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Evaluation of hearing levels in Crimean-Congo hemorrhagic fever with audiological and electrophysiological tests

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Abstract

Aim: Crimean-Congo Hemorrhagic Fever (CCHF) is a tick-borne viral disease, and Sensorineural Hearing Loss (SNHL) arises from pathologies in the cochlea or retrocochlear pathways. Viral infections, including Crimean-Congo hemorrhagic fever are considered possible etiological factors for Sensorineural hearing loss, as endothelial damage in Crimean-Congo hemorrhagic fever may impair inner ear blood flow. This study aimed to differentiate between cochlear and retrocochlear hearing loss in patients with Crimean-Congo hemorrhagic fever and assess the reliability of Auditory Steady-State Response (ASSR) testing by comparing its results with pure-tone audiometry.

Materials and Methods: The study included 30 Crimean-Congo hemorrhagic fever patients (Group CCHF) and 30 healthy controls (Group C). Hearing measurements were conducted using pure tone audiometry, otoacoustic emissions, tympanometry, and Auditory steady-state response before the patients' discharge. Data were analyzed using SPSS 22.0.

Results: The results showed no significant difference in audiometric thresholds between the right and left ears of Group CCHF at various frequencies. However, Auditory steady-state response results at 1000, 2000, and 4000 Hz in the right ear and at all tested frequencies in the left ear revealed significant differences between groups ($p<0.05$).

Conclusion: While this study did not establish a clear link between Crimean-Congo hemorrhagic fever and Sensorineural hearing loss, it suggests the need for further research with larger samples and testing during both the active and recovery phases of Crimean-Congo hemorrhagic fever.

Introduction

Crimean-Congo Hemorrhagic Fever (CCHF) is a zoonotic viral infection with a potentially fatal outcome. The causative agent, a tick-borne RNA virus, belongs to the Orthonairovirus genus of the Nairoviridae family [1]. This virus circulates in nature through a tick-vertebrate-tick cycle, with Hyalomma marginatum acting as both the reservoir and primary vector [1]. Transmission to humans occurs primarily through the bite of an infected tick or contact with the blood and tissues of viremic animals. Additionally, nosocomial transmission from infected individuals is possible [2]. Following a 3-7 day incubation period, the disease typically presents with sudden onset of fever, headache, muscle pain, weakness, nausea, vomiting, and, in severe cases, skin and mucosal bleeding [3].

Sensorineural Hearing Loss (SNHL) results from damage to the cochlea or subsequent auditory pathways. The causes of SNHL can be either congenital or acquired, with viral infections playing a significant role among acquired causes. Various viruses, including Herpes Simplex, Varicella Zoster, mumps, measles, rubella, and influenza, have been associated with hearing loss [4]. Two main mechanisms are believed to link viral infections to SNHL. The first involves direct viral invasion of the cochlea, cochlear nerve, or related structures, likely via a hematogenous route, although other routes such as the cerebrospinal fluid space or middle ear are possible [4]. The second mechanism involves reactivation of latent viruses within the inner ear tissues, which may later cause neuritis or cochleitis, leading to SNHL [4].

Although pure tone audiometry and speech audiometry are the primary methods for the evaluation of hearing loss, it is a subjective method since hearing thresholds can be affected by various individual factors. Methods used in the

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objective evaluation of hearing include otoacoustic emissions and auditory brainstem responses [5,6] Evoked OAE have a special place in the evaluation of peripheral hearing function because they are noninvasive, sensitive and objective tests [7,8]. The presence of OAE in a measured ear is an indication of normal cochlear function [9,10]. Auditory Steady-State Response (ASSR) measurement is a technique that has recently been intensively investigated. Although studies have given clues that ASSR can be used in clinics to determine the degree of hearing loss with frequency specificity, one of the primary effects of ASSR is the estimation of pure tone audiogram thresholds in difficult-to-test populations [11].

In this study, we hypothesize that CCHF may affect inner ear blood flow through the hematogenous spread of the virus, potentially leading to SNHL. We aim to assess hearing levels in adult CCHF patients using pure tone audiometry, ASSR, and OAE responses, to evaluate the risk of hearing loss, differentiate between cochlear and retrocochlear loss, and validate the reliability of ASSR compared to pure tone threshold audiogram.

