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Association between hepatitis B and hearing status

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Abstract. – OBJECTIVE: This study was performed to investigate the correlation between the chronic hepatitis B virus infection and hearing status.

PATIENTS AND METHODS: This research was based on 76 hepatitis-B infection as the case group (including 35 HBV carriers and 41 chronic hepatitis B (CHB) patients) and 54 normal cases as the control group. They were selected sequentially and audiologic tests were performed on the participants.

RESULTS: The average hearing thresholds (HTs) of control group and hepatitis-B infections were 10.70 and 12.42 dBHL respectively with statistically significant difference ($p < 0.01$). Frequency-specific HT of 114 ears in control group and hepatitis-B infection were found statistical differences for hearing frequency ranged 250 to 8000 ($p < 0.05$), and statistically significant differences for 250, 2000 and 4000 Hz ($p < 0.01$). Significant differences were only measured for HT at 250 Hz frequencies between control and HBV carriers ($p < 0.01$), while for control and CHB group, the differences were detected for all tested frequency ($p < 0.01$). The SNR for f2 frequencies (553, 1105, 2211, 3125, 4416, 4416, 6250 Hz) of the CHB patients and HBV carriers were compared with statistical differences ($p < 0.01$).

CONCLUSIONS: The results showed that the hepatitis-B patients were more prone to hearing loss and that the hepatitis B disease can cause hearing loss. The infection of the inner ear and the pathological changes of the patients with HBV infection still need to be further explored.

Key Words:
Hearing damage, Hepatitis B, Audiology, Chronic hepatitis B, HBS-Ag.

Introduction

Hepatitis B virus (HBV) infection, an infectious disease with significant hazard, currently is carried by over 350 million infectors globally. China is highly popular area with a prevalence rate of HBsAg in general population around 7.18%[1-3]. It is estimated that there are about 93 million HBV carriers in China, including 20 million with chronic hepatitis B (CHB)[4]. HBV infection leads to a wide spectrum of liver disease, including acute hepatitis, liver failure, chronic hepatitis, cirrhosis, and hepatocellular carcinoma. HBV colonized in extrahepatic tissues further lead to wide pathological damage, including hepatic, cardiovascular, digestive system, circulation, nervous system and endocrine system disorders[5]. The pathophysiology of these associated symptoms is mainly based on complex immune reactions that occur in the skin, joints, muscles, and kidneys[6]. Hearing loss is a known complication of viral infections related to acoustic neuritis with fibrosis for measles and direct viruses pathogenetically-induced cytolysis by atrophy of the Corti organ for mump viruses[7]. It has been reported that hepatitis-B patients are more susceptible to hearing damage and that hepatitis B disease can cause hearing loss. Pure tone average (PTA) of HBV-infected patients were significantly higher than control group, yet no marked pattern for hearing loss was described[8]. Moreover, the association between polyarteritis nodosa (a necrotizing vasculitis affecting medium-sized arteries) with hepatitis B virus is well documented, which supported that hearing loss may present as auditory manifestation[9]. Also, involvement of inner ear in complication of hepatitis B has been reported as well, potentially causing deafness[10]. In the present study, hearing injury in patients with positive hepatitis B is studied by comparing pure tone average, acoustic immittance, and distortion product otoacoustic emission of HBV infected patients and normal health controls so as to find out whether hearing loss can be a potential complication of HBV infection.

