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REVIEW ARTICLE

Hepatitis B Virus-associated Glomerulonephritis

Hossein Khedmat [1*], Saeed Taheri [1, 2]

[1] Baqiyatallah Research Center for Gastroenterology and Liver Disease, Baqiyatallah University of Medical Sciences, Tehran, Iran

[2] Dr. Taheri Medical Research Group, Tehran, Iran

Hepatitis B virus (HBV) infection has been shown to induce several extra-hepatic lesions, especially through deposition of immune complexes in different organs, and renal involvement is one of the most important of them. The association between chronic HBV infection and glomerular diseases was first described by Combes *et al.* in 1971, and since then, overwhelming observations have been reported in the literature by authors from all over the world. HBV-related nephropathy is one of the HBV infection manifestations that has provoked high sensitivities around the world, most especially in terms of the management and treatment of the infection and the renal involvement. In this literature review, we tried to address all important issues related to HBV associated nephropathies.

Keywords: Hepatitis B Virus, Nephropathy, Glomerular Disease

Introduction

Hepatitis B virus (HBV) infection has been shown to induce several extra-hepatic lesions, especially through deposition of immune complexes in different organs [1-5]. The exact mechanisms through which certain patients with chronic HBV infection develop glomerulonephritis are not well understood. However, several reports have suggested a role for hepatitis B surface antigen (HBsAg). The diagnosis of HBV-associated glomerulonephritis is done by serologic evaluations for HBV antigens or antibodies, by immunohistochemical demonstration of HBV-related antigens, as well as immune complexes in kidney biopsy [6]. The isolation of immune complexes from renal biopsies suggests that this complication may represent a hypersensitivity reaction to the viral infection.

HBV-related nephropathy is one of the manifestations of HBV infection of which overwhelming observations have been reported in the literature by authors from all over the world [7-9]. The association between chronic HBV infection and glomerular diseases was first described by Combes *et al.* in 1971 [10], and since then several morphological patterns for glomerular lesions, including membranous nephropathy, minimal change nephropathy, mesangial proliferative glomerulonephritis, membranoproliferative glomerulonephritis, and IgA nephropathy, have been reported [6, 11-36].

HBV-associated nephropathy (HBVAN) predominantly occurs in childhood and mainly in males [11, 12, 37-40]; the number of reports on adult patients is very limited [2, 31, 41]. Moreover, data suggests that compared to adults, the prognosis of HBVAN is more favorable in children [10] and progression to renal failure is rare [2, 38, 40]. The aim of this article is to review and classify the literature on various aspects of HBVAN to gather the scientific information together and show the existing gaps in our current knowledge on the topic.

*** Correspondence:**
Hossein Khedmat, M.D.
Baqiyatallah Research Center for Gastroenterology and Liver Disease, Baqiyatallah Hosp., Mollasadra Ave., P.O. Box: 14155-6437, Tehran 1435915371, Iran.

Tel/Fax: +98 21 8896 4763

E-mail: Khedmat.h@gmail.com

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Characteristics of the HBV Virus

Discovered in 1966, HBV is a small DNA-containing virus belonging to the family Hepadnaviridae [42] (Fig.1); all of the hepadnaviruses have similar hepatotropism and life cycles in their hosts [43-45]. The viral genome of HBV is a partially double-stranded circular DNA of approximately 3200 base pairs that encodes four frames: S, for the surface; C, for the core gene; X, for the X gene; and P, for the polymerase gene [44]. HBsAg has several immunogenic portions. Several specific antigenic determinants existing in HBsAg, including the "a" determinant, are of epidemiologic relevance. HBsAg is the substance that induces development of protective cellular and humoral immunity to HBsAg. Development of commercial HBV vaccines is based on recombinant HBsAg synthesis.

Hepatitis B core antigen (HBcAg) is the nucleocapsid that surrounds the viral DNA. Expression of HBcAg-derived peptides on the surface of hepatocytes induces cellular immune responses that lead to death for the infected cells. The P gene encodes the DNA polymerase as well as the enzymes needed for a reverse-transcriptase function. The X gene encodes two proteins that serve as transcriptional trans-activators, aiding viral replication. These proteins are supposed to play a part in the development of hepatocellular carcinoma in chronically HBV-infected patients [46].

Epidemiology of HBV Infection

HBV infection is a critical global health dilemma, and according to the most recent World Health Organization estimates, about 2 billion people worldwide have serologic evidence for a previous or present HBV infection; moreover, 360 million are chronically infected and are at risk for HBV-related diseases, of whom 75% are Asians [46-48]. Approximately one third of all cases of cirrhosis and half of all cases of hepatocellular carcinoma (HCC) can be attributed to chronic HBV infection. HBV is estimated to be responsible for 500,000–700,000 deaths each year [49-51], making it the tenth leading cause of death worldwide due to chronic hepatitis, cirrhosis, HCC, and other diseases associated with HBV infection. In Africa and Asia, where infection is endemic, HBV is usually acquired in the first decade of life.

