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A STUDY OF PREVALENCE OF THROMBOCYTOPENIA IN CHRONIC HEPATITIS B PATIENTS AND ITS ASSOCIATION WITH THE SEVERITY OF HEPATIC FIBROSIS IN A TERTIARY CARE HOSPITAL OF NORTH EAST INDIA.

General Medicine

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ABSTRACT

Background: Thrombocytopenia which is defined as circulating platelet count below 150×109/L, is one of the uncommon extra-hepatic manifestation of Chronic hepatitis B infection.1 Thrombocytopenia in Chronic hepatitis B infection mainly attributes to hepatic cirrhosis of liver, autoimmune destruction of direct platelets and megakaryocytes, impaired production of platelets due to impaired thrombopoietin production.2–4 **Objective:** To assess the platelet count in chronic hepatitis B patients and its association with the severity of hepatic fibrosis. **Materials and methodology:** A hospital based observational study was conducted among 70 chronic hepatitis B patients where chronic hepatitis B infection was confirmed by HbcIg-Total and HbcIgM ELISA kit test. Platelets were being counted with the help of microscope and neubauer slide. Severity of fibrosis is graded by liver point shear wave elastography machine. **Results:** Among the 70 Chronic hepatitis B patients 24 patients were found have thrombocytopenia. Value of mean platelet count (in ×109/L) were 327.14±62.07, 224.14±72.56, 191.88±18.89, 157.55±13.24 and 121.43±60.71 in normal hepatic status; mild, significant, severe fibrosis and cirrhosis respectively. **Conclusion:** From the study thrombocytopenia can be considered as one of the extra-hepatic manifestations in CHB patients where the platelet count is found to be inversely proportional to the severity of hepatic fibrosis with significant association (p value < 0.0001).

KEYWORDS

Thrombocytopenia, Chronic hepatitis B (CHB), Elastography.

INTRODUCTION:

Hepatitis B is a common disease and it is prevalent all over the world and countries. According to its endemicity, hepatitis B prevalent regions have been divided into three groups (high, intermediate and low). It is estimated that about 200 cores of the world's population is found to be exposed to the hepatitis B virus (HBV), of whom 350 million harbor it chronically. India falls in the intermediate endemicity zone with a disease burden of about 50 million. [5] In India, the prevalence of chronic HBV infection is between 3 and 4%. The Andaman Islands and Arunachal Pradesh locals have the highest prevalence rates. In one meta-analysis, the point prevalence of hepatitis B in non-tribal populations was found to be 2.1 per cent (95% CI 1.8 to 2.5) and among tribal populations the point prevalence was 19.4% (CI 15.3 to 23.5).[6]

Hepatitis B virus is a member of the Hepadna virus family having size 3200bp. It is capable of causing both acute and chronic infection. Chronic hepatitis B infection is defined as hepatic necro inflammation due to the persistent presence of infection (hepatitis B surface antigen-positive status) beyond 6 months. The serological markers of CHB is at the situation of HBsAg positive, Total Anti-HBcIg positivity with Anti-HBcIgM negative status.[7]

HBV can be transmitted through percutaneously (contaminated body fluid, tattooing, non-sterile IV drug users, surgical and dental procedures etc.), perinatal i.e. vertical transmission from mother to child and sexual route with no feco-oral transmission.

The principal pathogenesis of CHB is body innate response towards HBeAg and HBcAg through cytotoxic CD8+ cells invading host hepatocyte leading to necro-inflammatory damage to hepatocyte consisting perilobular infiltration, hepatic cells necrosis, hyperplasia of kupffer cells and variable degree of cholestasis which finally leads to fibrosis of liver then cirrhosis and hepatic cell carcinoma.[8]

