²³. To restore homeostatic conditions, organisms activate a complex range of responses involving the endocrine, nervous, and immune systems, collectively known as the stress response²⁴. The hypothalamic - pituitary - adrenal (HPA) axis, comprising the hypothalamus, pituitary gland, and adrenal glands, regulates adaptive response to stress²³. Activation of the HPA axis triggers neurons in the paraventricular nucleus (PVN) of the hypothalamus to release corticotropin-releasing hormone and antidiuretic hormone (ADH), which stimulate the anterior pituitary gland to secrete adrenocorticotrophic hormone (ACTH). In response, ACTH induces the synthesis and secretion of cortisol, aldosterone, and adrenal androgens (dehydroepiandrosterone sulfate [DHEAS]), which are released by the adrenal cortex into the blood circulation^{25,26}.

Some reports state that serum levels of stress-related hormone (cortisol, growth hormone, aldosterone, ADH, ACTH) are elevated in patients with ISSNHL patients. As mentioned earlier, stress hormones released from the

HPA axis as a response to stress contracts the blood vessels distributed in the inner and outer hair cells, resulting in sudden hearing loss due to oxygen transport disorder. They also affect homeostasis of the endolymph, resulting in sudden hearing loss²⁷. Kang *et al.* found that the proportion of stress hormones (cortisol, growth hormone, prolactin, ADH, ACTH) was significantly higher in the ISSNHL group than in the control group. Among them, ADH was statistically significantly higher in the ISSNHL group than in the control group²⁸. In addition, the Beck Depression Inventory (BDI) and Perceived Stress Scale (PSS) are commonly administered to evaluate the level of stress that is subjectively experienced against an objective indicator, stress-related hormones. According to another study, the PSS score was positively correlated with the cortisol level, so it can be evaluated by comparing the degree of subjective and objective stress²⁹. However, very few studies have investigated the psychosocial measures of patients with ISSNHL and their association with treatment response or therapeutic outcomes.

Therefore, we aimed to determine whether psychological factors and stress hormones in patients are associated with the severity of hearing loss and therapeutic outcomes. We hypothesized that the stress hormone level in the disease sequence is a strong prognostic factor of ISSNHL. Additionally, we investigated whether the subjective degree of psychological stress is likely to contribute to the therapeutic prognosis of ISSNHL, as determined using questionnaires.

II. Methods

A. Study participants

We conducted a prospective study of patients aged between 19 and 65 years admitted for the treatment of ISSNHL at the Department of Otorhinolaryngology-Head and Neck Surgery, Wonju Severance Christian Hospital. The study was approved by the Yonsei University, Wonju Severance Christian Hospital, Institutional Review Board (IRB No. CR319015). We defined ISSNHL as a sensorineural hearing loss of at least 30 dB in three consecutive speech frequencies that occurred within the previous 3 days, with the cause of hearing loss not being trauma, otitis media, tumors, drugs, etc.

We excluded patients with the following conditions: (1) previous ISSNHL, chronic otitis media, and history of Meniere's disease history; (2) anticipated side effects of oral steroids (immune suppressed diseases, diabetes mellitus, cardiovascular disease, and malignant tumors); (3) other medications or diseases related to the HPA axis (pituitary tumors, adrenal cortical diseases, etc.) that have an influence on the stress hormone levels; and (4) more than 1 week between the onset and treatment.

B. Treatment protocol

All patients were hospitalized for 5 days, and during the hospitalization period, oral administration of 48 mg methylprednisolone was maintained for 5 days, and then gradually tapered until 2 weeks after discharge. In addition, all patients were prescribed an antiviral agent (acyclovir

1000mg/day) for 7days and underwent stellate ganglion block (SGB) daily during hospitalization except on weekends. Patients with hearing loss of above 50 dB on initial pure tone audiometry (PTA) were administered an additional intratympanic steroid injection (ITSI, 5mg dexamethasone), and those with hearing loss above 70 dB additionally underwent hyperbaric oxygen therapy (HBOT, 2.8 ATA for 90minutes)(Figure 1). On the first day of hospitalization, a routine laboratory test (complete blood count, chemistry), chest radiography, electrocardiogram, and magnetic resonance imaging (temporal contrast) were conducted to rule out other underlying diseases.

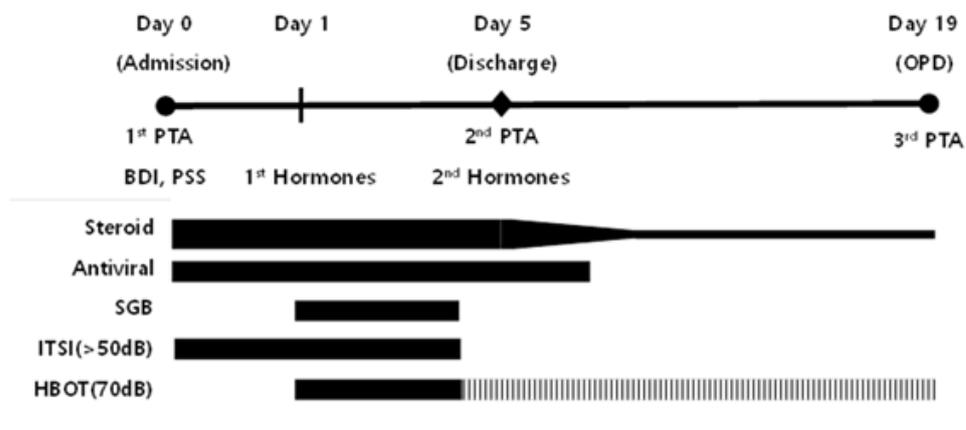


Figure 1. Treatment options and evaluation protocol.