The frequency with which the HBV carrier state develops is markedly influenced by age at initial infection with extremely higher rates in neonates. In most studies, the chronic HBsAg carrier state has been observed to be 2 times more frequent in men than in women. Genetic factors may also play a role. The epidemiology of HBV infection varies considerably, ranging from 0.1% to 20% in different parts of the world [52]. It is estimated that 45% of the world population lives in highly prevalent regions [50], where HBsAg seroprevalence is greater than or equal to 8 percent; countries with intermediate endemicity have a seroprevalence of 2–7 percent for HBV infection, and low endemicity is attributed to countries where seroprevalence is less than 2 percent. In the Middle East, Bahrain, Iran, and Kuwait are areas of low endemicity; Iraq and the United Arab Emirates have an intermediate endemicity; and Jordan, Oman, Palestine, Yemen and Saudi Arabia have high endemicity [47, 51].

Transmission

As mentioned in the previous section, HBsAg seroprevalence has marked geographic variations, and it is well documented that the degree of HBV endemicity has strong correlations with the predominant mode of transmission in various areas. In highly endemic regions, exposure to chronically infected family members (including mother to child transmission and horizontal routes) is condemned for most disease transmissions [53-56]. In intermediate areas of prevalence, HBV infection extension is horizontally, and in low-prevalence settings, HBV is primarily a disease of adolescents and young adults and is transmitted sexually or parenterally [57].

The major route of HBV transmission is through exchange or contact with body fluids and blood. In industrialized countries, the modes of transmission are different. In the USA, a larger proportion of cases are being observed in intravenous drug abusers and in active heterosexuals with multiple partners [58], whereas transmission through homosexuality among males has diminished drastically due to a decline in risky sexual behaviors. Immigrants or refugees from areas of high endemicity, as well as travelers and military servicemen in such areas, constitute other important high-risk groups.

In Africa, the predominant route of infection is horizontal [59]. Familial clustering of HBV infection has been extensively documented in regions such as South Africa [60]. In Eastern Asian and Mediterranean countries, maternal-infant perinatal transmission is the predominant route of HBV transmission, with vertical transmission being the major route of infection [61]. The general pattern of HBV infection, however, is similar in all of these

regions.

In Iran, potential risk factors for the spread of hepatitis B infection were evaluated in 500 chronic hepatitis-B subjects and 434 subjects negative for hepatitis B. Age, male sex, being married, history of contact with hepatitis-B-infected people, risky sexual activities, intravenous (IV) drug use, history of major surgeries, experimental dental visits, and some occupations (police, barber, and driver) were found to be independent risk factors for chronic infection with the hepatitis B virus [14].

Pathogenesis of HBV-Associated Nephropathy

HBV has been implicated as a causal factor for the development of nephropathy [33, 62]. The pathogenetic routes through which people with chronic HBV infection develop nephropathy are not precisely defined, although it is generally accepted that persistent viral infections that could lead to immune complex-mediated nephritis may provide an appropriate explanation [63, 64]. Genetic factors have also been proposed as playing a role in the pathogenesis of HBVAN [65].

Four major mechanisms have been suggested as the major routes of damage to renal tissue by HBV: cytopathic collisions induced by cellular virus infection; deposition of immune complex particles attributed to viral antigens and host antibodies; virus-induced specific immunological mechanisms damaging the kidney; and finally, indirect adverse effects of virus-induced cytokines or mediators in renal tissue.

As mentioned above, the immunopathogenetic mechanism is the most widely accepted mechanism associated with nephropathy that is described as the deposition of immune complexes of viral antigens and host antibodies. Germuth *et al.* [66] showed that exposure to foreign antigens can provoke nephritis in animals depending on the circulation of different proportions of antibodies and antigens. He also demonstrated that despite the existence of only antigens in the serum, with the absence of antibodies, no nephritis develops. Moreover, when antigens persisted in the serum with low levels of antibody, chronic nephritis developed. Evidence indicates that the hepatitis B envelope antigen (HBeAg) is the primary antigen related to the subepithelial deposits in patients with HBVAN [14, 67].

