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Research Article

Uncommon Extrahepatic Manifestations In HBV.

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Abstract

Introduction: Hepatitis B surface Antigen (HbsAg) positivity in the general population ranges from 1.1% to 12.2%, with an average prevalence of 3-4%. Based on some regional level studies, it is estimated that in India, approximately 40 million people are chronically infected with Hepatitis B which not only affects liver but has many extrahepatic manifestations like pre-icteric flu-like syndrome with joint pain and rash seen in acute infection. Chronic infection can lead to more serious complications like glomerulonephritis, polyarteritis nodosa, rheumatoid arthritis, sjogren's syndrome, diabetes mellitus, thyroid disorders, aplastic anemia, lichen planus and malignancies of biliary tract, stomach, and pancreas.

Aim of study: To estimate prevalence of Extrahepatic manifestations of Chronic HBV infection in respect to Dermatological, Hematological, Endocrinological and Dental involvement at tertiary care center of Northern India.

Material and Methods: This study was conducted at Medical Gastroenterology Department at PGIMS, Rohtak. It was a prospective study done over one year, from 01.11.2024 to 31.10.2025, during which 1000 confirmed hepatitis B patients were evaluated for Dermatological, Hematological, Endocrinological and Dental involvement or problems. All hepatitis B patients were confirmed on HbsAg on Enzyme linked immunosorbent assay (ELISA) test and HBV DNA Quantitative on Polymerase chain reaction test (PCR).

Observation and Results: On prospective analysis of 1000 confirmed hepatitis B patients, males were 680 (68%) and females were 320 (32%). Out of total pool of 1000 HBV patients, 81 patients (8.1%) were having dental involvement in form of dry mouth and oral ulcers. Out of these total 81, 43 patients (53.08%) were having dry mouth and 38 patients (46.92%) were having complaints of oral ulcers. In total pool of 1000 HBV patients, 72 patients (7.2%) were diabetics, 20 patients (2%) were having hypothyroidism and 50 patients (5%) were hypertensive. Lichen Planus and aplastic anemia was not seen in any patient. Rheumatoid Factor positivity was seen in 270 patients (27%).

Conclusion: The hepatitis B patients need to be evaluated not only from hepatic point of view but also its extra hepatic impact, of which dermatological, hematological, endocrinological, dental and musculoskeletal system are integral part. In Northeren India, as per our observations, rheumatoid factor positivity, dry mouth, oral ulcers and diabetes mellitus are more commonly seen than aplastic anemia or lichen planus which are almost negligible but these findings require confirmation on large scale studies.

Keywords: Hepatitis B, Dry mouth, Oral ulcers, Diabetes mellitus, Hypothyroidism, Lichen planus, Aplastic anemia, Rheumatoid Factor.

INTRODUCTION

Globally Viral hepatitis is now recognized as a major public health challenge as it caused 1.34 million deaths in 2015, a number comparable to deaths caused by tuberculosis and higher than those caused by HIV. (1) It is estimated that 325 million people worldwide are living with chronic HBV or HCV infection. (2) Viral hepatitis is increasingly being recognized as a public health problem in India. Hepatitis B surface Antigen (HbsAg) positivity in the general population ranges from 1.1% to 12.2%, with an average prevalence of 3-4%. Based on some regional level studies, it is estimated that in India, approximately 40 million people are chronically infected with Hepatitis B. (4) Chronic HBV infection accounts for 40% of Hepato-cellular Carcinoma (HCC) and 20-30% cases of cirrhosis in India. (3). HBV has both hepatic and extrahepatic manifestations which are believed to be immune mediated. The most commonly described include skin rash, arthritis, arthralgia, glomerulonephritis, polyarteritis nodosa, papular acrodermatitis, lichen planus, sjogren's syndrome, diabetes mellitus, aplastic anemia etc.

AIM OF STUDY

To estimate prevalence of Extrahepatic manifestations of Chronic HBV infection in respect to Dermatological, Hematological, Endocrinological and Dental involvement at tertiary care center of Northern India.

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MATERIAL AND METHODS

This study was conducted at Medical Gastroenterology Department at PGIMS, Rohtak. It was a prospective study done over one year, from 01.11.2024 to 31.10.2025, during which 1000 confirmed hepatitis B patients were evaluated for Dermatological, Hematological, Endocrinological and Dental involvement or problems. All hepatitis B patients were confirmed on HbsAg on Enzyme linked immunosorbent assay (ELISA) test and HBV DNA Quantitative on Polymerase chain reaction test (PCR).

OBSERVATION AND RESULTS

On prospective analysis of 1000 confirmed hepatitis B patients, males were 680 (68%) and females were 320 (32%). Out of total pool of 1000 HBV patients, 81 patients (8.1%) were having dental involvement in form of dry mouth and oral ulcers. Out of these total 81, 43 patients (53.08%) were having dry mouth and 38 patients (46.92%) were having complaints of oral ulcers. In total pool of 1000 HBV patients, 72 patients (7.2%) were diabetics, 20 patients (2%) were having hypothyroidism and 50 patients (5%) were hypertensive. Lichen Planus and aplastic anemia was not seen in any patient. Rheumatoid Factor positivity was seen in 270 patients (27%). The majority of patients having extrahepatic manifestations were males and in between 40-50 yrs of age group which is in accordance with their representation in total pool of patients. Except for Diabetes mellitus which was seen maximally in patients with significant fibrosis and cirrhosis, others were seen in majority of patients in inactive carrier stage and thus not requiring antiviral treatment.