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Patients and Methods

Inclusion of Patients

A total of 76 consecutive patients (152 ears) with hepatitis B (HBS-Ag positive) from October 2011 and April 2016 were recruited as test subjects for this study. Patients with a history of hepatitis B virus infection or HBsAg positive for over 6 months, as well as patients tested for HBsAg and/or HBV DNA positive, can be diagnosed as CHB. According to results of serological, viral, and biochemical examination, other clinical and supportive examinations, HBV infection can be divided into following categories: CHB, hepatitis B cirrhosis, hepatitis B virus carriers and occult CHB (based on Chinese Chronic Hepatitis B Prevention and Cure Guideline). Therefore, patients were allocated into following subgroups: 35 cases (70 ears) of HBV carriers and 41 cases (82 ears) of CHB. Subjects were aged 20 to 40 years (average age, 31 years), including 37 males and 39 females. Following clinical characteristics were collected: patient history (complaints, current condition, history of hepatitis, infection and previous treatment, etc.); vital signs and routine tests for the Department of Otolaryngology and Head Surgery; hepatic and biochemical tests (ALT, AST, GGT, ALP, PTA, ALB, blood routine test), hepatitis B virus load quantification (HBV-DNA). Patients with one or more condition listed as below should be excluded: previous history of systematic disorders such as hypertension and cardiac diseases; history of ear trauma, infection or tumor, and other known etiology hearing loss; history of being exposed to noisy experiment; recent viral infection; previous administration of ototoxic drugs; family history of deafness. This study was approved by Ethical Committee of Beijing Youan Hospital.

Inclusion of Control Group

A total of 54 patients without hepatitis B and of satisfactory physical condition were recruited as controls from October 2011 to April 2016, including 30 males and 24 females. Controls were aged 20 to 40 years (average age, 27 years). All the cases in control group were HBS-Ag negative. Following clinical characteristics were collected: necessary patient history (complaints, current condition, etc.); vital signs and routine tests for Department of Otolaryngology and Head Surgery; hepatic and biochemical tests; patients underwent complete clinical history, physical, hepatic examination, audiologic examinations, hepatitis B-related tests. Those with one or more condition listed as below should be excluded: previous history of chronic liver disease, syphilis, AIDS or other diseases; history of trauma to ear or skull, infection or tumor, and other known etiology hearing loss; history of being exposed to noisy experiment; recent viral infection; previous administration of ototoxic drugs; family history of deafness.

Monitoring and Observation

Monitoring to recruited subjects and controls included medical history collection, routine ENT examination, pure-tone audiometry (PTA), acoustic immittance, acoustic stapedius reflex, and distortion product otoacoustic emission (DPOAE) to exclude external and middle ear diseases. Three sets of PTA were tested in which hearing thresholds (HT) for 250, 500, 1000, 2000, 4000 and 8000 Hz) were performed for the two groups by a professional audiologist in standard soundproof chamber; diagnostic otoacoustic emission instrument was applied for DPOAE test. L1 and L2 were set as 65 dB and 55 dB SPL, f1/f2 = 1.22, and range of frequency (represented by F2) was 553, 1105, 2211, 3125, 4416 and 6250 Hz. The DPOAE response at the frequency 2f1-f2 (f2 > f1) was measured and acoustic distortion product (DP)-grams was established with f2 as horizontal coordinate and amplitude at 2f1-f2 as vertical coordinate. The difference between the DP value and the background noise is signal to noise ratio (SNR). SNR > 3 dB was considered as positive DPOAE. SNR values at f2 were recorded. The audiological assessment was performed before starting any medical treatment for hepatitis B patients (newly diagnosed as HBS-Ag positive) and hearing loss was considered if the threshold was more than 20 dB. It should be clarified whether the CHB patients had ear symptoms, such as tinnitus, vertigo, and hearing loss.

Statistical Analysis

Statistical analysis was done using SPSS 17.0 (Inc. Chicago, IL, USA) for windows and a p-value of $p < 0.05$ was considered statistically significant. This study was reviewed and approved by the Ethics Committee at Beijing Youan Hospital. The potential difference of PTA and pure-tone hearing thresholds (PTHT) between the test and control group, and PTA, PTHT, SNR between the

HBV carriers and CHB patients, were analyzed. Data follows normal distribution and comparison between two groups and among three groups were compared with *t*-test and analysis of variance, respectively. Dunnett's post hoc test was used after the ANOVA analysis.

