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Prevalence of Occult Hepatitis B in Patients with Lupus Nephritis and Primary Glomerulopathy

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ABSTRACT

Background: The conventional method for testing for hepatitis B surface antigen in patients cannot detect occult hepatitis B. If occult hepatitis B is not diagnosed in patients with lupus nephritis and glomerulopathy who are treated with immunosuppressive drugs, they can develop clear hepatitis B. Moreover, considering the potential role of occult hepatitis B in causing an incomplete response to treatment and continuing proteinuria, evaluation of the incidence of occult hepatitis B in these patients is important. In this study, we assessed the prevalence of occult hepatitis B in patients with lupus nephritis and primary glomerulopathy. **Methods:** This descriptive, cross-sectional study was conducted on 112 patients with lupus nephritis and primary glomerulopathy who were referred during a 5-year period to the nephrology and rheumatology clinic of Shahid Sadoughi Hospital in Yazd, Iran. Patients' levels of hepatitis B surface antigen and hepatitis B surface antibody were measured, followed by a hepatitis B virus DNA test for those with both positive and negative hepatitis B surface antigen. Demographic data were recorded using a predesigned questionnaire. Data were analyzed with SPSS version 20 software using statistical tests. **Results:** The mean age of patients was 40.84 ± 15.11 years. Forty-nine (43.8%) were men and 63 (56.2%) were women. Ninety-seven (86.6%) had primary glomerulopathy, and 15 (13.4%) had lupus nephritis. The prevalence of occult hepatitis B was 3.0% in patients with primary glomerulopathy and 13.3% in patients with lupus nephritis. A significant relationship was observed between the frequency of hepatitis B core antibody and the mean age of patients with the type of disease ($P<0.05$). **Conclusion:** The prevalence of occult hepatitis B in patients with lupus nephritis was greater than the prevalence in patients with primary glomerulopathy.

INTRODUCTION

Hepatitis B is usually diagnosed by the presence of hepatitis B surface antigen (HBsAg) together with respective antibodies circulating in the blood (1). Using sensitive molecular biology techniques, such as PCR, hepatitis B virus (HBV) DNA can be detected in patients with negative HBsAg with or without relevant antibodies (2). Occult hepatitis B infection is defined as the presence of HBV DNA in the liver or bloodstream; however, HBsAg is undetectable by current methods (3). The infection remains asymptomatic for many years. Recent studies have shown that co-infection, medications, and decreased immune activity can cause increased levels of HBV DNA without increasing HBsAg (3). The prevalence of occult hepatitis B varies throughout the world, owing to diagnostic methods of varying effectiveness and to whether an area is experiencing an epidemic of the disease.

Of particular interest at present is the prevalence of occult hepatitis B in patients with different types of glomerulopathy (4). The incidence of occult hepatitis B in hemodialysis patients has been reported as 3.7% in North America and 4.9% in India, as well as from 0% in a cohort study to 26.6% in another cohort study, both conducted in Italy (5). Lupus nephritis is one of the most prevalent and serious complications of lupus. Reportedly, 30% to 50% of lupus nephritis patients have clinical signs of renal failure at the time of diagnosis. Patients with autoimmune diseases, especially those with autoimmune liver disease, manage HBV more effectively than healthy people, and HBV has a lower incidence in patients with autoimmune diseases (6). An increase in the use of drugs such as rituximab and anti-CD20 monoclonal antibody has resulted in significantly increased reactivation of HBV in patients receiving chemotherapy and immunosuppressive therapy (7).

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HBV-related glomerulonephritis (HBV-GN) is a chronic and uncommon extrahepatic manifestations of hepatitis B and is associated with severe complications (8). HBV creates an immune complex that precipitates in the glomeruli and results in different types of glomerulonephritis. HBV-GN can appear with mild to moderate proteinuria, nephrotic syndrome, and hematuria. HBV-GN is diagnosed by HBV serological tests and kidney biopsy. Membranous nephropathy (MGN) and membranoproliferative glomerulonephritis (MPGN) are the most common manifestations on kidney biopsy. MGN is more prevalent in pediatric patients compared to adults, whereas MPGN is more common in adults (9). Various therapeutic approaches have been proposed for HBV-GN, including interferon, lamivudine, and entecavir with or without corticosteroids. Some studies have shown that antiviral treatment improves proteinuria and kidney function (10). HBV-related nephropathy is progressive in adults, and no effective therapeutic treatment is available. However, antiviral drugs have been proposed to treat HBV-related nephropathy, because they reduce HBV proliferation and proteinuria (11).

The conventional method for testing for hepatitis B surface antigen (HBsAg) in patients cannot detect occult hepatitis B. If occult hepatitis B is not diagnosed in patients with lupus nephritis and glomerulopathy who are treated with immunosuppressive drugs, they can develop clear hepatitis B. Moreover, considering the potential role of occult hepatitis B in causing an incomplete response to treatment and continuing proteinuria, evaluation of the incidence of occult hepatitis B in these patients is important. In this study, which is the first of its kind in Iran, we assessed the prevalence of occult hepatitis B in patients with lupus nephritis and primary glomerulopathy.