OPD: Out-patient department

C. Evaluation of hearing level

The PTA was performed using pure tone hearing equipment and headphones, and the frequencies of 125 Hz, 250 Hz, 500 Hz, 1 kHz, 2 kHz, 3 kHz, 4 kHz, and 8 kHz were tested. Threshold was obtained by 5 dB

rise-fall method at all frequencies, and both ears of all patients were examined.

The average hearing threshold was calculated using the equation $[a+2b+2c+d/6]$, 500 Hz(a), 1000 Hz(b), 2000 Hz(c), 4000 Hz(d)] in each hearing test. Recovery of the hearing threshold was evaluated by measuring the hearing level on day 1, day 5 and 2weeks after discharge (day 19). Hearing level after the day 19 was considered the final hearing level.

D. Evaluation of psychological stress

Various psychological stresses might be related to ISSNHL. We considered objective and subjective measures of stress. As an objective indicator of stress, we measured the level of HPA axis-related hormones dependent on catecholamine secreted by stimulation of the sympathetic nervous system under stress. We measure serum cortisol, ACTH, aldosterone and dehydroepiandrosterone sulfate (DHEAS) levels in the venous blood sample of patients on day 1 and day 5 after admission. Blood samples were collected at 8 am with patients in nothing-by-mouth status since the previous night, as the hormones are thought to undergo major fluctuations during the day and before and after meal.

In addition, for subjective stress measurements, depression and anxiety levels were assessed using self-reported questionnaires, BDI and PSS in the revised to Korean versions.

Depression symptoms were measured using the Korean version of BDI,

which was standardized for adults across the country by Rhee *et al.*²⁸. This scale consists of 21 observable behavioral symptoms including the emotional, cognitive, synchronous, and physiological areas of depression, and at the same time, the intensity of each symptom can be measured by self-report. Each item is scored from 0 to 3, so the total score ranges from 0 to 63. Depending on the total score range, 0–9 points indicate no depression; 10–15 points, mild depression; 16–23 points, moderate depression; and 24–63 points, severe depression. Cronbach's alpha of the standardized scale in Korean was 0.81 (Index 1).

PSS designed by Cohen *et al.*²⁹ and developed by Park and Seo³⁰, measures the degree to which an individual's life in the past month is perceived as unpredictable, uncontrollable, uncontrollable, or overwhelmed. It also enquires about stress-related experiences in the past month and can be used in a wide range of areas, focusing on the general context rather than on specific incident experiences. This tool consists of 14 questions, a 5-point Likert scale, and scores range from 0 to 40. The Cronbach's alpha in domestic research was 0.85 (Index 2).

E. Statistical analysis

Statistical analyses were performed using IBM SPSS ver. 26.0 (IBM Co., Armonk, NY, USA). We used Pearson's correlation coefficient, also referred to as Pearson's *r*, to determine whether hormone levels and questionnaire responses had a linear relationship with hearing. A *P*-value <0.05 was considered statistically significant.

III. Results

Eighteen patients diagnosed with ISSNHL at the Department of Otorhinolaryngology–Head and Neck Surgery were enrolled; however, 3 patients were lost to follow-up and were excluded from the study. Finally, 15 patients (9 males and 6 females) were included; the average age of the study sample was 54.5 years. Patients’ demographics and characteristics including age, sex, past medical history, affected site, onset of treatment, initial hearing level and treatment options are summarized in Table 1.

Patients No.	Age /Sex	Previous medical Hx.	Lesion site	Onset of Treatment (days)	Associated Symptoms	Initial hearing loss (dB)	Additional treatments (times)
1	53/F	HTN	Right	1	N/A	99.2	ITSI(4)/HBOT(17)
2	59/F	N/A	Right	3	N/A	38.3	N/A
3	35/F	N/A	Right	1	N/A	46.7	N/A
4	44/M	HBV carrier	Left	2	N/A	53.3	ITSI(4)
5	59/M	HNP C5-6	Left	1	N/A	54.2	ITSI(5)
6	59/F	N/A	Left	0	N/A	70	ITSI(4)
7	61/M	N/A	Right	1	N/A	120	ITSI(3)/HBOT(19)
8	46/M	HTN	Left	0	Dizziness	75	ITSI(4)/HBOT(15)
9	63/M	HTN	Left	3	N/A	72.5	ITSI(3)
10	64/F	Osteoporosis	Right	0	N/A	120	ITSI(4)/HBOT(5)
11	54/F	N/A	Right	3	Dizziness	49.2	N/A
12	27/M	N/A	Left	3	N/A	75.8	ITSI(6)/HBOT(12)
13	68/M	N/A	Right	1	Dizziness	119.2	ITSI(5)/HBOT(11)
14	65/M	HBV carrier	Left	0	N/A	35.8	N/A
15	61/M	N/A	Right	1	N/A	104.2	ITSI(5)/HBOT(5)

Table 1. Demographic and clinical characteristics of the patients

We analyzed the results of each of the three hearing tests in the patient group as a whole, and reported recovery in the about 20 days after treatment (the third hearing test), except in case of 1 patient. Hearing of the unaffected ear was generally below 20dB, indicating normal hearing (Figure 2A, 2B).