Thrombocytopenia (platelet count below 150×10^9/L) is one of the extra-hepatic manifestations of chronic hepatitis b infection. The other common extra-hepatic manifestations with acute and chronic hepatitis B infections are neuropathies, arthralgia, myalgia, glomerulonephritis, Sjogren's syndrome, Raynaud's syndrome and uveitis. Almost 20% patients of acute and chronic hepatitis B develops the extra-hepatic manifestations.[1,9] Though their mechanism of development is not properly known, few postulates have been produced till date. The most common is due to hypersplenism secondary to development of portal hypertension in case of cirrhosis of liver. The other causes are reduced production of thrombopoietin (TPO) by the diseased liver as liver is considered to be the principal source of TPO production after birth and immune mediated destruction of platelets and megakaryocytes.[2,3] Immune mediated destruction are because of presence of platelet associated IgG (PAIgG) and platelet surface IgG (PSIgG) in the serum of chronic hepatitis B patients.[4] Few studies done on the effect of CHB infection in bone marrow also showed bone marrow suppression in these patients.[10]

As thrombocytopenia is implicated with the liver injury mediated by chronic hepatitis B so this study has been undertaken to see the prevalence and its association with hepatic status in a tertiary care center of North-East India.

METHODOLOGY:

Aim and objective:

To obtain the prevalence of thrombocytopenia in chronic hepatitis B patients and its association with the severity of hepatic fibrosis.

Inclusion criteria:

- All the chronic hepatitis B patients admitted or attended to various departments of Assam medical college and hospital, Dibrugarh.

Exclusion criteria:

- Individuals co-infected with HIV and HCV.
- Alcoholic liver disease and NAFLD/NASH.
- Hepatic malignancy.
- Inherited liver diseases (Wilson's disease, alpha-1-antitrypsin deficiency, hemochromatosis).
- Autoimmune liver disease.

Study place:

Assam medical college and hospital, Dibrugarh, Assam.

Study duration:
One year (1st July 2021 to 30th June 2022).

Study design:
Hospital based observational study.

Study population:
All the chronic hepatitis B patients aged ≥ 13 years attending OPDs and admitted to various departments of Assam medical college and hospital, Dibrugarh, Assam.

Sample size:
Sample size was calculated and rounded off to 70.

Method of data collection:
All patients who fulfilled the inclusion and exclusion criteria were included in this study. A proforma was prepared which included detailed history, clinical examination and requisite investigations available in the hospital. History included all the features of chronic hepatitis B along with its complications, alcohol consumption, regarding autoimmune features and features of inherited diseases of liver. Patients were examined for pallor, icterus, clubbing, cyanosis, oedema, dehydration, pulse, BP and to look for the peripheral signs to rule out autoimmune and inherited causes of liver disease. All the systemic examination was done for the patients according to prespecified proforma.

Serological status regarding hepatitis B was confirmed by estimation of Anti-HBc-IgM and Anti-HBc-IgG by qualitative ELISA. HBC and HIV disease status were excluded by using screening kit test. Patients were screened for autoimmune and inherited liver disease when indicated by history and clinical examination.

Severity of hepatic fibrosis was measured by Samsung RS80 point shear wave elastography machine with acoustic radiation force impulse (AFRI) technique and expressed in the unit of kPa (kilo Pascal).

Due to prevalence of Harris platelet syndrome among the blood donors of North East India[11,12] so platelet count was checked manually by using improved Neubauer slide and light microscope.

Statistical analysis:
Descriptive statistical analysis has been carried out in the present study. Quantitative data were expressed as mean ± standard deviation (S.D). Qualitative data were expressed as number and percentage. Significance was assessed at 5% level of significance (p<0.05).The statistical analysis of all the data was performed using the computer program, Statistical Package for Social Sciences (SPSS for Windows, version 20.0 Chicago, SPSS Inc.) and Microsoft Excel 2010.

RESULTS

i. In our study, cases we found were ranging from 15-74 years and most of the cases we found in the age group of 30-39. The mean age of the cases were found to be 41.41±14.42 years (Table-1).

