ORIGINAL ARTICLE

Plasma Endothelin-1 Levels in Patients with Sudden Sensorineural Hearing Loss

Mehmet Koyuncu, Sinan Atmaca, Ahmet Yılmaz Çoban, Figen Başar, Şengül Çivici

Department of Otolaryngology and Head and Neck Surgery, (M. Koyuncu, S. Atmaca, Ş. Çivici); Department of Microbiology and Clinical Microbiology, (Y. Çoban); Department of Audiology and Speech Therapy, (F. Başar); Ondokuz Mayis University School of Medicine, Samsun, Turkey

Corresponding author:
Sinan Atmaca, MD
Assistant Professor Otolaryngology
Ondokuz Mayis Universitesi
Tip Fak. KBB Anabilim Dali
Kurupelit 55139 Samsun
TURKEY
Phone: 90-362-3121919/ 2749
Fax : 90-362-4576041
Email: sinanatmaca@yahoo.com

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OBJECTIVE: The aim of this study was to investigate the relationship between Endothelin-1 (ET-1) and hearing levels in patients with sudden sensorineural hearing loss (SSHL).

STUDY DESIGN: Prospective.

SETTING: Tertiary referral center.

PATIENTS AND METHODS: Thirty-seven patients with SSHL were included in the study. Patients who recieved treatment before admission or had symptoms for more than 3 days were not enrolled. Endothelin levels of 37 patients diagnosed as having SSHL were investigated admission and 3rd month follow-up with reference to the hearing recovery.

RESULTS: Fifteen patients, with complete recovery after treatment, had statistically lower endothelin-1 levels at 3rd month follow-up compared to the level at admission ($p<0.001$).

CONCLUSION: We suggest vascular reasons may play an important role in SSHL and the treatment should be planned accordingly.

Sudden sensorineural hearing loss (SSHL) is one of the most important diseases which should be treated immediately. The etiology of the disease couldn't have been explained completely until now, and the potential causes of SSHL are viral diseases, cochlear membrane breaks, autoimmune and vascular disorders [1].

Cochlea is supplied by spiral modiolar artery. Cochlea regulates its nourishment and functions by inner ear fluids besides vascular structures. Many inner ear disorders like sudden and fluctuating hearing loss and tinnitus may be due to a dysfunction of cochlear blood flow regulation [2].

Endothelin-1 is the predominant isopeptide of the ET family (ET-1, ET-2, ET-3) that is generated by vascular endothelium [3,4]. ET receptors have been identified on many structures of the lateral cochlear wall and vascular smooth muscle cells isolated from the spiral modiolar artery, indicating physiological efficacy of ET-1 on the arterial wall [5]. ET-1 may act widely as local hormonal regulator of pressure, fluid volume, ion balance, hormone secretion besides strong vasoconstrictor effect [6]. It has been shown that increased plasma levels of ET-1 results in spiral modiolar artery vasospasm [7].

In this prospective study, we investigated the relation between ET-1 and hearing levels on 37 patients with SSHL and 3 months after treatment.

MATERIALS AND METHODS

This study was approved by Institutional Ethics Comittee at Ondokuz Mayis University, School of Medicine. This study includes 37 patients who had SSHL with no specific etiology. SSHL was defined as hearing loss that is greater than 30 dB in three consecutive frequencies and present for less than 3 days [1,8]. Pure-tone audiogram and immittancemetry were performed on the patients initially, before the treatment. Presence of systemic disease was searched with hematologic and biochemical tests. Cranial and temporal computerized tomography and magnetic resonance imaging were performed in a few cases.

ET-1 levels were measured from serum with EDTA, at first admission and 3rd month follow-up. Measurements were studied with Human Endothelin-1 ELISA kits (Parameter, R@D SYSTEM GmbH, Germany).

The patients were put on low salt and cholesterol diet for 5 days after admission. Prednisolone 1mg/kg orally for 5 days, tapered off 15 mg every three days and piracetam 6 gr IV bid for 5 days were given to all patients with SSHL. Pure-tone audiogram was performed at the end of 5 day of treatment and 3rd month follow-up. Results were evaluated according to the criteria of "Sudden Deafness Research Team of the Japanese Ministry of Health and Welfare" [9]. The arithmetic means of hearing levels at 250, 500, 1000, 2000 and 4000 Hz were used for the evaluation of hearing recovery.

Complete recovery: Hearing level returns to the equal level of the unaffected contralateral ear.

Good recovery: Improvement in the hearing level is ≥ 30 dB

Fair recovery: Improvement in the hearing level is ≥10 dB

No change : Improvement in the hearing level is < 10 dB

RESULTS

This study was performed on 37 patients with SSHL aged 7 to 75 years (24 males and 13 females; average age, 37 years). All patients had unilateral SSHL and 21 of them had right and 16 had left ear involvement. Four patients had hypertension and 2 had diabetes mellitus. Systemic, neurologic and Ear-Nose-Throat examinations were normal. Immittancemetry showed normal tympanogram findings in all patients. No abnormal results were found at radiological investigations. The hearing level at 3 months after the treatment was considered as final, and hearing recovery was classified into four grades (complete recovery, good recovery, fair recovery and no change) according to the criteria proposed by the Ad Hoc

Committee of the Japanese Ministry of Health and Welfare, as shown in Table 1. Twenty-four patients had recovery. Of these; 15 had complete recovery, 5 had good recovery and 4 had fair recovery. Hearing levels of 13 patients had no change. Statistical analysis was made by Kruskal Wallis and Wilcoxon tests.