Results

Characteristics

76 patients and 54 non-hepatic B control (negative HBS-Ag) cases were enrolled in the study. The mean age was 31 ± 7.4 years in the patient group and 27 ± 12.5 years in the control group. Male-female ratio and other clinical observed characteristics were comparable. The external ear canal and drumhead were normal in the experimental and the control group, with Type A tympanogram of acoustic immittance. Acoustic stapedius reflex can be evoked. Medical history of CHB group was consulted and the results of the previous tests showed different degrees of increase of the levels of aminotransferase and HBV DNA loading. All received systematic medical treatment. In the experimental group, the normal level of aminotransferase was checked to be normal with the amount of HBV DNA decreased.

Hearing Thresholds Comparison

The average hearing thresholds (HTs) of 114 ears in control group and 152 ears in CHB group were 10.70 and 12.42 dBHL (Table I), with statistically significant difference ($p < 0.01$, independent sample *t*-test analysis). Frequency-specific HT of 114 ears in control group and 152 ears in CHB group were presented in Table II. A significant difference was detected for hearing frequency ranged 250 to 8000, and average HTs for 250, 2000 and 4000 Hz ($p < 0.01$). HT of speech threshold (500, 1000, 2000 Hz) for HBV carrier group was shown in Table III. HTs were comparable between HBV carrier and CHB group, but were statistically different between CHB patients and control ($p < 0.01$). Frequency-specific average hearing thresholds (HTs) for the three groups (control, CHB, and HBV patients) were presented in Table IV. A significant difference was only measured for HT at 250 Hz frequencies between control and HBV carriers ($p < 0.01$), while for control and CHB group, statistically different was detected for all tested frequency ($p < 0.01$).

Table I. Analysis of average speech frequency hearing threshold in normal and CHB patients (dBHL).

Group	N (ears)	Average hearing threshold (dBHL)
Control	114	10.69 ± 3.01
CHB	152	12.10 ± 4.81

Signal-To-Noise Ratio (SNR) Comparison

SNR criterion for f2 frequencies (553, 1105, 2211, 3125, 4416, 4416, 6250 Hz) of CHB patients and HBV carriers were presented in Table V, with statistical difference ($p < 0.01$).

Discussion

The etiology of sudden deafness remains unknown even though some evidence suggests that it could be viral in origin. Recently, researchers found that the etiology of idiopathic ear disease and virus infection is associated with advanced inspection technology[10], especially herpes virus, which closely linked to otitis media, deafness and vestibular diseases. The research on pathogenesis between virus infection and hearing impairment has become a hot spot. Hepatitis B virus (HBV) infection is a leading cause of illness and death in China. Approximately 60% of the population has a history of HBV infection, and 9.8% of people in China are chronically infected with HBV and at risk for premature

Table II. Analysis of frequency-specific hearing threshold ranged 250-8000 Hz for normal and CHB patients (dBHL).

Frequency (Hz)	Control (dBHL)	CHB (dBHL)	*p*-value
250	11.54 ± 4.00	15.36 ± 6.31	0.000
500	11.40 ± 3.79	11.76 ± 4.87	0.011
1000	10.96 ± 4.55	12.50 ± 5.40	0.013
2000	9.74 ± 4.09	11.94 ± 5.84	0.000
4000	9.87 ± 5.34	13.65 ± 7.76	0.000
8000	11.62 ± 5.86	14.05 ± 10.61	0.018

Table III. Speech frequency average hearing threshold analysis of HBV carriers group and CHB patients (dBHL).