Table-1: Age Distribution Of Cases

AGE	No. of Cases	%
<20	5	7.14
20-29	10	14.29
30-39	18	25.71
40-49	14	20.00
50-59	13	18.57
60-69	8	11.43
≥70	2	2.86
TOTAL	70	100
Mean ± SD	41.41±14.42	

ii. In our study most of the cases were found to be males (71.43%) and females were found to be 28.57% with M:F ratio was 2.5:1 (Table-2).

Table-2: Sex Distribution

SEX	No. of Cases	%
MALE	50	71.43
FEMALE	20	28.57
TOTAL	70	100
RATIO	2.5:1	

iii. Based on the data of liver elastography of cases, 14 cases (20%) were found to be normal. 14 cases (20%) were found to have mild fibrosis, 8 cases (11.43%) had significant fibrosis, 11 cases (15.71%) had severe fibrosis and 23 cases (32.86%) had cirrhosis. (Table-3)

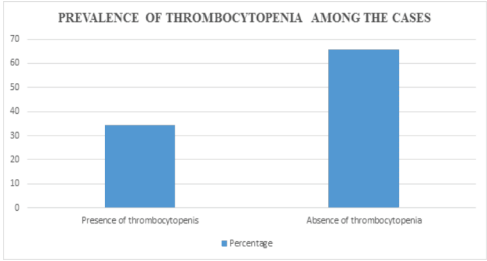
Table 3- Incidence Of Hepatic Fibrosis Among The Cases:

Elastographic values (kPa)	Liver fibrosis status	No. of Cases	%
< 5.3	Normal	14	20.00
5.3 - < 7.2	Mild Fibrosis	14	20.00
7.2 - < 9.4	Significant fibrosis	8	11.43
9.4 - < 12.2	Severe Fibrosis	11	15.71
≥ 12.2	Cirrhosis	23	32.86
Total		70	100

iv. Based on the study conducted, among 70 cases of chronic hepatitis B patients 24 cases (34.28%) were found to have thrombocytopenia.

Table 4- Prevalence Of Thrombocytopenia Among The Cases:

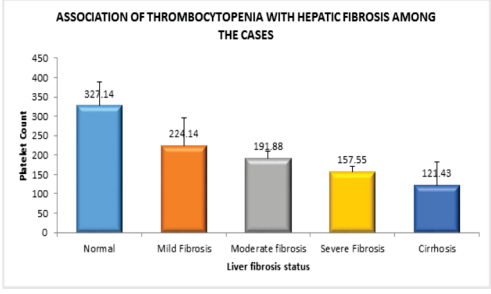
Presence of thrombocytopenia	Yes	No
Nos. of cases	24	46
Percentage (%)	34.28	65.71



v. In our study it was observed that the mean platelet count in patients with normal liver was 327.14±62.07, in mild fibrosis 224.14±72.56, in significant fibrosis 191.88±18.89, in severe fibrosis 157.55±13.24 and in cirrhosis patients 121.43±60.71.

Table 5- Association Of Thrombocytopenia With Hepatic Fibrosis Among The Cases:

Elastographic values (kPa)	Liver fibrosis status	Average platelet value (×109/L)		p-value
		Mean	SD	
< 5.3	Normal	327.14	62.07	<0.0001
5.3 - < 7.2	Mild Fibrosis	224.14	72.56	
7.2 - < 9.4	Significant fibrosis	191.88	18.89	
9.4 - < 12.2	Severe Fibrosis	157.55	13.24	
≥ 12.2	Cirrhosis	121.43	60.71	



DISCUSSION:

As thrombocytopenia is a known complication in chronic hepatitis B infections so the present study was conducted to see the prevalence and its association with hepatic injury due to CHB. In the present study it was found that the maximum numbers of cases were found to be in age group of 30-39 years which was followed by age group of 40-49 years and was followed by 50-59 years. Age group <20 years and age group >60 years were less affected with mean age found to be 41.41±14.42. Similar findings were also seen with the study in Taiwan conducted by