MATERIALS AND METHODS

In this descriptive, cross-sectional study, sample size was estimated at 120 and prevalence of occult hepatitis B was estimated at 6.4%, based on similar articles, with a 95% confidence interval. Eventually, 112 people were examined. After being informed of the research objectives and giving their consent, all patients with lupus nephritis and primary glomerulopathy diagnosed by biopsy were enrolled in the study. Enrolled patients were those referred to the nephrology and rheumatology clinic of Shahid Sadoughi Hospital in Yazd, Iran, during a 5-year period (2011-2016). The sampling method was census. Patients with glomerulopathy that was associated with malignancy, hepatitis B, hepatitis C, endocarditis, or other infections were excluded. After identifying the participants, 5 cc of their venous blood samples were tested for HBsAg and HBcAb. Patients with positive HBcAb and negative HBsAg were considered as having occult hepatitis B. Demographic information including age, sex, history of previous illness, blood transfusion, tattooing, type of disease, family history of hepatitis B, and biochemical laboratory findings were recorded in a predesigned questionnaire. Data were analyzed with SPSS version 20 software using independent t-tests, the analysis of variance test, and the chi-squared test.

RESULTS

In this study, our aim was to determine the prevalence of occult hepatitis B in 112 patients with lupus nephritis or primary glomerulopathy.

The mean age of patients was 40.84 ± 15.11 years (range, 17-80 years). Forty-nine (43.8%) were men and 63 (56.2%) were women. Ninety-seven (86.6%) had primary glomerulopathy, and 15 (13.4%) had lupus nephritis.

Of the 112 patients, 107 (95.54%) tested negative for hepatitis B core antibody (HBc-Ab) and five (4.46%) tested positive for HBc-Ab. The chi-squared test showed a statistically significant difference between the frequency distribution of HBc-Ab based on the type of disease ($P < 0.05$; Table 1).

As shown in Table 1, the prevalence of occult hepatitis B [(HBC-Ab (+) and HBSAg (-)] was 3.0% in patients with primary glomerulopathy (3/97 cases) and 13.3% in patients with lupus nephritis (2/15 cases) (Figure 1).

The results of our study on the frequency of HBc-Ab in terms of sex in the studied patients showed that 46/49 men (93.87%) tested negative for HBc-Ab and 3/49 (6.13%) tested positive for HBc-Ab. The chi-squared test showed no statistically significant difference in the frequency distribution of HBc-Ab in the patients ($P > 0.05$; Table 2).

The results also showed that the mean age was 41.59 ± 15.48 years in patients with primary glomerulopathy and 34.53 ± 10.65 years in patients with lupus nephritis. Independent t-tests showed a significant difference in the mean age of patients in terms of the type of disease ($P = 0.049$).

In addition, the mean age was 38.75 ± 6.13 years in patients who tested positive for HBc-Ab and 40.79 ± 15.37 years

Table 1. Frequency distribution of hepatitis B core antibody (HBc-Ab) based on type of disease

Type of disease	HBc-Ab (%)		Total
	Negative	Positive	
Primary glomerulopathy	94 (96.91)	3 (3.09)	97 (100)
Lupus nephritis	13 (96.7)	2 (3.3)	15 (100)
Total	107 (95.54)	5 (4.46)	112 (100)
P value		(0.047)	

Table 2. Frequency distribution of hepatitis B core antibody (HBc-Ab) in terms of sex

Gender	HBc-Ab (%)		Total
	Negative	Positive	
Male	46 (93.87)	3 (6.13)	49 (100)
Female	61 (96.78)	2 (3.32)	63 (100)
Total	107 (95.54)	5 (4.46)	112 (100)
P-value		0.546	

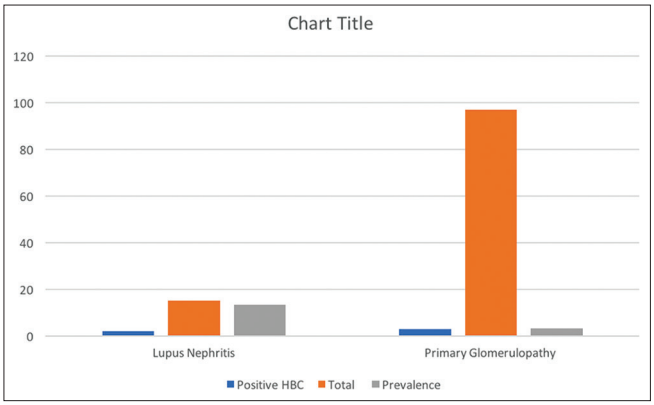

Figure 1. Comparison of hepatitis B prevalence in the two groups

in patients who tested negative for HBc-Ab. Independent t-tests showed no statistically significant difference in the mean age of patients based on HBc-Ab *(P* = 0.79).

DISCUSSION

Hepatitis B is a dangerous viral disease that can be transmitted by various means, especially by blood transfusions and blood products (12). The routine screening test to check for hepatitis B is HBs-Ag, which is not able to detect hepatitis B infection definitively and returns many false-positive and false-negative results (13). In recent years, studies of HBc-Ab as a potent indicator have focused on the diagnosis of HBV infection (14), and many countries employ this as a routine test in laboratories (15). We also applied this test as a criterion for the diagnosis of occult hepatitis B in patients with glomerulopathy and lupus nephritis, so that patients with HBc-Ab (+) and HBs-Ag (-) were diagnosed as having occult hepatitis B.