Materials and Methods

Sixty participants were involved in the study, comprising 30 patients diagnosed with Crimean-Congo Hemorrhagic Fever (CCHF) and undergoing medical treatment (Group CCHF), along with 30 healthy volunteers without a history of hearing loss (Group C). CCHF diagnosis in the study patients relied on positive serologic or molecular test results (ELISA and/or RT-PCR), aligned with compatible clinical and epidemiologic findings. Ethical clearance was secured from the University Clinical Research Ethics Committee (decision number: 2014-05/29), and written informed consent was obtained from all participating patients.

After a complete otolaryngology and head and neck examination, hearing was evaluated by OAE, tympanometry, pure tone audiometry (PTA) and ASSR during hospitalization and the findings were recorded. Exclusion criteria included a history of otologic disease or surgical interventions, syphilis, malignancy, acute or chronic otitis media, congenital cochlear malformations, mechanical trauma and neurologic disorders known to contribute to hearing loss. Additionally, participants were excluded if they had taken any ototoxic medications within the past month, had underlying etiological factors associated with hearing loss (such as hepatic or renal failure), or had received radiotherapy or chemotherapy for any reason within the last month.

Table 1. Auditory Steady-State Response (ASSR) parameters used in the patient and control groups.

Carrier Frequency	500,1000, 2000, 4000 Hz
Amplitude modulation	100%
Frequency modulation	20%
Booster gain	200K
High permeable filter	10Hz
Low-pass filter	105 Hz
Stimulus type	ASSR
Noise threshold level	AM/FM
Test set	0 Db
Masking level	>18 years awake
Electrode impedances	0 dB
ASSR: Auditory Steady-State Response	<5 kOhm

Fixed parameters used in ICS Chartr EP 200 software were used in this study.

Patients' air and bone conduction threshold values were assessed using a clinical audiometry device (INTERACOUSTICS AC 40 Clinical Audiometer), calibrated in accordance with ISO standards. All audiologic evaluations were conducted with the contralateral ear masked. Pure tone hearing thresholds were measured at frequencies of 0.25, 0.5, 1, 2, 4, 6, 8, and 12 kHz for each ear. Hearing thresholds were classified as follows: 0-20 dB indicated normal hearing; 21-40 dB indicated mild hearing loss; 41-60 dB indicated moderate hearing loss; 61-80 dB indicated severe hearing loss; 81-100 dB indicated profound hearing loss; and thresholds above 100 dB were classified as total hearing loss.

Subsequently, all patients underwent transient evoked otoacoustic emissions (TEOAE) testing using a TEOAE device (MAICO ERO-SCAN TEOAE), which was calibrated prior to the study. Disposable probe tips were utilized to seal the ear canal during testing. The results of the TEOAE test were displayed as "PASS" for ears that demonstrated a response and as "REFER" for those that did not. Ears yielding a "REFER" result underwent a repeat screening.

The click stimulus used during testing spanned a frequency range of 0.7-4 kHz, delivered at an intensity level of 83 dB SPL (± 3 dB). TEOAE responses were recorded separately for the right and left ears across frequencies of 1.5, 2, 2.5, 3, 3.5, and 4 kHz within the 1.5-4 kHz bandwidth. A TEOAE mean amplitude below 6 dB was interpreted as indicating no response to otoacoustic emissions.

The ASSR test was performed using Otometrics ICS Chartr EP 200 software. The test stimuli were delivered to the ear via a soft in-ear probe, and the electrodes used for recording were placed on the forehead, crown and earlobe of the test ear. The fixed parameters used in the Otometrics ICS Chartr EP 200 software for awake adults were also used in this study. These parameters are given in Table 1. All tests were completed on the same day in normal hearing subjects. The test frequencies were 500, 1000, 2000 and 4000 Hz. The ASSR test takes approximately 20 minutes in one ear. During this time, the subjects were asked to lie comfortably in the test chair and remain as still as possible during the test. The test started at the pure tone hearing threshold level obtained from the individuals at each frequency. When no response was obtained, the stimulus was increased at 10 dB intervals and the response was sought. When a response was obtained, the threshold level was determined by going down in 5 dB steps. The lowest level at which a response was obtained twice was accepted as the threshold Table 1.

