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Prognostic Value of Whole Blood Viscosity in Sudden Sensorineural Hearing Loss

Ani Sensörinöral İşitme Kaybında Tam Kan Viskozitesinin Prognostik Değeri

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ABSTRACT Objective: Sudden sensorineural hearing loss (SSNHL) is defined as hearing loss of at least 30 dB or more in three contiguous frequencies, occurring within 72 hours. Based on the association of increased whole blood viscosity (WBV) markers as a prognostic indicator in vascular disorders, we aimed to determine the association between whole blood viscosity (WBV) and sudden sensorineural hearing loss (SSNHL) prognosis. **Material and Methods:** In this retrospective study, 73 patients diagnosed with SSNHL were included. The WBV calculation was performed via validated formula by using hematocrit (HCT) and total plasma protein (TP) concentrations at high shear rate (HSR=208/s) and the low shear rate (LSR=0.5/s). Pre- and post-treatment pure-tone average (PTA) results were recorded. In addition mean values of LSR and HSR were compared between patients and healthy control group. **Results:** In the patient group, 54.8% were affected in the right ear and 45.2% in the left ear. Of the patients, 35.6% (n=26) were resistant to treatment (to Siegel criteria type 4). The higher mean HSR and LSR values in patients with treatment-resistant and severe SSNHL were not statistically significant. No statistically significant difference was found between the patient and control groups according to the WBV values. **Conclusion:** Blood viscosity LSR and HSR markers had no predictive value on SSNHL prognosis. However, it should be considered that direct measurement of WBV instead of measurement with a formula may cause different results.

Keywords: Sudden sensorineural hearing loss; whole blood viscosity (WBV); high shear rate (HSR); low shear rate (LSR)

ÖZET Amaç: Ani işitme kaybı (AİK) 72 saat veya daha kısa sürede aniden gelişen, ard arda üç frekansta minimum 30 dB veya üzerindeki sensörinöral işitme kaybıdır (SNİK). Artmış tam kan viskosite (TKV) markırlarının vaskuler bozukluklarda prognostik bir indikatör olarak ilişkilendirilmesine dayanarak çalışmamızda AİK tanısı alan hastalarda TKV'nin prognoza olan etkisinin belirlenmesi amaçlanmıştır. **Gereç ve Yöntemler:** Çalışmaya AİK tanısı almış toplam 73 olgu retrospektif olarak dahil edilmiştir. TKV, hematokrit (HCT) ve total plazma protein (TP) konsantrasyonları kullanılarak geçerliliği kabul edilmiş formul yardımıyla düşük (DKH=0.5/s) ve yüksek (YKH=208/s) kesme hızlarında hesaplanmıştır. Hastalarda tedavi öncesi ve sonrası ölçülen saf ses odyometri sonuçları ile TKV markırlarının (DKH, YKH) değişimi; karşılaştırılarak değerlendirildi. **Bulgular:** Hastaların %54,8'inde sağ kulakta, %45,2'sinde sol kulakta AİK tanımlanmıştır. Hastaların %35,6 (n=26)'sı tedaviye yanıt alınamayan (Siegel kriteri tip 4) olarak belirlenmiştir. Tedaviye yanıt alınamayan ve şiddetli AİK gözlenen gruplarda kan vizkosite ortalama YKH ve DKH değerlerindeki artış istatistiksel olarak anlamlı bulunmamıştır. Ayrıca kontrol ve hasta grupları arasında TKV değerleri açısından istatistiksel olarak anlamlı bir fark belirlenmemiştir. **Sonuç:** Çalışmamızda formuler olarak hesaplanan TKV markırlarının AİK prognozunda prediktif değeri olmadığı sonucuna varılmıştır. İleride daha çeşitli hemotolojik parametreleri kapsayan ve geniş örneklem grublarından oluşacak çalışmaların, AİK adına terapötik ve prognostik stratejilerin geliştirilmesi açısından katkı sağlayacağı kanaatindeyiz.

