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Article

Significant association of thrombocytopenia with chronic active hepatitis B virus infection in a tertiary care hospital of an intermediate prevalence HBV country

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Abstract: Thrombocytopenia is a relatively uncommon extra-hepatic manifestation of uncomplicated chronic hepatitis B virus (HBV) infection**.** This study has two aims: to assess the prevalence of thrombocytopenia in non-cirrhotic patients with chronic hepatitis B (CHB); and to determine the association of certain variables with thrombocytopenia in Duhok province. It is a case control study conducted in Azadi Teaching Hospital during June 2016 - May 2019. Chronic active hepatitis B was defined according to the following parameters: the presence of detectable hepatitis B surface antigen (HBsAg) in the blood longer than six months, positive or negative HBeAg, HBV-DNA level >2000 IU/ml, elevated ALT, and/or at least moderate histopathological fibrosis. Thrombocytopenia was defined as platelet counts below 150,000/µl. The obtained results were analyzed by entering data into Microsoft Excel 2010. A total of 379 CHB patients and 200 cases as control were enrolled in this study. Their mean ages were 33.62 ± 14.48 and 40.72 ± 18.56 for HBV and control cases, respectively. There were 236 (62.27%) males in the HBV patients and 109 (54.50%) males in the control group. Comparing both groups, significant association was found between HBV and younger age, cigarette smoking, and alcohol consumption**.** Chronic active hepatitis B without liver cirrhosis was strongly associated with an increased rate of thrombocytopenia. This finding is paramount as it is statistically significant (P = 0.042)**.** Significant association with younger age and Syrian nationality was found more in CHB patients with thrombocytopenia compared to non-thrombocytopenic. In conclusion, chronic active hepatitis B is strongly associated with thrombocytopenia. As hypersplenism resulting from liver cirrhosis was excluded in our patients, the cause of thrombocytopenia is due to other mechanisms. Therefore, it is important to consider CHB in the differential diagnosis of patients presenting with isolated thrombocytopenia. Older age and Syrian nationality were predictors for developing thrombocytopenia in chronic active HBV infection.

Keywords: chronic hepatitis B; thrombocytopenia; association

1. Introduction

Hepatitis B virus (HBV) infection is a serious public health problem as it may cause life threatening complications such as liver cirrhosis and hepatocellular carcinoma. Globally, approximately 350 – 400 million people are chronically infected with HBV, and more than 600,000 deaths occur annually as sequel of the infection and its complications (Schweitzer *et al.*, 2015).

In adults, the risk of developing chronic hepatitis B (CHB) infection after an acute episode is about 5%-10% (Dunn *et al.*, 2009). The clinical course of chronic HBV infection is diverse, ranging from an inactive carrier

state to active hepatitis (Marcellin *et al.*, 2005). Extra-hepatic manifestations can occur in about 20% of patients with acute and CHB and are believed to be mediated by circulating immune complexes (Cacoub *et al.*, 2005). The most common documented extra-hepatic manifestations are sensorimotor neuropathies, arthralgias, myalgias, glomerulonephritis, Sjogren's syndrome, Raynaud's syndrome, and uveitis (Cacoub *et al.*, 2005). Thrombocytopenia is a relatively uncommon extra-hepatic manifestation of uncomplicated chronic HBV infection (Mitchell *et al.*, 2016). Thrombocytopenia, a platelet count <150,000/ul, is a common laboratory finding, which often needs further investigations and follow ups (Gauer and Braun, 2012) .The most common infectious causes of thrombocytopenia are cytomegalovirus, Epstein-Barr virus, Helicobacter pylori, hepatitis C virus, human immunodeficiency virus, varicella-zoster virus infectious (Gauer and Braun, 2012).

In HBV infection, the pathogenesis of thrombocytopenia is not well known. However, in advanced HBV infection it is mostly attributed to hypersplensim secondary to portal hypertension (Mitchell *et al.*, 2016). Other less common mechanisms of thrombocytopenia in chronic viral hepatitis might be associated with impaired platelet production as a result of suppressed thrombopoietin synthesis, increased platelet destruction, anti-retroviral treatment, and direct damage to megakaryocytes and platelets by viruses (Bano *et al.*, 2016; Gauer and Braun, 2012). As CHB related advanced liver disease is vaguely associated with thrombocytopenia, this study has had been considered imperative. In short, this study has two aims: to assess the prevalence of thrombocytopenia in non-cirrhotic patients with CHB; and to determine the association of certain demographics and health related conditions with thrombocytopenia in Duhok province.