Table 1. Showing Sex and Geographical Distribution in HBV Patients

Total HBV Patients	Males	Females	Rural Background	Urban Background
1000	680 (68%)	320 (32%)	700 (70%)	300 (30%)

Table 2. Showing Extrahepatic Parameters Distribution in HBV Patients

Total HBV Patients	Dry Mouth/Eyes	Oral Ulcers	Diabetes Mellitus	R A Factor Positivity	Hypothyroidism	Lichen Planus	Aplastic Anemia
1000	43 (4.3%)	38 (3.8%)	72 (7.2%)	270 (27%)	20 (2%)	0 (0%)	0 (0%)

DISCUSSION

Hepatitis B infection is caused by HBV DNA (deoxyribonucleic acid) virus which belongs to Hepadnaviridae family and predominantly infect hepatocytes in their respective hosts. (5) HBV infection can be either acute or chronic and may range from asymptomatic infection or mild disease to severe or rarely fulminant hepatitis. (6) However, about 20% of patients experience extrahepatic manifestations such as polyarteritis nodosa, non-rheumatoid arthritis, non-Hodgkin lymphoma, cryoglobulinemic vasculitis, and glomerulonephritis. (7) There is a lack of a thorough analysis of the available treatments for extrahepatic HBV manifestations. Rheumatoid factor (RF) is an autoantibody that binds to the Fc portion of IgG. RF is commonly present in patients with rheumatoid arthritis (RA), and it has been used in the diagnosis of RA (8). However, RF positivity can be seen in several diseases other than RA, such as, Sjögren syndrome, systemic lupus erythematosus and infections as well as in normal individuals (9). Studies have found a correlation between the viral load of HBV and the RF titter, suggesting a direct link between viral activity and RF production. positive RF test in a patient with HBV is not a definitive sign of rheumatoid arthritis, as RF positivity can occur in other conditions. RF positivity can indicate chronic HBV infection and may be associated with older age, being female, and lower platelet counts in the context of chronic hepatitis B. Persistent HBV infection is an important cause for the positive RF in HBV endemic areas. Hepatitis B viral load is associated with RF titer. HBV vaccination may reduce the risk of RF formation. (10) Only few studies have reported on the RF positive rates in patients with HBV. (11-13) A hypothesis states that the HbeAg-antibody complex may play a role in the formation of RF in HBV infection. (11) The mechanisms suggested for the formation of RF by HBV include cytokine effect induced by viral infection of the cell, formation of immune complexes of the viral antigen and host antibody and virus induced specific immunological effecter mechanism. (14) In one study the prevalence of rheumatoid factor positivity was 12.5% and advanced age (≥30 years) was independently associated with rheumatoid factor positivity. (15) It is much lower than 27% reported in our study and may be due to the reason that in our study group we had patients belonging to chronic hepatitis and cirrhotic stages, in addition to just inactive stage, as reported in the above study. Oral manifestations related to HBV or liver disease in general are generally non-ulcerative and can include xerostomia (dry mouth) or oral ulcers. While non-specific oral sores or ulcers can sometimes be a general symptom of liver disease, they are not a primary, defining extrahepatic feature of HBV infection in the way that arthralgia, rash, or glomerulonephritis are and our study also in alignment with the same. In our study group very, few patients gave history of dry mouth, dry