Liu CC *et al.*[13] and the study performed in China by Jian Hu *et al.*[14] In our study it was observed that maximum cases were males, 50 cases (71.43%) and females were 20 (28.57%) with M:F ratio was 2.5:1. Results were similar to study done on Pakistani Punjabis by Khan F *et al.*[15] which also concluded that maximum cases were males, 68.15% and females were 31.85% and also comparable to study of Baigh S *et al.*[16] conducted in Karachi. Confirming the hepatic status in CHB patients by liver elastography, it was seen that 14 cases (20%) were found to be normal. 14 cases (20%) were found to have mild fibrosis, 8 cases (11.43%) had significant fibrosis, 11 cases (15.71%) had severe fibrosis and 23 cases (32.86%) had cirrhosis. This result was comparable with the study Lee J *et al.*[17] conducted in Seoul, Korea and the study of Zhou K *et al.*[18] conducted in China. As alcoholic liver disease and NAFLD/NASH excluded, it can be concluded that more patients had significant fibrosis and cirrhosis of liver after chronic hepatitis B infection.

The present study revealed the presence of thrombocytopenia in 24 (34.28%) among the cases whereas the platelet count in rest of the patients came out to be normal which is similar to the study Cacoub P *et al.*[9] which showing 31% thrombocytopenia in chronic hepatitis B patients and the study Behnava B *et al*[19]. As ultrasound of abdominal organs in most of the patients did not showed the evidence of portal hypertension (splenomegaly, dilated portal vein), there was the suspicion of association of another factors that can lead to decreased platelet count in presence CHB.

While comparing the mean platelet count in CHB patients with the hepatic fibrosis status, we found that the mean platelet count ($\times 10^9$/L) in patients with normal liver was 327.14±62.07, in mild fibrosis 224.14±72.56, in significant fibrosis 191.88±18.89, in severe fibrosis 157.55±13.24 and in cirrhosis patients 121.43±60.71 and was found to be significant with p-value <0.0001. This results was comparable to study of Lee J *et al.*[17] which revealed the platelet values of 231±51, 198±59, 194±82, 189±63, 129±55 in patients with normal liver, mild fibrosis, significant fibrosis, severe fibrosis and cirrhosis respectively in the unit of 10^9/L. Also the study Wu S Di *et al.*[20] concluded the presence of less platelet count in higher grades of fibrosis in CHB patients. So in absence of splenomegaly in most of the cases which was previously considered as a common cause for decreased platelet count in CHB patients, there had to be some other causes like immune destruction of platelets (Doi T *et al.,*2002), decreased production of thrombopoietin owing to extent of liver damage (Jelkmann W *et al.*,2001 and Toghill PJ *et al.*,1977) and bone marrow suppression in CHB patients (Zeldis JB *et al.*,1986) for decreased platelet count. Therefore in isolated thrombocytopenia in CHB patients to look for these causes also have some importance. Also the negative association of platelet count in CHB patient with the extent of liver damage was better demonstrated from the presence study showing more decrease in the platelet count with increase in the extent of liver damage.

Limitations

This was a single center study in limited region of North East India with short duration of time in smaller study population. Multi-centric large scale study may require to better understanding of the results in larger population which could not be done during our study due to limited resources and time.

CONCLUSION

To the best of our knowledge, this is the first study to be conducted in North Eastern India to assess the prevalence of thrombocytopenia in CHB patients and its association with extent of liver damage. Thrombocytopenia was demonstrated in CHB patients and negative association of platelet count with the extent of liver damage indicated towards the link of other mechanism of decreased platelet count in the absence of splenomegaly. Along with looking for the other causes of thrombocytopenia, platelet count can also be considered as one of the predictor of hepatic damage in CHB patients whereas further studies may require to extrapolate the results to larger populations.

Conflicts Of Interest: NIL

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