STUDY OF PREVALENCE AND PATTERN OF HEARING LOSS IN PATIENTS OF HEPATITIS B

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Abstract

Hepatitis B has been documented to cause various extra hepatic manifestations along with known hepatic complications. It has been reported that hepatitis-B patients are more susceptible to inner ear damage and hearing loss. The aim of this study is to evaluate hearing loss among patients of hepatitis B {all 6 categories Hepatitis B infection: chronic Hepatitis B infection, hepatitis B cirrhosis, Hepatitis B virus carriers, occult chronic Hepatitis B and Hepatitis B infection with poly arthritis nodosa, hepato cellular carcinoma with hepatitis B} compared with healthy subjects.

METHOD: In this case control study 100 Hepatitis B positive patients and 100 age and gender-matched healthy individuals were included over the period of 5 years. All of them were known cases of chronic hepatitis B positive for HBsAg at least for 18 months. All patients were aged 18 to 50 years to exclude presence of presbycusis. After base line investigations, they were subjected for all cases and controls were subjected otoscopic examination and hearing assessment using standard pure tone audiometry. Descriptive statistical analysis has been carried out in this study.

RESULT: In patients of Hepatitis B (94 patients, 6 patients had of natural death) pure tone average (mean thresholds 250, 500, 1000, 2000, 4000 & 8000 Hz) was 28.4 dB in the right ear and 27.3 dB in the left (hearing loss). In the control group (96 patients, 4 patients dropped out), PTA average was 9.9 dB in the right ear and 9.3 dB in the left (normal hearing). In both groups, Speech Discrimination score (SDS) was 100% in both ears. The percentage of hearing loss in the right and left ear over the total of six frequencies differed significantly in the two groups. Out of 94 patients of control group, 38 patients (40.4%) patients presented with Chronic Liver Disease (CLD), 14 patients (14.8%) patients presented with cirrhosis with Hepatitis B, 6 (6.3%) patients had Poly arthritis Nodosa with Hep-B, 18 (19.1%) patients were diagnosed as carrier of Hepatitis-B, 11 (11.7%) patients had occult Hepatitis-B and 7 (7.4%) patients were diagnosed with hepato cellular carcinoma.

Hearing loss was maximum in patients of PAN with Hep-B. Second highest mean SNHL was seen in patients of Hep-B with cirrhosis. Third highest mean hearing loss was noted in patients with HCC. Fourth highest mean hearing loss was noted in patients with occult Hep-B. Fifth highest mean hearing loss was noted in carriers of Hep-B. Lowest group with SNHL was chronic liver disease.

CONCLUSION: Regular audiometric tests are recommended for patients with HBV infection to assess their hearing ability and enable the earlier detection of SNHL. We also suggest that HBV presenting with the sudden onset of hearing loss should be examined for the possibility of acute exacerbation of chronic HBV infection.

KEYWORDS: Mean, Sensorineural, Hearing loss, Cirrhosis.

Introduction

Hepatitis B is a serious health problem causing approximately 1.4 million deaths globally per year recently. According to WHO, the South-East Asian region has an estimated 100 million people living with chronic hepatitis B and 30 million people living with chronic hepatitis C. In this region, viral hepatitis is responsible for an annual estimated 350,000 deaths with 81% of total mortality being attributed to liver cancer and cirrhosis due to hepatitis B and C.

India has over 40 million Hepatitis B infected patients, second only to China. Based on the prevalence of HBsAg, various geographic areas in the world are classified as having high ($\geq 8\%$), intermediate (2–7%) and low ($< 2\%$) endemicity. India falls into the category of intermediate endemicity for HBV. Chronic HBV infection accounts for 40–50% of hepatocellular carcinoma (HCC) and 20–30% cases of cirrhosis. Hepatitis B has been documented to cause various extrahepatic manifestations. HBV colonization in

extrahepatic tissues causes widespread pathological damage and has adverse effect on cardiovascular system, central as well peripheral nervous system, digestive system, circulatory and endocrine system. The pathophysiology of symptoms is mainly due to immune complex formation in the skin, joints, muscles, and kidneys.