eyes and oral ulcers. In many of them, it had been past history and they were not having these complaints in present time. Few of them got tested for sjogren's syndrome but none was proven for the same but we cannot comment on point that none had sjogren's syndrome, as all of them were not tested for the same with SSA/SSB (Anti RO/LA) antibody. Lichen planus (LP) can be associated with HBV infection, though the link is not as strong as with Hepatitis C. Some research suggests a potential connection, with cases of LP reported after HBV vaccination, possibly indicating an autoimmune reaction triggered by shared viral antigens. However, other studies have failed to find a significant association, and the relationship remains a subject of controversy and requires further investigation. Wang etal included 2454 patients with LP and 4768 age- and sex-matched control individuals. The incidence of hepatitis C in patients with LP (1.8%) was significantly higher than in control individuals (0.6%; P < .001). The incidence of hepatitis B in patients with LP (2.2%) was also significantly higher than in control individuals (1.1%; P < .001). (16) Our study is not in alignment with above study, as in pool of 1000 HBV patients, we had no proven case of LP. Diabetes mellitus and HBV infection have a significant association, with HBV increasing the risk of developing type 2 diabetes. The interaction between the two conditions can also increase the risk of liver fibrosis, cirrhosis, and hepatocellular carcinoma (HCC). The mechanism may involve the HBV X protein (HBx) disrupting glucose metabolism, leading to increased gluconeogenesis, thereby causing hyperglycaemia. Liver damage caused by HBV infection may lead to a glycometabolism disorder (17,18), and persistent inflammatory activities in the liver may cause defective glucose homeostasis. Inflammatory mediators, such as tumor necrosis factor-α and nitric oxide, have been shown to impair the metabolic action of insulin in the liver, which results in hepatic dysfunction and, in turn, leads to insulin resistance. (19-22) Furthermore, inducible nitric oxide synthase expression has been shown to be elevated in the liver of patients suffering from chronic HBV infection (23). Secondly, several studies (24,25) have found HBV infection in the pancreas. The replication of HBV in extrahepatic sites, such as the pancreas, is responsible for β-cell damage and may ultimately lead to diabetes. (26,27) In addition, insulin resistance may be involved in the pathogenesis of hepatogenous diabetes. Ji et al (28) reported that the pre-S2 protein of HBV decreased the expression of the insulin receptor gene, leading to insulin resistance. Cuixia etal showed that compared with uninfected patients, the pooled results suggest that HBV-infected patients have a higher risk of developing DM. (29) Certain studies have supported the increased risk of DM in HBV-infected patients when compared with non-HBV-infected controls (30) and certain studies have had different results (31). Our study group also showed association between HBV and Diabetes Mellitus as 7.2% had DM. Majority of these patients of HBV who developed DM, were having significant fibrosis or cirrhosis, in comparison to inactive carriers. It can also be explained on the basis that as HBV impact increases on liver, more are chances of developing diabetes mellitus. HBV can lead to thyroid disorders, including hyper or hypothyroidism and autoimmune thyroid diseases like Graves' disease. The virus damage on liver affects thyroid hormone metabolism, or through an autoimmune response triggered by the infection, particularly in those treated with interferon. Previous studies have suggested that HBV infection may alter thyroid function, particularly by modulating the hypothalamic–pituitary–thyroid (HPT) axis. Reduced TSH levels have been observed in HBV-infected individuals, sometimes in the absence of significant changes in FT4, raising questions about subclinical central suppression or early endocrine adaptation to chronic antigen exposure. (32,33). Yun etal findings (34) extended prior evidence by showing that TSH suppression occurred in HBsAg-positive individuals even without cirrhosis, thyroid disease, or antiviral treatment. TSH levels were significantly lower in HBsAg-positive vs. negative individuals, yet unaffected by viral load (<2000 vs. ≥2000 IU/mL), suggesting that HBV antigens (HBsAg, HBeAg) may alter HPT axis regulation via immune or hepatic-endocrine pathways, independent of replication intensity. (35-37) Mechanistically, HBsAg and related antigens may affect hypothalamic–pituitary function via immunomodulatory pathways, including cytokine-mediated crosstalk or molecular mimicry. HBV DNAemia can activate IL-6 or TNF-α, which suppress TRH and/or TSH secretion. Our study is in accordance with previous studies and 2% patients of total pool were having hypothyroidism and none had hyperthyroidism. Moreover, majority of patients were inactive carrier with low viral load which again highlights the fact that derangement in thyroid dysfunction does not solely depends upon viral load. Aplastic anemia (AA) can be caused by HBV infection, a condition known as Hepatitis-Associated Aplastic Anemia (HAAA) in which immune system attacks the bone marrow after an acute hepatitis attack, leading to bone marrow failure. HAAA is an uncommon but distinct variant of aplastic anemia in which pancytopenia appears two to three months after an acute attack of hepatitis. HAAA occurs most frequently in young male children and is lethal if leave untreated. The etiology of this syndrome is proposed to be attributed to various hepatitis and non-hepatitis viruses. Several hepatitis viruses such as HAV, HBV, HCV, HDV, HEV and HGV have been associated with this set of symptoms. (38) In our study pool of 1000 HBV patients, none developed HAAA, the reason for the same can be predominance of chronic cases whereas HAAA is usually seen in acute hepatitis stage and second reason could be that majority of patients were adults whereas HAAA is seen mainly in children.

CONCLUSION

The hepatitis B patients need to be evaluated not only from hepatic point of view but also its extra hepatic impact, of which dermatological, hematological, endocrinological, dental and musculoskeletal system are integral part. This approach will help in decreasing morbidity and mortality associated with HBV and also help in deciding the antiviral treatment for HBV. In Northeren India, as per our observations, rheumatoid factor positivity, dry mouth, oral ulcers and diabetes mellitus are more commonly seen than aplastic anemia or lichen planus which are almost negligible but these findings require confirmation on large scale studies.

Limitations of Study

The limitation of our study was almost negligible representation of acute hepatitis B patients and children, as certain extrahepatic manifestations are predominantly seen in them. Hence, large scale studies having equal representations from above two groups will be able to give clear picture of extrahepatic manifestations of HBV.

Conflicts of Interest

The authors have no conflicts of interest to declare.

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