Anahtar Kelimeler: Ani işitme kaybı (AİK); tam kan viskosite (TKV); yüksek kesme hızı (YKH); düşük kesme hızı (DKH)

Sudden sensorineural hearing loss (SSNHL) is generally defined as hearing loss of 30 dB or more in three contiguous frequencies, occurring within 72 hours.[1] SSNHL usually occurs idiopathically and unilaterally between the ages of 30 and 60 years with unknown etiology. It comprises only 1% of all

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sensorineural hearing loss with an estimated annual incidence of 5-30 cases/100000.[2] Although infectious, autoimmune, vascular, traumatic, neoplastic, metabolic, and neurologic causes are related to SSNHL etiopathogenesis, there is evidence that impaired cochlear perfusion, inflammation, and viral infections are more prominent in these patients.[3] Therefore, anti-inflammatory drugs are administered in addition to single high-dose steroids as soon as possible after SSNHL symptom onset, and treatment also includes antiviral agents, vasodilators, and calcium antagonists.[3,4]

Blood viscosity is a dynamic intrinsic resistance to blood flow caused by frictional force between the blood vessel walls. Blood is a non-Newtonian fluid, and its viscosity depends on the shear rate. The shear rate varies according to the endpoint, the blood vessels' radius and length, and the red blood cells' aggregation and deformation abilities.[5] Whole blood viscosity (WBV) can be calculated at low shear rates (LSR) of 0.5/s and high shear rates (HSR) of 208/s via validated formulas using hematocrit (HCT) and total plasma protein (TP) levels.[6]

OBJECTIVE

Increased WBV has been identified as the major rheological variable in the risk assessment of atherothrombotic diseases. As a prognostic indicator it is frequently associated with adverse cardiovascular events, vascular disorders, and vasculopathies in several diseases.[7-9] Therefore, it is widely accepted as a simple, minimally invasive, rapid, and cost-effective parameter in clinical applications.[10] In this study, we aimed to determine the predictive value of WBV markers in SSNHL prognosis in patients with severe hearing loss and treatment resistance by using the pre- and post-treatment audiometry results. We also compared the mean values of LSR and HSR between the SSNHL patients and healthy controls.

MATERIAL AND METHOD

ETHICAL CONSIDERATIONS AND FUNDING

This study was approved by the Institutional Review Board of the Department of Otorhinolaryngology, University of Health Sciences(ref 40-2019/9-71). The study was carried out in Samsun Training and Research Hospital and the study received no funding.

STUDY SUBJECTS

The study included 73 patients aged between 20 and 65 years, who had been diagnosed with SSNHL, and 32 healthy participants. Patients with hearing loss of at 30 dB or more in three contiguous frequencies within 72 hours were enrolled in the study. Subjects with a history of otologic surgery, any neuropsychiatric, metabolic, systemic, or autoimmune disease, as well as participants using anticoagulants, antiaggregants, alcohol and tobacco, were excluded from the study. Participants were enrolled in the study after their written informed consent had been obtained. A detailed history of hearing loss (including onset time and duration) was recorded. Complete otorhinolaryngologic, pure-tone audiometry, and immitancemetric examinations were performed in all participants.

MEASURES

Cell blood count and biochemical analysis were performed on participants' venous blood samples. Hematological parameters were analyzed using a hematology analyzer (Cell-Dyne 3700, Abbott, Abbott Park, IL, USA). Biochemical analysis was performed on serum samples using an electrochemiluminescence immunoassay analyzer (Beckman Coulter Unicel DXI 800, Beckman Coulter, Miami, FL, USA). The WBV calculation was performed via a validated formula using HCT and TP concentrations at an HSR of 208/s) and an LSR of 0.5/s:

HSR: WBV (208 s^{-1})=(0.12xHCT)+0.17 (TP-2.07).

LSR: WBV (0.5 s^{-1})=(1.89xHCT)+3.76 (TP-78.42).

Pure-tone audiometry was performed at 500, 1000, 2000, and 4000 Hz frequencies in the pre- and post-treatment periods using an audiometry device (Madsen Orbiter Audiometer, 922, Taatstrup,Denmark). The patients were classified into two groups according to the pure-tone average (PTA) results: mild SSNHL (<65 dB) and severe SSNHL (>65 dB). Siegel criteria were used to evaluate hearing results after treatment. According to Siegel criteria; type 1 complete recovery, type 2 significant improvement, type 3 slight improvement, type 4 no improvement.

Patients of the fourth type were grouped as treatment-resistant and patients of the other types were cured. The WBV marker measurements (LSR and HSR), according to the SSNHL severity and treatment response, were evaluated. The LSR and HSR mean values were also compared between patients and healthy control group.

STATISTICAL ANALYSIS

The data were analyzed using the Statistical Package for the Social Sciences (SPSS) software v21.0 (IBM, Armonk, NY, USA). Individual and aggregate data were expressed using descriptive statistics, including the mean, standard deviation, median and percentages. Data distribution was screened using the Kolmogorov-Smirnov test. Normally distributed data were compared by the Student's t-test, and non-normally distributed data were evaluated by the Mann-Whitney test. Evaluation of the categorical variables was performed by the Chi-square test. P values of <0.05 were considered statistically significant.