It has been reported that hepatitis-B patients are more susceptible to inner ear damage and hearing loss. Its otological manifestations are due to probably access of the virus to the inner ear via the hematogenous route and induce severe pathophysiologic changes due to an immunemediated reaction. Polyarteritis nodosa (PAN) is a life threatening necrotizing vasculitis that affects medium-sized arteries, and its association with hepatitis B virus is well-documented. Studies have claimed that 30% of people with PAN are hepatitis B carriers and are more susceptible to HBV infection. Hearing loss may be the presenting symptom of HBV infection according to few reports. Acute exacerbation of viral hepatitis may lead to sudden onset SNHL or a chronic HBV infection can lead to chronic hearing loss. As a part of multisystem involvement advanced HBV infection may even lead to deafness. Qualitatively and quantitatively hearing loss in HBV patients have immense adverse effect on day to day activities.

AIM OF THE STUDY

1. To evaluate hearing loss among patients of hepatitis B {all 6 categories Hepatitis B infection: chronic Hepatitis B infection, hepatitis B cirrhosis, Hepatitis B virus carriers, occult chronic Hepatitis B and Hepatitis B infection with poly arthritis nodosa, hepato cellular carcinoma with hepatitis B} compared with healthy subjects.
2. To measure the magnitude of hearing loss in each category of patients.

STUDY DESIGN

Case control, observational and analytical study.

Materials and Methods

Study area: Department of MEDICINE, Mursidabad Medical College, Berhampore. West Bengal. India.

Study period: July, 2014 – July, 2019.

Ethical clearance: Institutional ethics committee clearance was taken prior to the commencement of the study.

Study sample

Cases- 100 consecutive hepatitis B (HBS-Ag positive) adult patients ageing between 18-50 years were

studied as cases. All of them were known cases of chronic hepatitis B positive for HBsAg positive at least for 18 months. Particularly, age was limited to 50 years for purposes of excluding presence of presbycusis.

Control- As control group of 100, age and gender-matched healthy HBsAg negative individuals were included in this study. These are the individuals without any history of ototoxic medications within the last three months, as well as those with no chronic diseases such as diabetes, hypertension, renal impairment and rheumatoid diseases, without family histories of hearing loss, no prolonged noise exposure, no history of otosclerosis other ear diseases and ear surgery.

METHODOLOGY

Written informed consent was obtained from Hepatitis patients and controls.

All patients were interviewed using a uniform proforma containing

- Information on age, gender, and risk factors, including diabetes, hypertension, and history of ototoxic drug use.
- Time since diagnosis of Hepatitis B virus infection was documented.
- Both case and control groups were subjected to have complete haemogram, coagulogram, fasting and post prandial blood sugar, serum LFT and RFT, electrolytes, viral serology of HIV 1, HIV 2 and HBs Ag.
- All patients and controls were subjected otoscopic examination and hearing assessment using standard pure tone audiometry at 250, 500, 1000, 2000, 3000, 6000, 7000, and 8000 Hz. Because bone conduction hearing testing is limited to 4000 Hz, measurements ≥ 4000 Hz were performed using air conduction testing alone. The sensorineural hearing at high frequencies (8000 Hz) tested by air conduction is unaffected by and independent of middle ear effusion. An average of the threshold levels of >26 db was considered as abnormal. A hearing loss of 26–40 db was classified as mild, 41–55 db as moderate, 56–70 as moderately severe, 71–90 as severe, and >90 db as profound hearing loss. Air and bone conduction thresholds were compared to identify the type and degree of hearing loss.

Descriptive statistical analysis has been carried out in this study. Results on continuous measurements are presented on mean standard deviation (minimum

and maximum) and results on categorical measurements are presented in number (%). Chisquare test is used to compare the difference in proportions. The significance is assessed at 5% level of significance. Differences were considered

Significant if the p value was less than 0.05.

RESULT & ANALYSIS

Six (6) patients and four (4) control cases were excluded because of ear trauma or disease. 94 cases and 96 controls were ultimately studied.

Table 1: Mean pure tone average (dB) results of the hepatitis B cases and control groups.

Side of ear	Hepatitis B patients	Healthy Controls
Right	28.4	9.9
Left	27.3	9.3

Table 2: Mean frequency-specific results in PTA (dB) of the patients with hepatitis B and the control groups.

Frequency group Ear	250 Hz		500Hz		1000Hz		2000Hz		4000Hz		8000Hz	
	Right	Left	Right	Left	Right	Left	Right	Left	Right	Left	Right	Left
CASES	19.2	18.3	22.5	22.4	24.3	22.7	28.6	27.3	34.6	33.7	41.2	39.5
CONTROLS	8.6	8.1	9.5	8.7	8.2	7.8	9.7	9.1	12.4	11.8	11.5	10.8

Mean frequency specific PTA results shows significant difference ($p=0.01$) as shown in Table 2. Hearing loss was mainly sensori-neural (SNHL) in nature and mostly asymmetric. The percentage of hearing loss in the right and left ear over the total of six frequencies differed significantly in the two groups.