Many similar studies have focused on the prevalence of occult hepatitis B in various diseases, most on the prevalence of occult hepatitis B in hemodialysis patients. In some of these studies, HBV-DNA (+) and HBs-Ag (-) have been considered as criteria for detecting occult hepatitis B (16); in others, including our study, HBc-Ab (+) and HBs-Ag (-) were the criteria for detecting occult hepatitis B (17). In similar studies, contradictory results were reported on the prevalence of occult hepatitis B. The prevalence of occult hepatitis B was high in some cases and low in others. In a 2005 study in Italy, the prevalence of occult hepatitis B was reported to be 0% in hemodialysis patients (17). In a 2004 study in North America, the prevalence of occult hepatitis B was reported to be 3.8% in hemodialysis patients (16), which did not match the results of the Italian study. The reason for this discrepancy can be attributed to how occult hepatitis B was measured. In the North American study, occult hepatitis B was measured by HBV-DNA; in the Italian study, occult hepatitis B was measured by the HBc-Ab test. An analysis of the two studies suggests that HBV-DNA measurement is more accurate than HBc-Ab for detecting occult hepatitis B infection.

Another study conducted in Egypt (2010) reported a 6.3% prevalence of occult hepatitis B in hemodialysis patients with hepatitis C virus and 3.8% in hemodialysis patients without hepatitis C virus, which was consistent with the results of the North American study (18). It turns out that hepatitis C virus infection increases the risk of occult hepatitis B in hemodialysis patients. Some studies in Iran, similar to those from other countries, have further investigated the prevalence of occult hepatitis B in hemodialysis patients. Therefore, given that no study has been conducted on the prevalence of occult hepatitis B in patients with lupus nephritis and primary glomerulopathy, our study was necessary and important.

We found that the prevalence of occult hepatitis B by measuring HBc-Ab was 2.1% in patients with primary glomerulopathy and 13.3% in patients with lupus nephritis, which was more prevalent than in hemodialysis patients from other countries, as reported in the studies listed above (16-18). Differing results have been reported in Iran regarding the prevalence of occult hepatitis B. A study performed in Tehran on hemodialysis patients showed a 9.4% prevalence of occult hepatitis B (19); however, another study performed in Gorgan on hemodialysis patients reported a 0% prevalence of occult hepatitis B (20). The reason for this inconsistency in the results of these two studies and in our results appears to be due to differences in sample size: the sample size was 100 in the study in Gorgan and 2,218 in the study in Tehran, the latter of which reported a higher prevalence. Although in our study the prevalence of occult hepatitis B was close to the prevalence reported in the study in Tehran, these results cannot be consistent because a 9.4% prevalence was reported for 2,218 patients in the study in Tehran but for only 112 patients in our study.

A study in 2012 of 248 patients with lupus aimed to determine the prevalence of occult hepatitis B. It found that the prevalence of occult hepatitis B was 2.4% in patients with lupus (21), which was lower than our study (13.3%). The reason for this discrepancy can be attributed to differences in the location of the studies. Also, our study did not consider the beneficial effects of adjuvant Herceptin in patients.

We recommend that complementary studies with larger sample sizes and more variables be conducted to compare the prevalence of occult hepatitis B in patients with glomerulopathy. Various types of glomerulopathy should be examined separately in these complementary studies. In addition, the prevalence of occult hepatitis B should be measured and compared with the prevalence of occult hepatitis B in patients with lupus nephritis, to estimate the most common glomerulopathy that leads to occult hepatitis B. By this, we can identify the closest glomerulopathy to lupus nephritis in terms of the prevalence of occult hepatitis B. To determine the best laboratory test for screening for and diagnosing occult hepatitis B in patients with various types of glomerulopathy, we also recommend that complementary studies use different types of screening and diagnostic tests for hepatitis B.

CONCLUSION

We found that the prevalence of occult hepatitis B in patients with lupus nephritis was higher than in patients with primary glomerulopathy. Failure to diagnosis occult hepa-

titis B in patients with lupus nephritis and glomerulopathy who are treated with immunosuppressive drugs can result in them developing clear hepatitis B. Moreover, considering the potential role of occult hepatitis B in causing an incomplete response to treatment and continuing proteinuria, an evaluation of the incidence of occult hepatitis B in these patients is important. It seems that patients in both groups, especially those with lupus nephritis, require regular and periodic follow-up (tests) and further care to prevent the transmission of HBV. Therefore, we recommend that patients with both lupus nephritis and glomerulopathy be tested for HBc-Ab before starting immunosuppressive therapy, especially patients with lupus nephritis, due to the higher prevalence of occult hepatitis B. Furthermore, the non-significant relationship between sex and age variables with the frequency of HBc-Ab indicates that both sexes at any age are at an increased risk for occult hepatitis B. We recommend complementary care for both sexes at any age.

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