Sample size and Power analysis

The aim of the study was to distinguish cochlear and retrocochlear hearing loss in patients with Crimean-Congo

Hemorrhagic Fever and to evaluate the reliability of the Auditory Steady-State Response (ASSR) test by comparing its results with pure tone audiometry. Thus, according to the theoretical power analysis performed using the G*Power 3.1 program, in the comparison of these two groups, the minimum sample size required to find a significant difference with the Type I error amount (alpha) 0.05, the power of the test (1-beta) 0.80, the effect size 0.74 (medium effect), the alternative hypothesis (H1) two-way and the distribution ratio to the groups (1:1) with the independent two-sample t-test (Mann-Whitney u) should be 30 in the CCHF patients group and 30 in the control group, in total 60.

Statistical analysis

IBM SPSS Statistics for Windows, Version 22.0 (Armonk, NY: IBM Corp.) statistical package program was used to record the data obtained. Since the parametric test assumptions could not be fulfilled in the evaluation of the data (Kolmogorov-Simirnov), Mann Whitney U Test, Chi-Square test and correlation analysis were applied. Pearson distributions were used to examine the distributions between variables.The level of error was taken as 0.05 and p values less than 0.05 were accepted as significant.

Results

The mean age of the 30 patients in Group CCHF was 45.53 ± 14.58 years and 39.93 ± 11.57 years in Group C. Thirty percent (n = 9) of the cases in group CCHF and 53.3% (n = 16) of group C were female, 70% (n = 21) of group CCHF and 46.7% (n = 14) of group C were male. When both groups were compared in terms of age and gender, no statistical difference was found between the groups (p>0.05). When the hearing measurements of the right and left ears of the patients in Group CCHF and Group C were compared, no statistically significant difference was found (p>0.05) as shown in Table 2.

When the hearing thresholds at 500, 1000, 2000, 4000 Hz in the right and left ears of the subjects in Group CCHF and Group C were compared, the difference was not statistically significant (p>0.005) as shown in Table 3.

When comparing the ASSR hearing threshold measurements at 500 Hz for the right ear between subjects in Group CCHF and Group C, no statistically significant difference was observed (p>0.05). However, significant differences were noted at the frequencies of 1000 Hz, 2000 Hz, and 4000 Hz (p<0.05). Additionally, the comparison of ASSR hearing threshold measurements at 500, 1000, 2000, and 4000 Hz for the left ear revealed statistically significant differences between the two groups (p<0.05), as presented in Table 4.

In the correlation analysis between pure tone threshold averages and ASSR threshold values at 500, 1000, 2000, 4000 Hz in the left and right ears of the subjects, although there was a same directional correlation in group CCHF and a negative correlation in group C, these results were not statistically significant (p>0.05).

Table 2. Hearing measurements by otoacoustic emission in the right and left ears of patients in Group CCHF and Group C.

OAE Result		Group CCHF (n = 30)	Group C (n = 30)	Result
Right ear	PASSED	86.7% (n = 26)	100.0% (n = 30)	p= 0.112
	STAYED	13.3% (n = 4)	0% (n = 0)	
Left ear	PASSED	86.7% (n = 26)	100.0% (n = 30)	p= 0.112
	STAYED	%13.3 (n = 4)	0% (n = 0)	

OAE: otoacoustic emission.

Table 3. Airway hearing thresholds in the right and left ear at different frequencies in group CCHF and group C patients.