Diagram 1: Distribution of Hepatitis B patients

Out of 94 patients of control group, 38 patients (40.4%) patients presented with Chronic Liver Disease (CLD), 14 patients (14.8%) patients presented with cirrhosis with Hepatitis B, 6 (6.3%) patients had Poly arthritis Nodosa with Hep-B, 18 (19.1%) patients were diagnosed as carrier of Hepatitis-B, 11 (11.7%)

The mean age was 36.3 years in the patient group and 33.7 years in the control group. Male-to-female ratio in the patient group was 6 to 4 and 6.5 to 3.5 in the control group. There were no statistical differences in age and sex between the two groups.

Pure tone average (mean thresholds 250, 500, 1000, 2000, 4000 & 8000 Hz) was 28.4 dB in the right ear and 27.3 dB in the left (hearing loss).

In the control group, PTA average was 9.9 dB in the right ear and 9.3 dB in the left (normal hearing). In both groups, Speech Discrimination score (SDS) was 100% in both ears. There was no significant difference in both ears ($p>0.1$ [Table -1]).

patients had occult Hepatitis-B and 7 (7.4%) patients were diagnosed with hepato cellular carcinoma.

Diagram 2: Mean hearing loss in each category of patients with Hepatitis B

Hearing loss was maximum in patients of PAN with Hep-B and mean SN loss in those patients were 45.7 dB in right ear (RE) and 43.5 in left ear (LE). Second highest mean SNHL was seen in patients of Hep-B with cirrhosis and the losses were 37.8 dB in RE and 35.5 dB in LE. Third highest mean hearing loss was noted in patients with HCC and mean losses were 34.6 in RE and 32.1 for LE. Fourth highest mean

hearing loss was noted in patients with occult Hep-B and mean losses were 32.3dB in RE and 31.2 dB in LE. Fifth highest mean hearing loss was noted in carriers of Hep-B and the mean losses were 27.4 dB in RE and 26.2 dB in LE. Lowest group with SNHL was chronic liver disease and their mean losses were 23.4 dB in RE and 21.23 dB in LE.

So the highest prevalence of SN hearing was noted in patients were PAN with Hepatitis B and the prevalence was 6.3%(6/94 x 100).

DISCUSSION

HBV is a DNA virus of Hepadnaviridae family. It is transmitted by percutaneous or mucosal exposure to infected body fluids or blood products and it replicates through an RNA intermediate that can integrate itself into the host genome. The spectrum of HBV infection ranges from acute to chronic depending on the duration of persistence of HBV surface antigen (HBsAg) in the serum. Studies narrate, maximum patients with acute infection would remain asymptomatic and only 30% develop icteric hepatitis. The incidence of developing fulminant hepatic failure remains low (0.1–0.5%). When HBsAg persists in the serum for over 6 months, the patient has chronic HBV infection.

The HBV infection passes through three phases of its natural history – (a)Firstly, there is immunotolerant phase with e+ve and high DNA load with normal enzymes, (b)Secondly, immune active phase with surge in enzymes, hepatitis B e antigen (HBeAg) negativity (a state known as e–ve) and clearance of DNA, and (c)Third and last phase is, inactive carrier phase with development of HBe antibody (antiHBe), normal enzyme levels and negativity for HBV DNA. A section of inactive carriers may revert back to DNA positivity with e–ve state and develop e–ve hepatitis. Some will remain as occult infection (hepatitis B surface antigen (HBsAg)-negative and HBeAg-negative but DNA-positive). As per reports, 15–25% cases will progress to CHB, decompensated cirrhosis and hepatocellular carcinoma (HCC). Risk factors for progression are HBeAg-positivity (the state known as e+v) and high DNA load, among others, and all treatment modalities target e seroconversion and DNA negativity as practically achievable end points.

The predominant mode of transmission of HBV in India is horizontal, although a recent study by Dwivedi et al. has shown 56.8% of pregnant women with HBV infection to be in the high replicative phase and

having HBeAg positivity, suggesting vertical transmission to play a significant role in India. In spite of the fact that the majority of cases are e negative disease, most patients present in the advanced stage and even with hepatocellular carcinoma, the leading cause of which is hepatitis B. High-risk groups especially tribals harbour significant disease burden and have a high prevalence of occult infection, supporting the potential of unknowingly spreading the disease.