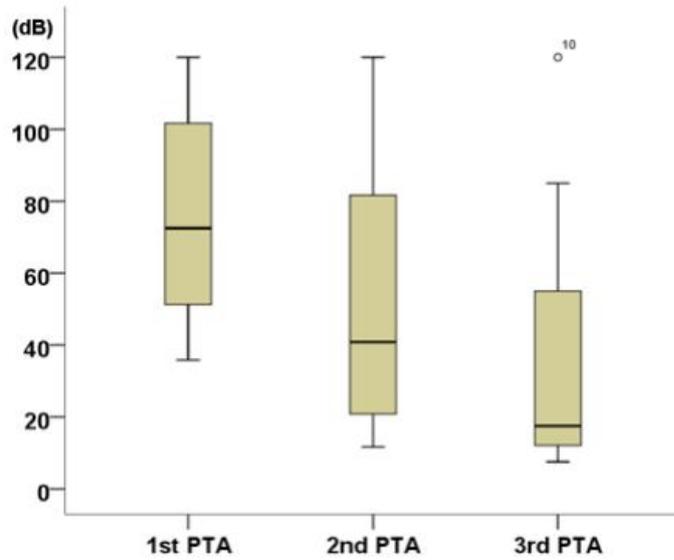


Figure 2A. Results of average hearing level of affected ear and contralateral ear in ISSNHL patient in 3 PTAs.

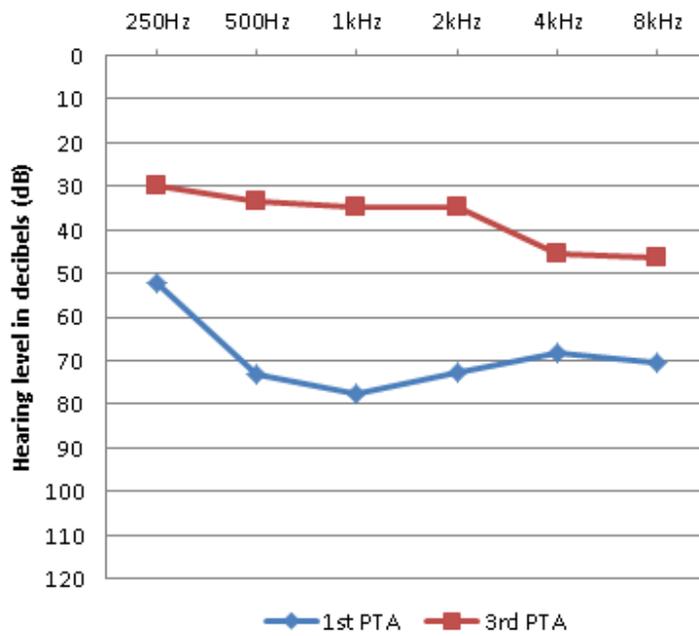


Figure 2B. Average hearing threshold by frequency in the first and third PTAs.

We analyzed the results of the three hearing tests to investigate the effect of each stress-related factor on ISSNHL. The first test was performed at the time of diagnosis, and the results reflected the severity of disease at the time of onset and results of the last hearing test can be regarded as recovery results. Therefore, if factors are related to the results of the first hearing test, they can be considered risk factors of the disease, whereas if they are related to the results of the last hearing test, they can be considered valuable prognostic factors.

When the relationship between stress-related hormones cortisol, ACTH, aldosterone, and DHEAS in patients' serum and average hearing level was analyzed using Pearson's correlation, a significant correlation was found between the ACTH level reported on day 1 and average hearing thresholds in all three hearing tests ($p=0.037$, 0.033 , and 0.018 , respectively). Likewise, the DHEAS level reported on day 1 showed a statistically significant correlation with the hearing threshold in the hearing test performed at the time of diagnosis ($p=0.037$). On the other hand, there was no statistically significant relationship between other hormone levels reported on day 1 and hearing loss and serum hormone level performed on day 5 and 19 and average hearing level (Table 2). Serum DHEAS level evaluated on day 1 and the average hearing threshold at diagnosis were positively correlated, and the R^2 value was 0.293 (Figure 3).

Pearson correlation coefficient (ρ -value)	1 st _Cortisol	1 st _ACTH	1 st _Aldosterone	1 st _DHEAS
1 st _Hearinglevel	0.426 (0.114)	0.542 (0.037*)	0.108 (0.702)	0.541 (0.037*)
2 nd _Hearinglevel	0.441 (0.100)	0.552 (0.033*)	0.103 (0.714)	0.508 (0.053)
3 rd _Hearinglevel	0.401 (0.139)	0.602 (0.018*)	0.071 (0.802)	0.434 (0.106)

Table 2. Correlation (Pearson's r) between the mean hearing thresholds of 1st PTA in affected ear and serum level of stress related hormones.