Frequencies	Right ear		
	Group CCHF (n = 30) Median(Min-Max)	Group C (n = 30) Median(Min-Max)	p-value
500 Hz	25.00 (5.00 - 40.00)	17.50(10.00-35.00)	0.615
1000 Hz	10.00 (5.00-40.00)	10.00 (1.00-25.00)	0.871
2000 Hz	15.00 (5.00-50.00)	15.00 (5.00-25.00)	0.950
4000 Hz	20.00 (10.00-85.00)	20.00 (5.00-30.00)	0.739
Frequencies	Left ear		
	Group CCHF (n = 30) Median(Min-Max)	Group C (n = 30) Median(Min-Max)	Rp-value
500 Hz	15.00 (5.00-40.00)	20.00(10.00-25.00)	0.449
1000 Hz	10.00(5.00-40.00)	10.00(10.00-20.00)	0.882
2000 Hz	15.00(5.00-50.00)	10.00(5.00-20.00)	0.430
4000 Hz	20.00(10.00-85.00)	20.00(5.00-35.00)	0.868

Table 4. Auditory Steady-State Response (ASSR) threshold measurements in the right and left ear at different frequencies in Group CCHF and Group C subjects.

Frequencies	Right ear		
	Group CCHF (n = 30) Median(Min-Max)	Group C (n = 30) Median(Min-Max)	p-value
500 Hz	40.00(10.00-60.00)	40.00(20.00-60.00)	0.205
1000 Hz	40.00(10.00-60.00)	30.00(10.00-50.00)	0.002*
2000 Hz	40.00(10.00-70.00)	27.50(10.00-70.00)	0.001*
4000 Hz	50.00(20.00-70.00)	32.50(10.00-60.00)	0.004*
Frequencies	Left ear		
	Group CCHF (n = 30) Median(Min-Max)	Group C (n = 30) Median(Min-Max)	Rp-value
500 Hz	40.00(20.00-60.00)	40.00(10.00-80.00)	0.026*
1000 Hz	50.00(20.00-70.00)	30.00(10.00-70.00)	0.003*
2000 Hz	40.00(20.00-70.00)	30.00(10.00-70.00)	0.003*
4000 Hz	50.00(20.00-70.00)	30.00(10.00-60.00)	0.001*

Discussion

CCHF is one of the most common viral hemorrhagic fever diseases in the world. The virus is transmitted by ticks or by contact with blood and body fluids of infected humans or animals [2]. The disease was first reported in Turkey in 2002, with more than 10 000 cases reported between 2002 and 2016 and a mortality rate of roughly 5% [12,13]. Although the pathogenesis of viral hemorrhagic fevers varies, findings such as endothelial damage and disruption of hemostasis are shared [14]. The pathogenesis of CCHF has not been fully elucidated. Inflammatory mediators play an important role in fatal cases. Cytokines such as interleukin-6 (IL-6), IL-12, IL-10 and tumor necrosis factor-alpha (TNF-α) were found to be significantly higher in patients who died of CCHF compared to survivors [14]. In CCHF, disseminated intravascular coagulation is an early and prominent feature. Especially when the deceased cases were examined, it was observed that disseminated intravascular coagulation developed in the early period [3]. The main targets in CCHF are endothelial cells, mononuclear phagocytes and hepatocytes. Endothelial damage activates the intrinsic coagulation cascade by stimulation of platelet aggregation and degranulation. As a result, diffuse intravascular coagulation, perfusion disorder and multiple organ failure syndromes occur [3].

Although sensorineural hearing loss can be caused by lesions in a wide area starting from the cochlea to the auditory center, almost 90% are of cochlear origin. Although many factors play a role in the etiology of sensorineural hearing loss, viral infections are one of the most common causes in the etiology of sensorineural hearing loss [15]. It is known that mumps, rubella, measles, Herpes Zoster and CMV infections cause damage to cochlea hair and support cells in the active phase of infection, leading to destructed tectorial membrane and atrophic stria vascularis, vascular thrombosis and inner ear fibrosis [16]. As a result, viral infections are known to play a role in inner ear damage.

In studies on autoimmune inner ear disease, it has been reported that various interleukins, proinflammatory cytokines and cytokines such as TNF-α, whose release increases with the induction of immune response, are associated with cochlea damage [17]. As mentioned above, these cytokines are known to play a role in the etiopathogenesis and prognosis of CCHF patients. Based on this point, hearing loss may be observed in CCHF patients due to the release of various cytokines.