Hepatitis B virus-associated polyarteritis nodosa (HBV-PAN) is a typical form of classic PAN whose pathogenesis has been attributed to immune-complex deposition with antigen excess. PAN is a systemic disease which affects the small- to medium-sized muscular arteries. Numerous extrahepatic manifestations have been reported in patients with both acute and chronic hepatitis B like - arthralgias or arthritis, skin rashes, glomerulonephritis and neuritis due to HBV expression in peripheral blood mononuclear cells, pancreas, spleen, skin, kidney and other tissues.

All of them are present in polyarteritis nodosa (PAN) which is the most unique and spectacular extrahepatic manifestation. In the 1970s, the frequency of PAN due to the hepatitis B (HBV) reached 30%. An immunization program has decreased down to 7% now. PAN usually occurs within 6 months of infection. Clinical manifestations reflect this most classic form of PAN, Hepatic manifestations including, ALT/AST elevations are mild and usually overlooked. It is reported that hearing loss in HBV-PAN is due to blood vessel changes due to immune complex deposition of Hbs Ag-Immunoglobulins and complement in the vessel walls as a part of immunologic phenomena.

The relationship between hepatitis B virus and deafness has been mentioned in different studies. **Nasab et al** reported that Hepatitis-B patients are more prone to hearing loss and indeed can cause hearing loss. This study also suggested that hepatitis B prophylaxis is important in decreasing hepatitis-B involvement and, therefore, hearing loss. **Huang et al** reported about sudden deafness as a presenting

Symptom of Chronic Hepatitis B(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 noted. Serum HBV DNA test revealed serum HBV DNA concentration of 6.40×10^8 copies/mL, suggested 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 ultimately leading to sudden deafness. **Hsin-Chien Chen** et al also reported that hepatitis virus infection has a very strong impact on the risk of SSNHL. In Brazil **Bianca Messenberg Pacher** et al had first epidemiological study of hepatitis B and C in the deaf community.

In our present study, statistically significant difference was observed in each mean average of frequency-specific results in PTA (dB) of the patients with hepatitis B and the control groups (Table-2). Surprisingly it was noted that, higher was the audiometric frequency, higher was the hearing loss in Hepatitis B patients. At the average PTA frequencies of 1000 Hz and 2000 Hz the difference was more than 15 dB and at PTA 4000 Hz and 8000 Hz the difference was more than 20 dB between the case and control groups. This type of hearing loss is reportedly stable and is not treatable with medication and as it affects the quality of the hearing perception so the quality of life is adversely affected as well.

We hypothesized that, in patients with HBV infections, SSNHL could occur due to an acute exacerbation of viral hepatitis and subsequent SNHL or a chronic viral reaction causing chronic hearing loss. Viruses could gain access to the inner ear via the hematogenous route and induce severe pathophysiologic changes or an immunemediated reaction. HBV infections can stimulate the production of inflammatory cytokines such as tumor necrosis factor- α , interleukin-1, and interleukin-6, which are injurious to the cochlear hair cells. In addition, hepatitis virus infection has a well-documented association with polyarteritis nodosa, which is a life-threatening necrotizing vasculitis that may result in hearing loss.

Our research has two major limitations. First, demonstration of exact mechanism addressing the association between HBV infection and SNHL by

extracting cochlear tissue pathogens or detecting cochlear injury through imaging was not possible. Secondly, the patients who developed SNHL due an ototoxic effect after antiviral drug administration for HVB infection (which has been reported in some studies) could not be excluded. Despite these limitations, our study contributes to the awareness of the increased risk of SNHL in HBV infected populations.

CONCLUSION

Regular audiometric tests are recommended for patients with HBV infection to assess their hearing ability and enable the earlier detection of SNHL. We also suggest that HBV presenting with the sudden onset of hearing loss should be examined for the possibility of acute exacerbation of chronic HBV infection.

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ABBREVIATIONS

1. **Hep B** - Hepatitis B
2. **HBV** - Hepatitis B Virus
3. **HBsAg** - Hepatitis B virus surface Antigen
4. **WHO** - World Health Organisation
5. **HCC** - Hepato Cellular Carcinoma
6. **PAN** - Poly Arthritis Nodosa
7. **SNHL** - Senserineural hearing loss
8. **LFT** - Liver Function test
9. **RFT** - Renal Function test
10. **Hz** - Hertz
11. **dB** - Decibel
12. **PTA** - Pure tone audiometry
13. **SDS** - Speech Discrimination Score
14. **CLD** - Chronic liver disease
15. **RE** - Right Ear
6. **LE** - Left Ear

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