RESULTS

The 73 SSNHL patients in this study included 45 (61.6%) males and 28 (38.4%) females. The mean age of the patients was 41.92±14.78 years (range: 20-65) years. The 32 healthy participants comprised 20 males and 12 females with a mean age of 39.44±13.92 years. The right ear was affected in 54.8% (n=40) of the patients and the left ear in 45.2% (n=33) of the patients. Before treatment, SSNHL was determined to be mild (<65 dB) in 49.3% (n=36) and severe (>65 dB) in 50.7% (n=37) of the cases, according to the PTA results (Table 1). Overall pre-treatment PTA (67.60±28.60 dB) significantly improved (53.45±31.89 dB) after treatment in the affected ears (p=0.000) (Figure 1).

Of the patients, 64.4% (n=47) had significant improvement in PTA results, while 35.6% (n=26) did not respond to treatment. The mean HSR was calculated as 3.94±0.34 in the treated group, while it was 4.00±0.50 in the patients who did not respond to treatment. The mean LSR was 24.11±5.58 in the treated group, while it was 24.91±8.27 in the treatment-resistant group. The higher HSR and LSR values in the treatment-resistant group were not statistically significant (p=0.618 and 0.663, respectively) (Table 2).

TABLE 1: Patients' characteristics.

Clinic Variable[a]	n (%)
Gender	
Male	45 (61.6%)
Female	28(38.4%)
Affected Ear	
Left	33 (45.2%)
Right	40 (54.8%)
SSNHL[b]	
Mild <65 PTA	36 (49.3%)
Severe >65 PTA	37 (50.7%)
Treatment Response	
Cured	47 (64.4%)
Resistant	26 (35.6%)

[a]PTA: Pure-tone average; [b]SSNHL: Sudden sensorineural hearing loss.

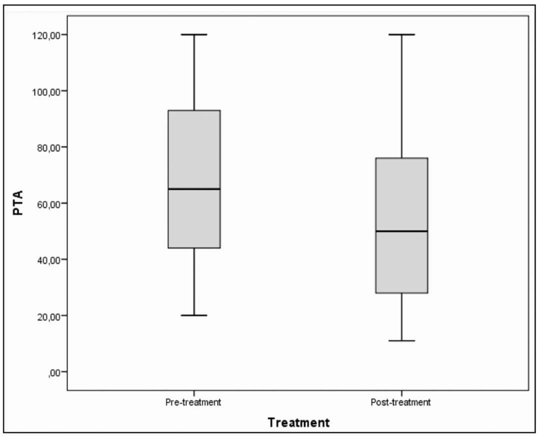

FIGURE 1: Pre- and post-treatment pure-tone averages (PTA).

The mean HSR was 4.02±0.39 in patients with mild SSNHL, while it was calculated as 3.91±0.42 in patients with severe SSNHL. The mean LSR was 25.20±6.30 in patients with mild SSNHL, while it was 23.61±6.90 in patients with severe SSNHL. Thus, there was no statistically significant difference between the mild and severe SSNHL groups, according to the HSR and LSR values (*p*=0.285 and 0.310, respectively) (Table 2).

In the total patient group, the mean HSR was 3.96±0.40, while it was 4.11±0.47 in the control group. The mean LSR was 24.39±6.62 in the total pa-

TABLE 2: Comparison of blood viscosity markers according to SSNHL severity and treatment response.

	Clinical Variables	LSR[a] (Mean±SD)	p value	HSR[b] (Mean±SD)	p value
SSNHL[c]	Mild <65	25.20±6.30	0.310	4.02±0.39	0.285
	Severe >65	23.61±6.90		3.91±0.42	
Treatment Response	Cured	24.11±5.58	0.663	3.94±0.34	0.618
	Resistant	24.91±8.27		4.00±0.50	
Groups	Patients	24.39±6.62	0.060	3.96±0.40	0.115
	Control	27.20±7.73		4.11±0.47	

[a]LSR: Low shear rate; [b]HSR: High shear rate; [c]SSNHL: Sudden sensorineural hearing loss.

tient group, while it was 27.20±7.73 in the control group. There was no statistically significant difference between the patient and the control groups in the HSR and LSR values (p=0.115 and 0.060, respectively) (Table 2).