Group	N (ears)	CHB (dBHL)
Control	114	10.70 ± 2.95
CHB	82	13.74 ± 4.49
HBV carriers	70	10.88 ± 3.06

death from liver disease. The seroepidemiological survey on HBV infection conducted in 2006 showed that HBsAg carrier rate was 7.18% in the overall population. Accordingly, there were an estimated 93 million HBV carriers, and among them 30 million were patients with CHB. It is already widely agreed that HBV is non-hepatotropic virus. HBV replication in extra hepatic tissues has been confirmed long ago with animal experiment. With the development of molecular biology technology, HBV expression in peripheral blood mononuclear cells, pancreas, spleen, skin, kidney and other tissues has been described[10,12], indicating that extra hepatic planting of HBV contributed to pathological injuries involving kidney, cardiovascular, digestive, circulation, nervous system and endocrine system. Association between otology, especially hearing impairment and HBV infection has rarely been reported. The relationship between hepatitis B virus and sudden deafness has been mentioned in the previous report. Patients administrated with hepatitis B vaccination experienced a sense of ear fullness with the right ear and tinnitus, which resolved on the next day. Similar feeling repeated after getting second injection on the second day accompanied with sensorineural deafness on the right side. The disorder was considered HBV-related, suggested that the condition may be caused by abnormal inner ear immune system[13]. Nasab et al[8] conducted audiologic tests to 95 hepatitis-B patients as the case group and 97 normal cases as the control group. Pure tone average (mean thresholds of 500, 1000 and 2000 Hz) were 22.1 dB for the left ear and 23.95 dB for the right ear in hepatitis-B group and 8.4 dB for the left ear and 8.95 dB for the right ear in the control group (HBsAg negative). The hearing thresholds of the two groups were compared using the *t*-test and results show that hepatitis-B patients are more prone to hearing loss, and that hepatitis B disease can cause hearing loss. This study suggests that hepatitis B prophylaxis is important in decreasing hepatitis-B involvement and, therefore, hearing loss. It was indicated that the reported hearing loss may be related to blood vessel change and polyarteritis nodosa (PAN), a systemic disease which affects the small- to medium-sized muscular arteries[11]. Moreover, the presence of hepatitis B antigenemia (HbsAg) in approximately 30% of patients with PAN, as well as immune complexes of Hbs Ag-Immunoglobulins and complement in the blood vessel walls strongly suggest the role of immunologic phenomena. Huang et al[10]

Table IV. Analysis of frequency-specific hearing threshold ranged 250-8000 Hz for normal and HBV carriers.

Frequency (Hz)	Control (dBHL)	HBV carriers (dBHL)	CHB (dBHL)
250	11.54 ± 4.00	14.21 ± 5.75	16.34 ± 6.62
500	11.40 ± 3.79	11.79 ± 4.82	13.72 ± 5.43
1000	10.96 ± 4.55	10.71 ± 4.11	14.02 ± 5.90
2000	9.74 ± 4.09	10.14 ± 5.03	13.48 ± 6.07
4000	9.87 ± 5.34	11.29 ± 5.50	15.67 ± 8.81
8000	11.62 ± 5.86	10.14 ± 6.14	17.37 ± 12.38

Table V. Analysis of frequency-specific hearing threshold ranged 250-8000 Hz for HBV carriers and CHB patients.

Frequency (Hz)	HBV carriers (dBSPL)	CHB (Dbspl)	*p*-value
553	7.03 ± 6.61	2.77 ± 8.20	0.001
1105	18.89 ± 8.05	15.15 ± 7.60	0.007
2211	19.95 ± 6.25	16.47 ± 6.99	0.003
3125	18.39 ± 5.40	14.47 ±7.50	0.001
4416	16.12 ± 6.57	11.17 ± 8.17	0.000
6250	17.25 ± 6.68	12.71 ± 9.85	0.003