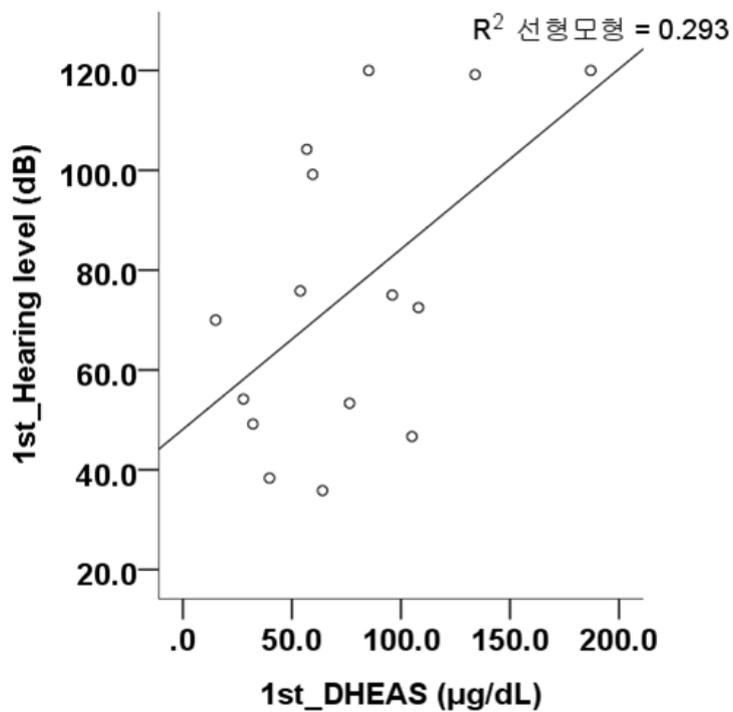


Figure 3. Positive correlation between serum level of 1st DHEAS and average hearing thresholds of 1st PTA ($R^2=0.293$).

Based on the ACTH cut-off value of 1.5 pg/mL, patients were divided into the normal and elevated groups. When the correlation between the average hearing threshold from the hearing tests and ACTH levels was analyzed, the degree of hearing loss on day 0 and 5 was significantly higher in the elevated group with ACTH level of ≥ 1.5 pg/mL than in the normal group with ACTH level of < 1.5 pg/mL ($p=0.040$, 0.015 , respectively). In the third hearing test, the last test, the elevated group showed lower recovery than the normal group but not at a statistically significant level ($p=0.089$) (Figure 4, Table 3).

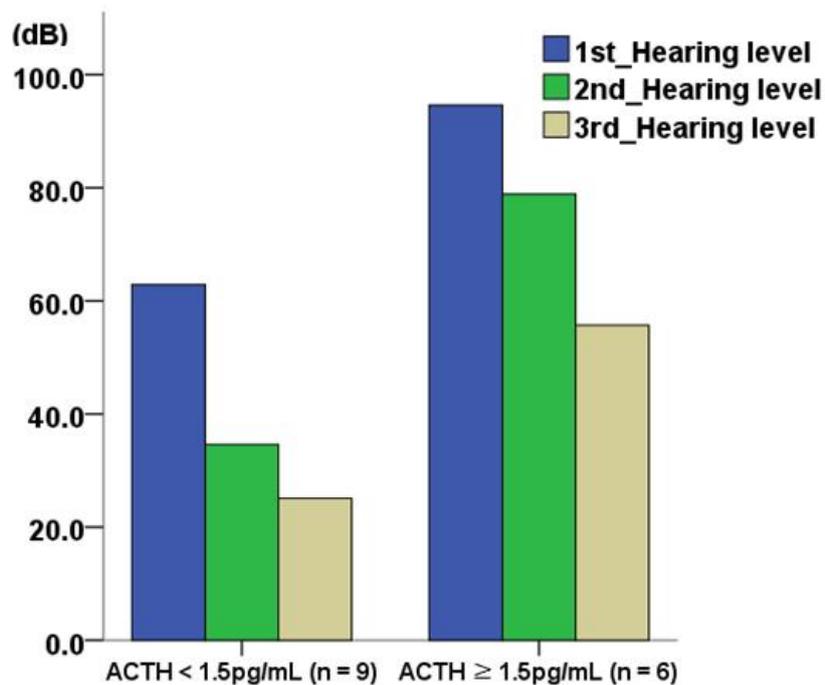


Figure 4. Difference of hearing loss level in normal and elevated ACTH group (cut off value=1.5pg/mL)

	ACTH \geq 1.5pg/mL (n=6)	ACTH < 1.5pg/mL (n=9)	<i>p</i> -value
1 st _Hearinglevel(dB)	94.6 \pm 22.8	62.9 \pm 28.5	0.040*
2 nd _Hearinglevel(dB)	78.9 \pm 31.5	34.6 \pm 28.6	0.015*
3 rd _Hearinglevel(dB)	55.7 \pm 40.2	25.1 \pm 24.8	0.089

Table 3. Difference of hearing loss level in normal and elevated ACTH group (cut off value 1.5pg/mL)

The relationship between the self-reported stress-related questionnaires immediately after diagnosis and degree of hearing loss was analyzed through Pearson's correlation. There was a statistically significant correlation between the BDI score and hearing threshold at the third hearing test, i.e., the last test ($p=0.015$) but not between the BDI score and hearing threshold at the first and second hearing tests. The PSS score also showed no significant results in the three hearing tests (Table 4). There was a positive correlation between the BDI score and the last follow-up hearing level after treatment, with R^2 value of 0.376 (Figure 5).