DISCUSSION

Cochlear blood flow is provided by the labyrinthine artery, which has no collateral vasculature. Therefore, hypoxia related to vascular disorders may lead to cochlear damage and SSNHL. The thromboembolic events that may disturb cochlear microcirculation have also been associated with SSNHL in published data.[11] Rudack et al. identified increased fibrinogen levels and smoking as risk factors for SSNHL in a study that included 142 patients and determined total cholesterol, HDL and LDL concentrations, and fibrinogen polymorphisms, compared to 84 healthy controls.[12] Local blood flow predominantly depends on blood viscosity. In addition, numerous risk factors that are already associated with increased blood viscosity, such as advanced age, obesity, hypertension, diabetes, thromboembolic events, and smoking, may disturb blood flow to tissues.[8]

Moreover, red blood cells, total plasma proteins/fibrinogen have a major impact on blood viscosity. Rheological treatment (hemodilution, platelet-erythrocyte aggregation inhibition, defibrinogenesis, and plasmapheresis) improves microcirculation and capillary blood flow by reducing blood viscosity, and thereby cochlear oxygen concentration increases. In a meta-analysis of 2229 articles, Li evaluated the efficacy of blood viscosity management in patients diagnosed with SSNHL. The researcher concluded that hemodilution, anticoagulant, and plasmapheresis therapies, in particular, relieve tinnitus and vertigo and improve hearing results, but the requirement for further randomized controlled trials with larger sample groups was highlighted.[13] Lucia et al. evaluated hemorheological parameters, including WBV, plasma viscosity, and the erythrocyte deformability index, in 63 patients diagnosed with SSNHL and 67 healthy controls. They concluded that viscosity, coagulation, and fibrinolysis mechanisms may play a prominent role in SSNHL pathophysiology.[14] In a prospective study conducted with 85 SSNHL patients, García-Callejo et al. reported a significantly increased WBV and a decreased erythrocyte rigidity index (ERI) along with a significant improvement in PTA results. They concluded that WBV and ERI parameters may contribute to predicting risk, prognosis, and treatment in SSNHL patients.[15] On the contrary, in a meta-analysis, Wang et al. reviewed 28 published studies and evaluated vasodilator efficacy in SSNHL patients; they concluded that vasodilators were no more effective than a placebo.[16] Similarly, in another meta-analysis Gong et al. screened 13 published studies that included 1155 patients; the outcomes did not support vasodilator treatment in SSNHL patients.[17] Additionally, Koçak et al. demonstrated that Mean Platelet Volume (MPV), which is associated with platelet predisposition, was not found to be predictive in SSNHL prognosis in a study consisting of 93 SSNHL patients and 93 healthy controls.[18] In the present study, the post-treatment PTA results were significantly improved in patients. However, the higher mean HSR and LSR values in patients with treatment-resistant and severe SSNHL (>65 dB), compared to the patients who responded to treatment and had mild SSNHL, was not statistically significant. Moreover, there was no statistically significant difference between the patient and control groups, according to the WBV values. The published data evaluating hemorheological factors that directly affect blood viscosity is inconsistent. In our study, blood viscosity was assessed extensively via LSR and HSR parameters, and WBV markers had no predictive value on SSNHL prognosis.

Although SSNHL etiopathology is unknown, the sudden and mostly unilateral onset of hearing loss and treatment with predominantly microcirculation-targeted therapies highlights vascular causes. In the current study, the LSR and HSR markers had no predictive value on SSNHL prognosis. However, it should be considered that direct measurement of WBV instead of measurement with a formula may cause different results, like viscometer. To contribute to SSNHL treatment and prognosis, further research should be performed with larger study groups that evaluate more hematological parameters.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Doğukan Özdemir**; Design:*** *Doğukan Özdemir;* ***Control/Supervision:*** *Doğukan Özdemir, Abdulkadir Özgür, Mehmet Çelebi;* ***Data Collection and/or Processing:*** *Dursun Mehmet Mehel, Mahmut Yıldırım;* ***Analysis and/or Interpretation:*** *Doğukan Özdemir, Mahmut Yıldırım, Semih Van;* ***Literature Review:*** *Doğukan Özdemir, Tuğba Yemiş;* ***Writing the Article:*** *Doğukan Özdemir;* ***Critical Review:*** *Doğukan Özdemir, Abdulkadir Özgür, Mehmet Çelebi;* ***References and Fundings:*** *Semih Van, Tuğba Yemiş;* ***Materials:*** *Semih Van, Suat Albayrak.*

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