reported about sudden deafness as a presenting symptom of CHB with acute exacerbation. Specifically, a 20-year-old man presented with sudden onset of left ear hearing loss and continuous high-pitch tinnitus without vertigo, neurological alterations, or any triggering factors, lasting for two days. The patient has a history of being HBV carrier since childhood, but no associated symptoms were found. Physical examination revealed normal findings and the patients had intact bilateral tympanic membranes, no icteric sclera, and no hepatomegaly. Routine admission work-up showed that serum alanine aminotransferase (ALT) increased to 51 U/L and serum alanine aminotransferase (ALT) flared up to 106 U/L. Serum HBV DNA test revealed serum HBV DNA concentration of 6.40 × 108 copies/mL, suggestive of CHB with acute exacerbation. Based on brain MRI indicating labyrinthitis, author inferred that increasing HBV loading caused systemic viral disease, in which the virus may affect the inner ear through circulation, causing serious pathological and physiological change, or immune change. Both mechanisms can cause damage to sudden deafness; however, it is difficult to isolate the cochlear tissue extracts to find out the relationship between acute exacerbation of hepatitis B and sudden deafness. The patients showed no common signs, such as loss of appetite, vomiting, fever, jaundice, abdominal pain[6]. The correlation between deafness and hepatitis B raised by the author is worth further study. There are a large number of hepatitis B patients in China; however, there is no relevant research on the hearing status of patients with hepatitis B in our country. The etiology of sensorineural deafness remains to be further clarified. The mechanism is mainly considered related with infection, vascular and autoimmune system[13]. At present, there are many studies on the immunological factors of deafness in China, but our knowledge remains blank when it comes to group of patients with liver diseases. The subjects of this work are HBV carriers and chronic hepatitis B patients, among which carriers were not treated and CHB patients used to be treated with oral antiviral drugs. The average hearing thresholds (HTs) of control group and CHB group were 10.70 and 12.42 dBHL, respectively with statistically significant difference ($p < 0.01$). Frequency-specific HT of 114 ears in control group and CHB group found significant difference for hearing frequency ranged 250 to 8000, and average HTs for 250, 2000 and 4000 Hz ($p < 0.01$). HTs were statistically different between CHB patients and control ($p < 0.01$). SNR for f2 frequencies (553, 1105, 2211, 3125, 4416, 4416, 6250 Hz) of CHB patients and HBV carriers were compared with statistical difference ($p < 0.01$). Results indicated that the amplitude of each frequency in the CHB group was significantly lower than that in the HBV group. Nasab et al[8] resulted that significant difference was observed of frequency-specific HTs between hepatitis B patients and control. However, no objective audiometry or stratification was performed for patients with hepatitis B. Results of our research are consistent with the conclusions of this study. Moreover, HBV carriers and CHB patients were examined separately, and DPOAE tests were supplemented additionally to achieve more objective results. Distortion product acoustic emission (DPOAE) records excellent frequency characteristics with recordable frequency ranged 500-8000 Hz or even higher, which detects functional damage to hair cells in advance. Possible reasons for the decline of hearing in patients with hepatitis B included: (1) Elevated HBV viral load resulting in systemic viral disease; virus affects the inner ear through circulation, which leads to severe pathological and physiological changes; (2) Natural immune and specific immune damage in patients with chronic hepatitis B; the infection control of HBV is closely related to the state of immune response, especially virus-specific T CD8+ lymphocyte mediated cytotoxic T cell (CTL) response and immune response induced by T CD4+ helper cells. CTL and the multi-specific Thl cell immune response and secretion of cytokines such as IFN-r and IL-2 can be detected in patients with acute HBV infection, which may last over the years after clinical symptom recovery. However, limitation exists which it makes necessary to interpret the results with caution. Further study with expanded case number is expected in the future.

Conclusions

We observed that compared with normal control, CHB patients are prone to hearing impairment reflected with decreased speech frequency hearing and hearing thresholds ranged 250-8000 Hz, while only significant damage was detected for HBV carriers at 250 HZ. A significant difference of SNRs of chronic hepatitis B patients

and HBV carriers was detected. Results indicated about potential infection and pathological changes of inner ear in CHB patients. Expanded research is expected to cover patients with liver cirrhosis and perform immunological study to further explore the effect of hepatitis B virus on inner ear. Therefore, special attention should be paid to HBV infected patients with precaution and in-time and active treatment in case of any complaint.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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