2. Patients and Methods

2.1. Setting

The viral hepatitis clinic is a specialized center in Azadi Teaching Hospital, for managing all viral hepatitis patients. All patients with chronic HBV visit the center on regular intervals according to the treating physician's advice. The demographic and clinical information of the patients were collected in standardized case files.

2.2. Study design and patients

All patients during June 2016 - May 2019 were enrolled in this study and were compared with control group from general clinical practice settings. This study was approved by the ethical committee of Kurdistan Board for Medical Specialties. An informed written consent was obtained from all participants. The patients' data were retrieved from the patients' case notes in the registry unit of the viral hepatitis clinic.

Chronic active hepatitis B was defined according to the following parameters: the presence of detectable hepatitis B surface antigen (HBsAg) in the blood longer than six months, positive or negative HBeAg, HBV-DNA level >2000 IU/ml, elevated ALT, and/or at least moderate histopathological fibrosis (EASL, 2017). Patients with compensated or decompensated liver cirrhosis were excluded based on clinical, laboratory, and imaging studies. Platelet counts were recorded from both patients and control groups. Thrombocytopenia was defined as platelet counts below 150,000/µl. Previous history of thrombocytopenia was an exclusion criterion for both patients and controls. In CHB patients, the clinical parameters based on platelet levels were analyzed for possible association with age, gender, smoking habit, alcohol consumption, and nationality.

2.3. Statistical analysis

The obtained results were analyzed by entering data in a binary format using Microsoft Excel 2010 Spreadsheets. A p value ≤ 0.05 was considered statistically significant.

3. Results

A total of 379 CHB patients and 200 cases as control were enrolled in this study. Their mean ages were 33.62 ± 14.48 and 40.72 ± 18.56 for HBV and control cases, respectively. There were 236 (62.27%) males in the HBV patients and 109 (54.50%) males in the control group. The characteristics of both groups are shown in Table 1.

Table 1. Characteristics of the patients and control group.

Variable		HBV (no. = 379) No. (%)	Control (no. = 200) No. (%)	OR	95% CI	P value
Age	(Mean ± SD)	33.62 ± 14.48	40.72 ± 18.56	7.100	4.3526 to 9.8474	0.0001
Sex	Male	236 (62.27)	109 (54.50)	1.378	0.974 - 1.950	0.075
	Female	143 (37.73)	91 (45.50)			
Smoker	Yes	223 (58.84)	77 (38.50)	2.283	1.608 - 3.243	0.000
	No	156 (41.16)	123 (61.50)			
Alcohol	Yes	89 (23.48)	26 (13.00)	2.954	1.275 - 3.305	0.003
	No	290 (76.52)	174 (87.00)			
Nationality	Iraqi	356 (93.93)	193 (96.50	1.781	0.751 - 4.226	0.238
	Syria	23 (6.07)	7 (3.50)			

The prevalence rate of thrombocytopenia was higher among CHB patients (Table 2).

Table 2. Prevalence of thrombocytopenia among CHB and control group.

Variable		CHB* (no. = 379) No. (%)	CG** (no. = 200) No. (%)	OR (95% CI)	P value
Thrombocytopenia	Yes	16 (4.22%)	2 (1.00%)	4.364 (0.993 to 19.172)	0.042
	No	363 (95.78%)	198 (99.00%)		

*CHB: chronic hepatitis B
**CG: control group

Table 3 demonstrates a comparison of baseline characteristics between CHB with and without thrombocytopenia showed significant association with younger age and Syrian nationality.

Table 3. Comparison of baseline characteristics of chronic hepatitis B according to platelet count level.

Variable		CHB with thrombocytopenia (no. = 16) No. (%)	CHB without thrombocytopenia (no. = 363) No. (%)	OR	95% CI	P value
age	(Mean ± SD)	49.56 ± 17.16	32.92 ± 13.94	16.6700	9.5967 - 23.7433	0.0001
Sex	Male	13 (81.25%)	223 (61.43%)	2.720	0.762 - 9.717	0.123
	Female	3 (18.75%)	140 (38.57%)			
Smoker	Yes	13 (81.25%)	210 (57.85%)	3.157	0.884 - 11.271	0.072
	No	3 (18.75%)	153 (42.15%)			
Alcohol	Yes	7 (43.75%)	82 (22.59%)	2.66	0.963 - 7.376	0.068
	No	9 (56.25%)	281 (77.41%)			
Nationality	Iraqi	12 (75.00%)	344 (94.77%)	6.035	1.778 - 20.488	0.012
	Syria	4 (25.00%)	19 (5.23%)			