Pearson correlation coefficient (<i>p</i>-value)	BDI score	PSS score
1 st _Hearinglevel	0.413 (0.126)	0.228 (0.414)
2 nd _Hearinglevel	0.500 (0.058)	0.368 (0.178)
3 rd _Hearinglevel	0.613 (0.015*)	0.425 (0.115)

Table 4. Correlation (Pearson's r) between the mean hearing thresholds of PTA and score of stress questionnaire.

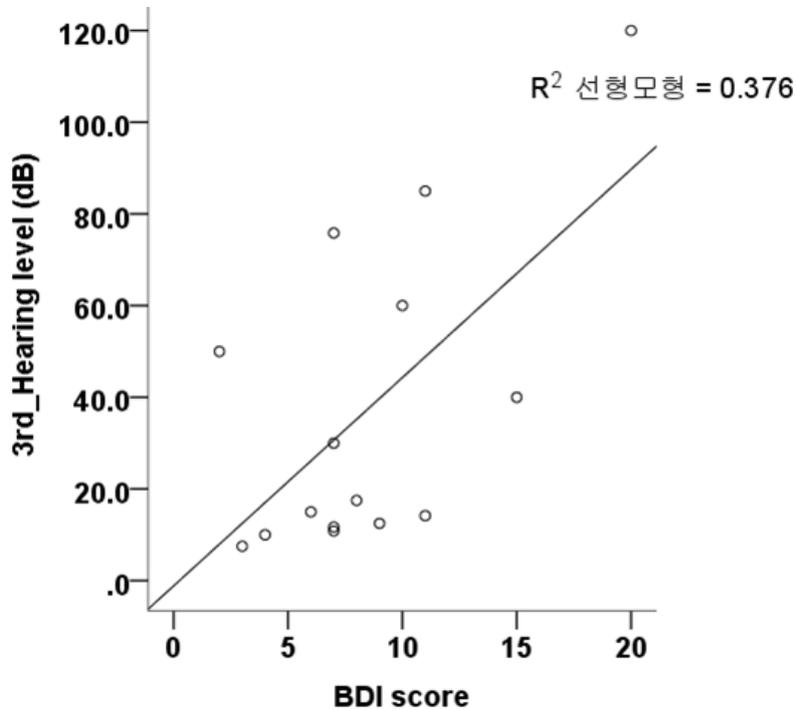


Figure 5. Positive correlation between the BDI score and the mean hearing thresholds of 3rd PTA ($R^2=0.376$).

Lastly, correlation between the stress-related questionnaire scores and stress-related hormones was analyzed, and there was a statistically significant relationship between the BDI score and serum ACTH level measured on day 1 ($p=0.039$) (Table 5). However, when ACTH was divided into normal and elevated groups based on the 1.5 pg/mL threshold, there was no statistically significant association with the BDI score, but the PSS score was statistically significantly higher in the elevated group, with increased serum ACTH level ($p=0.012$) (Table 6).

Pearson correlation coefficient (<i>p</i> -value)	1 st _Cortisol	1 st _ACTH	1 st _Aldosterone	1 st _DHEAS
BDI score	0.103 (0.714)	0.538 (0.039*)	-0.329 (0.231)	-0.028 (0.921)
PSS score	0.231 (0.407)	0.338 (0.217)	-0.039 (0.891)	0.238 (0.394)

Table 5. Correlation (Pearson's *r*) between score of stress questionnaires and serum level of stress related hormones.

	ACTH ≥ 1.5pg/mL (n=6)	ACTH < 1.5pg/mL (n=9)	<i>p</i> -value
BDI score	9 ± 6	8.1 ± 3.8	0.729
PSS score	20.7 ± 2.3	16.3 ± 3.1	0.012*

Table 6. Difference of BDI and PSS score in normal and elevated ACTH group (cut off value 1.5pg/mL)

IV. Discussion

The incidence of ISSNHL is more common than expected (approximately 5-20 in every 100,000 individuals), and ISSNHL is also one of the few emergency diseases in the field of otology³³. However, despite advances in otology over the past decades, the etiology of ISSNHL remains unclear. Over 100 possible causes have been implicated, but most cases are idiopathic⁸. Several factors affect the prognosis of ISSNHL, including initial degree of hearing loss, time from disease onset to treatment, age, presence of vertigo and tinnitus, and type of hearing loss³⁴. Recently, some authors reported the correlation between mental health problems and sudden hearing loss^{21,35}. The exact pathophysiology of the action of psychosocial stress remains to be verified. Merchant and Adams suggested the "stress response theory" examining how systemic stress is associated with cochlear dysfunction. They reported that ISSNHL might be a result of the pathologic activation of the nuclear factor κ -light-chain-enhancer of activated B cells (NF- κ B) in the cochlear lateral wall. It plays a pivotal role in regulating the expression of genes associated with immune system and inflammatory responses, such as interleukin-6 (IL-6), tumor necrosis factor- α (TNF- α), inducible nitric oxide (iNOS), and intercellular adhesion molecule 1 (ICAM-1). NF- κ B is activated by various stressors, acting as "stress sensors"³⁶. Tseng *et al.* conducted nationwide population-based retrospective cohort study and found that a high percentage of patients with ISSNHL exhibit depressive symptoms³⁷.