Engin et al. drew attention to the fact that the virus causing CCHF disease may cause cochlea damage with the transient otoacoustic emission results obtained in a study conducted in adult CCHF patients [18]. In a study conducted on pediatric CCHF patients, the hearing of 28 pediatric patients was evaluated with transient otoacoustic emissions, tympanometry, acoustic reflexes and pure tone audiometry (PTA) [19]. The results of the study revealed that there were no statistical difference between the hearing of pediatric patients with CCHF and healthy subjects and emphasized that the virus causing CCHF does not cause cochlea damage. No other study on this subject was found in the literature, and the results obtained in our study were similar to those of Uysal et al. It is thought that saying that the virus causing CCHF does not cause cochlea damage is a limitation in our study due to the small number of cases. In addition, it should be considered that variables such as the stage and severity of the disease in these patients may affect the reliability of the results obtained. It is also thought that comparing the hearing results of the patients not only with the results of healthy adults but also with the results obtained in different periods of the disease such as hospitalization and complete recovery of the patient may contribute more to the literature and further studies are needed.

As is known, CCHF is among the diseases that cause hemorrhagic fever. There are various studies in the literature showing that there may be a relationship between other viral diseases that cause this picture and hearing loss. For example, in a study published in 2016 on ebola virus, tinnitus, ear fullness and hearing loss were detected in 24% of cases [20]. In another study conducted in 2015 on patients with ebola virus infection, it was pointed out that hearing loss may be observed in this patient group [21].

One of the viral infection agents causing acute hemorrhagic disease is Lassa fever. In studies conducted on this subject, it has been pointed out that acute hearing loss develops in one third of patients and hearing loss may be permanent in two thirds of these patients [22-24]. According to a study conducted by the World Health Organization, hearing loss is observed in 25% of patients infected with this virüs [25]. Hearing loss is observed at all frequencies and tends to be bilateral [26]. Although the pathogenesis of this hearing loss is not fully known, it has been suggested that it may be the result of an immunologic reaction between circulating virus antibodies and the basement membrane or outer hair cells in the cochlea [27]. In a study conducted by Ibekwe et al. on patients with lassa fever in 2011, the incidence of sensorineural hearing loss was 13.5% in this patient group and they pointed out that hearing loss may be an indicator of a poor prognosis [26]. Although it has been pointed out that hearing loss may be the result of an imminulogic reaction between viruses and inner ear structures in these studies in the literature related to diseases with hemorrhagic fever, the etiopathogenesis has not been clearly revealed in any of them. This study was planned based on the hypothesis that CCHF virus may cause hearing loss by affecting the inner ear. As mentioned above, the results of both studies are not consistent with each other. Although the results of our study are similar to those of Uysal et al. It is not appropriate to conclude that CCHF disease does not cause hearing loss [19].

ASSR is approximately 10 dB more sensitive than Auditory Brainstem Response (ABR) for threshold detection in the presence of hearing loss in infants, children and adult patients. While the sensitivity of the test is lower in individuals with normal hearing, the sensitivity of the test increases as the severity of sensorineural hearing loss increases. It is superior to click ABR with its frequency specificity and objectivity, and it is a superior hearing measurement method to tone-burst ABR with its much shorter time and objective results [28]. ASSR testing can be used to determine the extent to which patients with clinical SNHL can functionally benefit from amplification, to identify cochlear implant candidates, and to evaluate people who are difficult to test, such as infants with perina-