4. Discussion

Thrombocytopenia is a recognized complication of advanced liver disease related to CHB infection; however, the association is not well understood with uncomplicated HBV infection. To the best of our knowledge, this is the first insight study about the frequency of thrombocytopenia and few variables associated with CHB patients. In this study, comparing the characteristics of HBV patients and control group, significant association was found between HBV and younger age, cigarette smoking, and alcohol consumption. The younger age group in this study is in favor to other studies (El-Hazmi, 2004), where such age group are more prone to having HBV through intimate contact and sexual practices as they are more active in their life. In the current study, although HBV was more frequent among males, the difference was not statistically significant. Similarly, the majority of HBV cases reported were among men aged 25-44 years (Van Buren and Schaffner, 1991). In our study, the higher rate of smoking and alcoholism among HBV patients were similar to the findings of other studies (Gitto *et al.*, 2014). Singal *et al.* (Singal and Anand, 2007) stated that alcoholic people are more prone to HBV

infection because they are more likely to demand hospitalization including blood transfusion. In addition to this, risky sexual practices are more common among alcoholics. Although HBV was more frequent among Syrian patients, the finding was not statistically significant. The seroprevalence of HBV is higher in the Syrian population ranging from intermediate to high (Bashour and Muhjazi, 2016), whereas, in Iraq, it is ranging from low to intermediate (Alsamarai *et al.*, 2016; Merza *et al.*, 2014; Merza *et al.*, 2016). Hence, the frequency of HBV infection is higher among Syrian patients.

In the present study, chronic active hepatitis B was strongly associated with an increased rate of thrombocytopenia. This finding is paramount as it is statistically significant ($P = 0.042$) in the absence of liver complications such as liver cirrhosis or splenomegaly. Correspondingly, a large cohort study by Joo *et al.*, found an increased incidence of thrombocytopenia among HBV patients in comparison to those in the control group (Joo *et al.*, 2017). Similarly, another study from Iran documented a significant association between chronic active HBV and thrombocytopenia (Behnava *et al.*, 2006). In contrast, other studies did not find this association (Nwokediuko and Ibegbulam, 2009). Several studies have shown a link between viral infections such as hepatitis A, B, C viruses and thrombocytopenia through directly inhibiting the growth and differentiation of human bone marrow progenitor cells in vitro (Zeldis *et al.*, 1986). However, this link is more prominent in patients with HCV infection due to direct bone marrow suppression (Wang *et al.*, 2004). As hypersplenism resulting from liver cirrhosis was excluded in our patients, the cause of thrombocytopenia is due to other mechanisms. Therefore, it is important to consider CHB in the differential diagnosis of patients presenting with isolated thrombocytopenia.

Considering comparative analysis between thrombocytopenia with and without HBV, the only independent risk factors associated with thrombocytopenia were older age (49.56 ± 17.16 vs 32.92 ± 13.94) and Syrian nationality (Table 3). Older age has been found to be a risk factor for developing thrombocytopenia in chronic viral hepatitis patients, particularly HCV infection, despite non-advanced liver diseases (Wang *et al.*, 2004). It seems that cumulative effect of the infection duration on older aged patients with chronic HBV is a potential factor offering sufficient time for developing thrombocytopenia. The Syrian nationality was a predictor of thrombocytopenia in HBV patients. This finding can be explained by a higher prevalence of HBV infection in Syria as discussed previously. A significant association was not found between thrombocytopenia in HBV patients and health related behaviors i.e. cigarette smoking and alcohol consumption. Hence, such variables are unlikely to be implicated in the mechanism of thrombocytopenia in patients with chronic HBV.

There are certain limitations in this study. First, the sample size was small. Second, the extent of liver disease was assessed according to clinical, laboratory and ultrasound examinations, but liver biopsy was not performed in the majority of cases for precise evaluations.

5. Conclusions

Younger age, cigarette smoking, and alcohol consumption were independent risk factors for CHB infection. Chronic active hepatitis B is strongly associated with thrombocytopenia. As hypersplenism resulting from liver cirrhosis was excluded in our patients, the cause of thrombocytopenia is due to other mechanisms. Therefore, it is important to consider CHB in the differential diagnosis of patients presenting with isolated thrombocytopenia. Older age and Syrian nationality were predictors for developing thrombocytopenia in chronic active HBV infection.

Further prospective studies with larger sample sizes that include other variables such as body mass index, HDV co-infection…etc are warranted to better understand the association between the two clinical conditions.

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Conflict of interest

None to declare.

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