Several HBV antigens have been found to be deposited to the glomerulus including HBsAg, HBcAg, and HBeAg. [12, 31, 32, 66, 67]. However, according to a study by Takekoshi et al. [68], HBeAg in association with IgG is essential in the pathogenesis of HBVAN. In another study [69] investigators measured serum HBeAg circulating immune complexes during the acute nephrotic phase of HBVAN and in the carrier stage of HBV. They found that the level of circulating immune complexes was low in the HBVAN patients; circulating immune complexes were absent in the HBsAg+/HBeAg+ patients without HBVAN and in the HBsAg+/HBeAg– asymptomatic carriers. This provides an answer to the question, "Why don't all individuals infected with HBV infection develop glumerulonephritis?" Other studies have proposed that the existence of HBV DNA in the patient's renal tissue plays a role in the pathogenesis of HBVAN [34, 70]. The authors of these studies concluded that the existence of the HBV genome in the kidney leads to the expression of viral antigens in this tissue causing immunological responses against the renal tissue. Immune complexes containing different combinations of HBV antigens may be responsible for different syndromes related to HBVAN.

Genetic Factors

It is generally believed that the pathogenetic mechanisms through which people develop nephropathy are possibly due to interactions between viral, environmental, and host factors. Therefore, a chronic HBV infection alone cannot lead to the development of nephropathy without participation of genetic and environmental factors in specifically vulnerable individuals.

In a study by Bhimma *et al.* [71], HLA DQB1*0603 was shown to be more frequently represented in patients with HBVAN compared to controls. Although HLA-DRB1*07 and DQB1*02 were also found at a higher frequency in the study subjects, statistical significance was not achieved for either of the two. No significant differences in the frequencies of class-1 antigens in the study group were found compared to the control group. From these findings, Bhimma *et al.* proposed a possible genetic predisposition to the development of HBVAN.

Another study compared the HLA-DRB and DQB1 alleles in children with HBVAN [72] with healthy children and a control group (patients chronically infected with HBV without any renal involvement). The results of the study showed that there was a significant increase in the frequency of DQB1*0303 in the HBVAN patients *vs.* the healthy controls and nonsignificant increases in the frequency of DRB1*0301 and DQB1*0603 in the

HBVAN patients (38% vs. 31% in controls). The authors suggested that the insignificant frequency of DQB1*0603 in Caucasians may have been due to a poor clearance of HBeAg, leading to HBeAg deposition on the glomerular basement membrane and to the development of nephritis.

Clinical Presentation of HBV Nephropathy and Prognosis

The clinical manifestations of HBVAN tend to be different in pediatric and adult patients (Table 1). Several chronic, pediatric carriers of HBV are asymptomatic, and in a high number of them HBVAN is detected by routine urine and serological screening [1]. The other common clinical presentation in children is the nephritic syndrome, which has a strong predominance in male children [14, 18, 31, 67]. In adults, the most common features of HBVAN are proteinuria and nephrotic syndrome. The gender disparity of nephritis in the adult population is not as prominent as the disparity in pediatric patients [32, 71, 73]. The manifestations of the disease is also different depending on the regional endemicity of HBV infection. Adults with HBVAN from non-endemic areas are more likely to represent acute hepatitis than children. It is suggested that this diversity is due to the higher incidence of unusual sexual relationships [74], drug abuse [74], and AIDS [75].

The natural history of HBVAN is not well understood. Previous studies have found a spontaneous regression of nephrotic syndrome in about half of their HBVAN patients, with a higher incidence among patients who were symptomatic for at least one year [14, 76] and the remaining patients having persistent proteinuria with fluid retention [76]. Seroconversion to anti-HBeAg has been reported to be associated with remission of proteinuria [14]. Evidence also suggests a progression to renal insufficiency in patients who remain positive

Table 1. Clinical presentation of HBV-associated membranous nephropathy [104, 105].

		Children	Adult
Route of HBV infection			
	Vertical	In the Far East	Not well known
	Horizontal within family members	USA, Africa and Europe	In areas of high endemicity
	IV drug abuse	-	In areas of low endemicity
	Blood transfusion	-	In areas of low endemicity
	Homosexuality	-	In areas of low endemicity
Ma1e:female ratio		4: 1	2-3:l
Mean age at presentation			
	Horizontal transmission	5–7 years	Any age group
	Vertical transmission	Infancy	
History of liver disease		Absent	Present in areas of low endemicity
Abnormal liver functions		Uncommon	Mild rise in ALT
Presenting symptoms			Nephrotic syndrome/proteinuria
	Asymptomatic	Yes	-
	Nephrotic syndrome	Yes	Yes
Hypertension		<25%	25-40%
Histology of renal lesions		>85% membranous	Membranous and IgA nephropathy
Progression to renal failure		<5%	25%
Serum for HBeAg and anti-HBc		+(88.2%)	+ (87.5%)

for viral components [77]. On the other hand, the majority of these children have been found to have a benign course [78].