tal brain injury and auditory neuropathy spectrum disease [29]. Several studies in the literature have also examined the effect of the degree or configuration of SNHL on the prediction of behavioral hearing thresholds with ASSR in adults [30]. Initially, Rance et al. stated that the greater the SNHL (60 dB HL or more), the more accurate the results obtained with ASSR [30]. Herdman and Stapells emphasized that the degree and configuration of hearing loss in adults with SNHL can be accurately estimated by multifrequency ASSR [31]. They argued that there is a significant correlation between behavioral pure tone hearing thresholds and ASSR hearing thresholds for all carrier frequency sound stimuli between 500 and 4000 Hz. Herdman and Stapells showed that the configuration of the SNHL has little or no effect on the accuracy of ASSR hearing thresholds estimation. Ahn et al. concluded that there was a high correlation between PTA and ASSR in their study of 105 patients with hearing loss, especially based on the frequencies at which hearing loss was observed [32]. Beck et al. in their study in which they compared the hearing thresholds determined by PTA and ASSR in the 1000-4000Hz frequency range of 26 adult subjects with no history of hearing loss or any otologic disease, they pointed out that ASSR can be a reliable method in threshold determination, provided that it is not used alone [33]. Komazec et al. revealed that there was a difference of less than 10 dB between the hearing thresholds determined by ASSR and PTA methods in 85% of the subjects [34]. In their study based on four frequencies, they reported that this difference was approximately 4 dB in individuals with moderate hearing loss and 7.2 dB in individuals with normal hearing. In these results, they concluded that although the ASSR test is reliable, it should not be used alone.

The ASSR test is commonly employed to assess hearing levels; however, the results do not directly correlate with PTA values. This study aimed to investigate early hearing loss in patients with CCHF, a condition endemic to Turkey, and to explore potential early intervention strategies. We specifically evaluated hearing thresholds using the ASSR test, which is advantageous for patients who may be difficult to assess due to neurological impairments such as loss of consciousness and dizziness.

Our findings indicated a directional correlation between mean PTA and ASSR threshold values in both ears of CCHF patients, though this correlation was not statistically significant. A frequency-specific analysis revealed that the average PTA threshold for the right ear was 17.83 ± 7.73 dB HL at 500 Hz, whereas the ASSR threshold averaged 40.33 ± 11.29 dB HL, resulting in a difference of approximately 23 dB HL. This threshold discrepancy was consistent across frequencies up to 4000 Hz and similarly observed in the left ear.

These results align with findings from Dimitrijevik and Picton [12,35], suggesting that although PTA results indicated normal hearing, ASSR thresholds reflected mild to moderate hearing loss at certain frequencies. This divergence may be attributable to several factors, including the parameters used during testing, test duration, and environmental conditions. Extended test durations can decrease response precision due to increased discomfort and tension, while alertness levels influence background noise perception. Furthermore, the heightened stress levels of hospitalized patients might have affected their responses compared to the control group.

Consequently, asserting a definitive relationship between ASSR and PTA thresholds in CCHF patients may be premature. Due to the limited sample size, we caution against concluding that ASSR cannot be utilized to predict PTA threshold levels in this patient population. Nevertheless, we advocate for the inclusion of ASSR in the audiologic assessment of CCHF patients to evaluate hearing status effectively.

Notably, our study is the first to apply the ASSR test in the context of CCHF, addressing a gap in the existing literature, which primarily focuses on comparisons of ASSR thresholds with PTA or ABR thresholds in hearing loss populations. Further research is necessary to substantiate these findings.

In our study, it was shown that ASSR test method can provide information about the hearing threshold of patients with CCHF, which has an endemic course in Turkey, with a difference of approximately 20-25 dB from the pure tone hearing threshold averages. In addition, when our results are evaluated in terms of pure tone threshold averages and otoacoustic emission test results of CCHF and healthy individuals, it shows that the cochlea is not affected in this patient group. There are limited studies in the literature on this subject and it is difficult to make a comparison with our study and report a conclusion considering the method of evaluation of the patients in each study, the small number of cases and the difference in age groups [18,19,36]. However, it is noteworthy that cochlear involvement and development of sensorineural hearing loss are frequently observed in different viral diseases with hemorrhagic fever and it should be kept in mind that the virus causing CCHF is in this group. Therefore, it is thought that studies using a larger number of cases, including all age groups and evaluation methods, and taking into account the severity and stage of the disease are needed to support the presence of cochlear involvement in CCHF.

Ethical approval

Ethical approval was obtained for this study from Cumhuriyet University Clinical Research Ethics Committee (Decision no: 2014-05/29).

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