In the context of these hypotheses, various studies were also conducted

with a focus on stressors as prognostic factors of other cardiovascular diseases (CVDs), such as stroke and myocardial infarction^{38,39}. The situation of ischemia that causes CVD is a known etiological cause of ISSNHL. Previous reports suggested the possibility of ischemia being an etiological and prognostic factor of ISSNHL^{40,41}. The cochlea is vulnerable to ischemic damage because it is an end organ only supplied by a few branches of the internal auditory artery and has no vascular collateral circulation⁴². Therefore, we infer that stress may lead to vasomotor instability, vasoconstriction, and a higher risk of thrombosis, thereby serving as a prognostic and even etiological factor of ISSNHL. In a similar example, patients with diseases of the inner ear, such as Meniere's disease, had higher level of stress hormone than controls⁴³. However, to confirm this hypothesis, further studies of stress-related biomarkers of vascular dysfunction in ISSNHL patients are needed to confirm the underlying pathophysiological mechanisms.

In our study, serum DHEAS level on day 1 showed a significant difference corresponding to the initial hearing loss level (p -value=0.037, R^2 =0.293). DHEAS level under stress has been thought to be beneficial and play a role in resilience and adaptation to stress^{44,45}. However, under conditions of chronic stress, DHEAS level decreases⁴⁶. Stress-induced ISSNHL is a response to accumulated stress rather than acute stress, making it difficult to interpret this result. Conversely, as suggested by Blauer *et al.*, DHEAS may play a role in anti-stress and neuroprotective activities, protecting the cochlea against acoustic injury or ischemic changes, so our result can be attributed to the increase in hearing loss

levels and in the need for cochlear protection⁴⁷. Further studies are needed to confirm our present results. Serum ACTH level measured on day 1 was significantly different in three consecutive PTA results in our study (p -value=0.037, 0.033, and 0.018, respectively). However, in our hospital, ACTH level below 1.5pg/mL could not be measured, so when the analysis categorized ACTH into the normal and elevated groups based on the 1.5pg/mL threshold, hearing loss levels of day 0 and 5 were statistically significantly poor in the group with high ACTH level (p -value=0.040, 0.015, respectively).

To examine the relationship of the BDI score with the subjective stress level, stress-related questionnaires were administered at the time of diagnosis. In our findings, the BDI score, rather than the PSS score significantly predicted treatment response. The BDI score showed a statistically significant correlation with the hearing loss level in the last hearing test performed on day 19 (p -value=0.015, $R^2=0.376$), whereas the PSS score did not show a statistically significant correlation with the hearing loss level. Perhaps, because PSS is concerned about stress-related experiences over the past month, individual recall abilities can lead to distorted results. Second, PSS focuses on a general situation rather than a stress-inducing event and may be less relevant than BDI, which is composed of observable behavioral symptoms. Similarly, Chen *et al.* and Schussler *et al.* reported that anxiety and depression levels were higher in the ISSNHL group than in the control group^{48,49}. In contrast, Mert *et al.* reported that depression and anxiety levels (BDI, STAI-II) were similar in the recovery and no-recovery groups of patients with ISSNHL⁵⁰.

There were some limitations to our research. First, it was conducted as a prospective study and had a small sample size, in that only a patient without a history of DM, CVD, etc. could be included and all patients had to undergo inpatient treatment for 5 days. In addition, as the study involved inpatients, the results may not be generalizable to other populations. Stress level measurements via blood work and questionnaire administration were impossible to perform before hearing loss occurred, so it was performed at the time of diagnosis, which may cause some confusion in understanding the causal relationship between stress and hearing loss. Nevertheless, this study is a well-controlled study that used appropriate patient recruitment, treatment, and examination methods and is meaningful as it assessed both objective and subjective stress levels by means of blood work and questionnaire survey.

V. Conclusion.

Stress may be a cause of ISSNHL, but this has not yet been clarified. In this sense, stress level measurements, e.g., measurement of DHEAS and ACTH levels and the BDI scores, can be used as predictors of disease prognosis because the degree of stress that causes illness can affect prognosis. Considering that maximizing the probability of hearing restoration is the ultimate therapeutic goal, stress management could be a part of the essential treatment plan for ISSNHL.

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Index

벡 우울 척도(BDI: Beck Depression Inventory) 한글판

다음의 문항을 읽어보시고 각 번호의 여러 란 중에서 요즈음 자신에게 가장 적합하다고 생각되는 번호를 하나씩만 골라 ○표를 하십시오.