Treatment of HBV-Associated Nephropathy

Because HBVAN does not essentially improve in all patients and the treatment is of extreme interest because of its impact on the overall outcome of patients, considerable attempts have been made to find effective treatment strategies to the disease to resolve complications related to nephritic syndrome such as hyperlipidemia, edema, and venous thrombosis in these patients. Moreover, improvements in liver disease and renal function have been reported following clearance of HBsAg from the body [32].

Corticosteroids

Corticosteroids have been administered to some patients with HBVAN, mainly for symptomatic relief of proteinuria [17, 73]. However, there is no evidence showing that corticosteroids administered at the onset of nephrotic syndrome in HBVAN have any ameliorative impact on the nephrotic state or clearance of the virus [79]. On the other hand, withdrawal of corticosteroids can lead to exacerbation of liver impairment in patients with chronic hepatitis B [80]. A prospective trial showed that although patients who did not receive corticosteroids experienced remissions, these remissions occurred later than for patients who received the drug [80]; however, another histological evaluation did not show a protective role for corticosteroids [81].

Other therapies

Alpha interferon (IFN-α) has anti-viral, anti-proliferative, and immunomodulatory effects [82]. A meta-analysis showed that 3 to 6 months of IFN-α therapy was beneficial in HBeAg-positive patients [83], with a higher tendency to produce anti-HBe and normalization of liver enzymes [84]. There are several reports in favor of using IFN-α in patients with HBVAN [82, 83, 85, 86]. In a randomized trial [40], patients who showed no response to corticosteroid treatment were divided into two groups: one was given supportive treatment only and the other received IFN-α. At the end of the study, all patients treated with IFN-α were free of proteinuriabut, 40% of patients in the group treated with only supportive therapy had nephrotic range proteinuria, and 60% had mild proteinuria with frequent relapses.

The mechanism of clearance of HBV antigens induced by IFN-α has not been fully understood, although the general belief is that the impacts of IFN-α on the cytokine cascade and immune system is the cornerstone of the process [84, 87, 88]. Stimulation by IFN α results in proliferation of cytotoxic CD8+ T cells [84, 87-89]. Lamivudine, famcyclovir, pegylated interferon, lobucavir, and adepovir are among the new agents that seem to be effective for chronic HBV infection therapies.

Prevention Approach

Table 2 shows the recommendations of Advisory Committee on Immunization Practices from the Centers for Disease Control and Prevention, an American institution, for HBV immunizations in this country. The major part of prevention strategies for HBV infection and its related nephropathy are immunization together with screening and appropriate treatment of HBV infection. Using prevention programs, we can eradicate HBV infections and subsequently reduce the occurrence of HBV-related diseases. This issue becomes even more relevant when we consider children in endemic areas, where most infections are acquired in early childhood. Several reports of the impact of mass immunization with the HBV vaccination [90-102] have documented a significant reduction in the prevalence of HBsAg carriage. In a study conducted in Durban, South Africa, it has been shown that the incidence of HBVAN in children after immunization fell sharply compared to the period with no immunization [103]. The authors concluded that even low coverage rates of HBV routine vaccination are highly effective within the framework of childhood immunization programs in reducing the incidence of HBVAN.

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Table 2. Recommended adults for hepatitis B vaccination in the United States [106].

Persons at risk for sexual transmission; Sex partners of persons who are positive for hepatitis B surface antigen (HBsAg)
All sexually active persons who are not in a long-term, mutually monogamous relationship (*e.g.*, persons who had >1 sex partner in the previous 6 months)
Persons evaluated or treated for sexually transmitted diseases, including human immunodeficiency virus infection
Men who have had sex with men; Persons at risk for transmission by percutaneous or mucosal exposure to blood
Household contacts of HBsAg-positive persons
Current or recent injection drug users, including needle sharing contact with HBsAg-positive persons
Healthcare and public-safety workers with a reasonably anticipated risk of exposure to blood or blood-contaminated body fluids
Persons with end-stage renal disease, including predialysis, hemodialysis, peritoneal dialysis, and home-dialysis patients
All persons seeking protection from hepatitis B virus infection
International travelers to areas with high or intermediate levels of endemic hepatitis B virus infection (HBsAg prevalence >2%)
Persons with chronic liver disease
People working in settings involved with sexually transmitted disease treatment facilities
People working in settings involved with human immunodeficiency virus testing facilities
People working in settings involved with facilities providing drug abuse treatment and prevention services
People working in settings involved with correctional facilities
People working in settings involved with healthcare settings serving men who have sex with men
People working in settings involved with chronic hemodialysis facilities and end-stage renal disease programs
People working in institutions and nonresidential day-care facilities for developmentally disabled persons

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