Data were given as median and minimum-maximum (Table 2). In the complete recovery group of 15 patients, there was significant difference in ET measurements between admission and 3rd month follow-up ($p<0.001$). However, there was no significant difference in comparisons of other groups ($p>0.05$).

DISCUSSION

Treatment of SSHL could be possible with identification and elimination of the cause of the disease. Nutritional and circulatory disorders besides viral infections, vascular pathologies and trauma can cause SSHL by impairing cochlear blood flow. Therefore, microcirculation of the inner ear should be well known.

Capillary blood flow is primarily regulated by the resistance of precapillary arteries. The vascular resistance is a function of the contractile status of the vascular smooth muscle cells. Constriction of vascular smooth cell results from an increase in intracellular Ca^{+2} and/or by an increase in the Ca^{+2} sensitivity of the contractile apparatus [10,11]. One key mechanism enhancing Ca^{+2} sensitivity and thus vascular tone is Rho-kinase signalling, which results in inhibition of myosin light chain phosphatase [11,12]. One of the strongest Rho-kinase activators described so far is the vasoconstrictor ET-1. ET-1 receptor plays a fundamental role in the maintenance of basal vasomotor tone in arterial resistance [13]. Small amounts of ET-1 are released by endothelial cells toward underlying smooth muscle cells to maintain vascular tone and blood pressure [14]. The long lasting effect of ET-1 may result from tonic stabilization of the arterial wall rather than circumscribed constrictions of the arterial smooth muscle layer. In addition, minimal

Table-1: Recovery rates according to audiogram configurations

Recovery	Hf	Lf	Fa	Td
Complete	3	8	4	–
Good	–	1	4	–
Fair	–	2	2	–
No change	1	–	4	8

Hf: High frequency; Lf: Low frequency; Fa: Flat audiogram; Td: Total deafness

Table-2: Comparison of ET-1 measurement in patients

	Endothelin measurements (median, min-max) (pg/ml)		p
Recovery	At Admission	At 3rd month follow-up	
Complete	0.43 (0.22-1.15)	0.22 (0.22-0.69)	p<0.001
Good	0.22 (0.22-0.36)	0.22 (0.22-0.89)	p>0.05
Fair	0.63 (0.22-1.27)	0.26(0.21-0.83)	p>0.05
No change	0.22 (0.22-0.55)	0.22 (0.22-0.63)	p>0.05

(tonic) contractions of arteries can be hardly detected with intravital microscopy and scanning electron microscopy [15,16]. It has been shown by Franz et al [17] that ET-1 was identified in arterial and venous endothelium of the cochlear vascular bed and contractions of venous wall pericytes focally narrows the vascular lumen. Miller et al [18] suggested that venules are more sensitive than arteries to the vasoconstrictor effect of ET. In this way, pericytes on postcapillary venules should be susceptible to ET-1 and may contribute to the regulation of blood flow in the preceding capillary bed. ET may play a role in the maintenance of the stria vascularis function via the activation of sodium pump or interfering with nitric oxide, prostoglandins and atrial natriuretic peptide in the lateral cochlear wall [17].

Distribution and localization of ET-1 has been reported in the endolymphatic sac, vestibule and cochlea of normal guinea pigs [19,20,21]. In addition, ET-1 like activity was clearly localized to the epithelium of the endolymphatic sac, sensory epithelial cells, dark cells, vestibular ganglion cells, endothelium of vessels, organ of Corti, spiral ligament and stria vascularis. Jinouchi [22] suggested that ET-1 may be produced in the small vessels of the bony labyrinth adjacent to the spiral ligament and may play an important role in the cochlear function. These results showed that ET-1 may act in maintaining the homeastasis of inner ear pressure, fluid and electrolyte balance and may modulate the release of neuropeptide at the nerve ending.

Reduced cochlear blood flow has been implicated as a possible etiological factor in sudden deafness, Meniere's disease, and other inner ear disorders [3]. The synthesis of ET-1 can be increased by hypoxia and elevated oxidized low-density lipoproteins and has been implicated in the pathogenesis of a number of cerebrovascular disorders, including stroke, ischemia, and in particular, cerebral vasospasm [23,24,25].

Elevated levels of ETs are evident during vascular pathophysiologies such as essential hypertension, ischemic stroke and migraine headaches [26,27]. Quirk et al [28] tested the plasma concentrations of ET following noise exposure. Significant elevations of plasma ET has been shown following excessive exposure to noise while minor alterations were reported with brief exposure [28]. They stated that their study raised several questions concerning the blood pressure changes accompanying these elevated levels of ET, and the nature of the interactions between ET and other vascular maintenance mechanisms.

These low circulating levels of ET are probably due to short half life and rapid clearance of these peptides [29]. Additionally, there is evidence that ETs are released and act locally on surrounding smooth muscle and endothelium, thereby limiting ET in the blood stream [28].

In this study, patient numbers in "good recovery" and "fair recovery" groups weren't sufficient enough for statistical analysis. ET-1 levels at admission and 3rd month follow-up in "complete recovery" group revealed statistically significant difference whereas no significant difference was observed in "no change" group. Higher ET-1 levels in "complete recovery" group compared to "no change" group suggest presence of factors, other than arteriolar vasospasm or increased ET-1 secretion by disruption of inner ear circulation and fluid dynamics, that can't be controlled by anti-inflammatory and vasodilator regimens existing in our treatment protocol.

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