1. 1) 나는 슬프지 않다. ()
 2) 나는 슬프다. ()
 3) 나는 항상 슬프고 기운을 낼 수 없다. ()
 4) 나는 너무나 슬프고 불행해서 도저히 견딜 수 없다. ()
2. 1) 나는 앞날에 대해서 별로 낙심하지 않는다. ()
 2) 나는 앞날에 대해서 용기가 나지 않는다. ()
 3) 나는 앞날에 대해 기대할 것이 아무것도 없다고 느낀다. ()
 4) 나는 앞날은 아주 절망적이고 나아질 가망이 없다고 느낀다. ()
3. 1) 나는 실패자라고 느끼지 않는다. ()
 2) 나는 보통사람들보다 더 많이 실패한 것 같다. ()
 3) 내가 살아온 과거를 뒤돌아 보면, 실패투성이인 것 같다. ()
 4) 나는 인간으로서 완전한 실패자라고 느낀다. ()
4. 1) 나는 전과같이 일상생활에 만족하고 있다. ()
 2) 나의 일상생활은 예전처럼 즐겁지 않다. ()
 3) 나는 요즘에는 어떤 것에서도 별로 만족을 얻지 못한다. ()
 4) 나는 모든 것이 다 불만스럽고 싫증난다. ()
5. 1) 나는 특별히 죄책감을 느끼지 않는다. ()
 2) 나는 죄책감을 느낄 때가 많다. ()
 3) 나는 죄책감을 느낄때가 아주 많다. ()
 4) 나는 항상 죄책가 멍 시달리고 있다. ()
6. 1) 나는 별을 받고 있다고 느끼지 않는다. ()
 2) 나는 나는 어쩌면 별을 받을지도 모른다는 느낌이 든다. ()
 3) 나는 별을 받을 것 같다. ()
 4) 나는 지금 별을 받고 있다고 느낀다. ()
7. 1) 나는 나 자신에게 실망하지 않는다. ()
 2) 나는 나 자신에게 실망하고 있다. ()
 3) 나는 나 자신에게 화가 난다. ()
 4) 나는 나 자신을 증오한다. ()
8. 1) 내가 다른 사람보다 못한 것 같지는 않다. ()
 2) 나는 나의 약점이나 실수에 대해서 나 자신을 탓하는 편이다. ()
 3) 내가 한 일이 잘못되었을 때는 언제나 나를 탓한다. ()
 4) 일어나는 모든 나쁜 일들은 다 내 탓이다. ()
9. 1) 나는 자살같은 것은 생각하지 않는다. ()
 2) 나는 자살할 생각을 가끔 하지만, 실제로 하지는 않을 것이다. ()
 3) 자살하고 싶은 생각이 자주 든다. ()
 4) 나는 기회만 있으면 자살하겠다. ()
10. 1) 나는 평소보다 더 울지는 않는다. ()
 2) 나는 전보다 더 많이 운다. ()
 3) 나는 요즘을 항상 운다. ()
 4) 나는 전에는 울고 싶을 때 울 수 있었지만 요즘은 울래야 울 기력조차 없다. ()

11. 1) 나는 요즈음 평소보다 더 짜증을 내는 편은 아니다. ()
 2) 나는 요즈음 항상 짜증이 나고 귀찮아 진다. ()
 3) 나는 요즈음 항상 짜증을 내고 있다. ()
 4) 전에는 짜증스럽던 일에 요즘은 너무 지쳐서 짜증조차 나지 않는다. ()
12. 1) 나는 다른 사람들에 대한 관심을 잃지 않고 있다. ()
 2) 나는 전보다 다른 사람들에 대한 관심이 줄었다. ()
 3) 나는 다른 사람들에 대한 관심이 거의 없어졌다. ()
 4) 나는 다른 사람들에 대한 관심이 완전히 없어졌다. ()
13. 1) 나는 평소처럼 결정을 잘 내린다. ()
 2) 나는 결정을 미루는 때가 전보다 더 많다. ()
 3) 나는 전에 비해 결정내리는 데에 더 큰 어려움을 느낀다. ()
 4) 나는 더 이상 아무 결정도 내릴 수가 없다. ()
14. 1) 나는 전보다 내 모습이 나빠졌다고 느끼지 않는다. ()
 2) 나는 나이가 들어 보이거나 매력 없어 보일까봐 걱정한다. ()
 3) 나는 매 모습이 매력 없게 변해버린 것 같은 느낌이 든다. ()
 4) 나는 내가 추하게 보인다고 믿는다. ()
15. 1) 나는 전처럼 일을 할 수 있다. ()
 2) 어떤 일을 시작하는 데에 전보다 더 많은 노력이 든다. ()
 3) 무슨 일이든 하려면 나 자신을 매우 심하게 재촉해야만 한다. ()
 4) 나는 전혀 아무 일도 할 수가 없다. ()
16. 1) 나는 평소처럼 잠을 잘 수 있다. ()
 2) 나는 전에 만큼 잠을 자지는 못한다. ()
 3) 나는 전보다 한두 시간 일찍 깨고 다싱 잠들기 어렵다. ()
 4) 나는 평소보다 몇 시간이나 일찍 깨고, 한번 깨면 다시 잠들 수 없다. ()
17. 1) 나는 평소 보다 더 피곤하지는 않다. ()
 2) 나는 전보다 더 쉽게 피곤해 진다. ()
 3) 나는 무엇을 해도 피곤해진다. ()
 4) 나는 너무나 피곤해서 아무 일도 할 수 없다. ()
18. 1) 내 식욕은 평소와 다름없다. ()
 2) 나는 요즈음 전보다 식욕이 좋지 않다. ()
 3) 나는 요즈음 식욕이 많이 떨어졌다. ()
 4) 요즈음에는 전혀 식욕이 없다. ()
19. 1) 요즈음 체중이 별로 줄지 않았다. ()
 2) 전보다 몸무게가 2Kg 가량 줄었다. ()
 3) 전보다 몸무게가 5Kg 가량 줄었다. ()
 4) 전보다 몸무게가 7Kg 가량 줄었다. ()
- *나는 현재 음식 조절로 체중을 줄이고 있는 중이다. (예, 아니오)
20. 1) 나는 건강에 대해 전보다 더 염려하고 있지는 않다. ()
 2) 나는 여러 가지 통증, 소화불량, 변비 등과 같은 신체적인 문제로 걱정하고 있다. ()
 3) 나는 건강이 염려되어 다른 일은 생각하기 힘들다. ()
 4) 나는 건강이 너무 염려되어 다른 일은 아무 것도 생각할 수 없다. ()
21. 1) 나는 요즈음 성에 대한 관심에 별다른 변화가 있는 것 같지는 않다. ()
 2) 나는 전보다 성(sex)에 대한 관심이 줄었다. ()
 3) 나는 전보다 성(sex)에 대한 관심이 상당히 줄었다. ()
 4) 나는 성(sex)에 대한 관심을 완전히 잃었다. ()

한국판 지각된 스트레스 척도

이 척도는 지난 한 달 동안 어떤 감정과 생각이 들었는지 물어보는 것입니다. 각 질문에 대해 당신이 얼마나 자주 느끼거나 생각했는지를 "V" 표시해 주시기 바랍니다.

	0=전혀 아니다	1=거의 아니다	2=가끔	3=꽤 자주	4=매우 자주
	◀전혀 아니다			매우 자주▶	
1	0	1	2	3	4
2	0	1	2	3	4
3	0	1	2	3	4
4	0	1	2	3	4
5	0	1	2	3	4
6	0	1	2	3	4
7	0	1	2	3	4
8	0	1	2	3	4
9	0	1	2	3	4
10	0	1	2	3	4

국 문 요 약

특발성 돌발성 감각 신경성 난청에서 예측 및 예후인자로서 스트레스 호르몬(Cortisol, Aldosterone, DHEAS, ACTH)의 유용성

이전의 연구에 따르면 스트레스는 특발성 돌발성 감각신경성 난청의 원인 중 하나로 알려져 있다. 특히 시상 하부 뇌하수체-부신 축을 이루는 호르몬인 코티솔, 성장 호르몬, 프로락틴, 항이노 호르몬, 부신피질 자극 호르몬 등의 혈장 농도가 돌발성 난청 환자에서 증가해 있다는 결과가 있으나 호르몬 및 스트레스의 정량적 정도가 발병 당시 병의 정도와 치료에 대한 반응 또는 예후와의 연관성에 대해서는 알려진 바가 거의 없다. 이에 우리는 환자의 심리적 스트레스 요인이 난청의 정도 예측 및 예후인자로서의 가치가 있는지에 대해 알아보고자 한다.

특발성 돌발성 감각신경성 난청으로 원주 세브란스 기독병원 이비인후과에서 입원 치료를 한 15명을 대상으로 전향적 연구를 진행하였다. 환자는 모두 경구 스테로이드 및 항바이러스제, 성상신경 차단술을 시행 받았고, 난청의 정도가 50dB 이상인 환자에게는 고실 내 스테로이드 주사를 시행하였고 70dB 이상인 환자에게는 고압산소치료를 추가적으로 시행하였다. 청력검사는 진단 당시, 5일 째 퇴원하는 날, 첫 번째 외래 추적관찰인 2주 후 시행하였으며, 혈장 호르몬 수치는 Cortisol, ACTH, Aldosterone, DHEAS를 입원 1일 째, 5일 째 혈액검사를 통해 측정하였다. 주관적 스트레스 정도를 파악하기 위하여 백 우울척도와 지각된 스트레스 척도, 두 가지의 설문지를 진단 당시 시행하였다.

입원 후 1 일째 시행된 혈청 DHEAS 수치는 진단 당시 난청의 정도와 통계적으로 유의한 양의 상관관계를 나타냈다 ($p = 0.037$, $R^2 = 0.293$). 또한 1 일째 측정된 혈청 ACTH를 1.5pg/mL를 기준으로 두 그룹으로 나누었을 때, 정상 그룹은 비정상 그룹보다 진단 당시와 퇴원 시 시행한 청력검사에서 통계학적으로 유의하게 더 나은 청력역치 값을 보였다 ($p=0.040$, 0.015). 스트레스 관련 설문지에서는 BDI 점수와 최종 청력검사에서의 청력역치와 통계적으로 유의한 양의 상관관계를 나타냈다 ($p = 0.015$, $R^2 = 0.376$).

본 연구는 돌발성 난청에서 스트레스 관련 호르몬과 설문지가 병의 정도와 예후를 예측할 수 있는 인자로써의 역할을 할 수 있는 가능성을 보여주고 있다. 혈청 DHEAS 수치는 돌발성 난청의 진단 당시 난청의 정도와 유의한 상관관계를 보였으며 BDI 점수가 높을수록 최종 청력검사에서 난청의 정도가 심한 것을 보아 치료에 반응이 적을 수 있음을 암시하고 있다. 그러나 내이 및 내 림프 항상성에 대한 스트레스에 대한 반응에 대한 병리 생리학적인 메커니즘에 대해서는 가설은 있으나 여전히 밝혀진 것이 없다. 또한 스트레스와 난청간의 명확한 선후관계를 파악하기 어려워 추후 대규모 전향적 추가 연구가 필요하다.

핵심되는 말 : 특발성 돌발성난청, 감각신경성 난청, 청력, 스트레스, 호르몬, 설문지