



HBV Hepatitis and Related Renal Nephropathies: Pathogenesis and Treatment

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Abstract

The extrahepatic manifestations of hepatitis B virus (HBV) infection include reactive arthritis, vasculitis (panarteritis nodosa), and primary glomerulonephritis (membranous nephropathy, membranoproliferative glomerulonephritis, and, less frequently, IgA nephropathy, focal and segmental glomerulosclerosis, and minimal change disease). No specific histomorphological patterns have been reported in association with HBV infection. The treatment of HBV-related glomerulopathies is essentially antiviral. Peginterferon and nucleos(t)ide drugs are the treatment of choice. Corticosteroids have been proved to be ineffective (except in panarteritis nodosa), while immunosuppressants can lead to exacerbation of HBV infection.

Keywords: antiviral treatment; HBcAg; HBeAg; HBsAg; hepatitis B-associated glomerulonephritis

Received: 6 October 2020; Accepted after Revision: 2 November 2020; Published: 09 November 2020

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How to cite: Maurizio Salvadori and Aris Tsalouchos. HBV Hepatitis and Related Renal Nephropathies: Pathogenesis and Treatment. *J Ren Hepat Disord.* 2020;4(2): 67–74.

Doi: <http://dx.doi.org/10.15586/jrenhep.2020.85>

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Introduction

Hepatitis B virus (HBV) is probably the most common virus found globally, affecting approximately 400 million subjects worldwide, although its incidence is decreasing due to the vaccination. The most severe complication is the hepatocellular carcinoma (HCC) that represents the ninth cause of death (1). In addition to the hepatic disease, the HBV is a frequent cause of extra hepatic disorders, among which the most common are glomerulonephritis (GN), vasculitis, and arthritis.

Genetic and Structure of HBV

HBV may be distinguished in 10 different genotypes; each of them is further divided in several subtypes. Genotypes

are distinguished according to alphabetical letters. According to the genotype and subtype, HBV has a different geographical localization and causes different aggressive diseases (2).

Initially, genotype A seemed to be the most frequent cause of glomerular disease (3), but, subsequently, a more accurate study (4) has not confirmed a significant association between HBV genotype and renal disease.

HBV is a member of Hepadnaviridae. HBV genome is represented by a round DNA. There are four genes encoded by the genome: *C*, *X*, *P*, and *S*. The core protein is encoded by the *C* gene (HBcAg). The early antigen (HBeAg) is derived from a proteolytic action of gene *P*. Gene *S* encodes the surface antigen (HBsAg) (5, 6). The structure of HBV is

important to explain its effects and, in particular, different pathogenetic pathways of glomerular disease.

Extra Hepatic Manifestations of HBV Infection

The principal targets of HBV are hepatocytes. According to the status of viral replication, different conditions have been described ranging from an immune-tolerant phase to an immune-reactive phase with occurrence of hepatic necrosis and fibrosis. As this phase prolongs or repeats, fibrogenesis develops with subsequent cirrhosis. HCC is a major complication that can occur in the presence or absence of cirrhosis (7).

Extra hepatic manifestations of HBV infection may include dermatological manifestations, such as keratolysis, urticaria, purpura, and lichen planus, systemic diseases, such as serum sickness syndrome, polyarthralgia, polyarthritis, and, most importantly, renal diseases (7, 8). The latter include membranous nephropathy (MN), membranoproliferative glomerulonephritis (MPGN), immunoglobulin A (IgA) nephropathy, and focal segmental glomerulosclerosis (FSGS) (9). Less frequently, minimal change disease (MCD) and amyloidosis have been described in association with HBV, although this association is debated. Additionally, polyarteritis nodosa (PAN) is strongly associated with HBV. The disease is characterized by a necrotizing small and medium vessel vasculitis.

Pathogenesis

Three different factors may contribute to the development of HBV-associated renal diseases:

1. HBV antigens containing immune complexes
2. Direct viral effect
3. Host and viral genetic factors

Immune complexes

The role of immune complexes containing an HBV antigen is a certain factor, although it is still controversial whether the immune complexes are formed *in situ* or come from the blood and trapped into glomerular structures.

Several HBV antigens have been documented in the glomeruli, including the surface antigen (HBsAg), the early antigen (HBeAg), and the core antigen (HBcAg) (10). HBsAg and HBcAg are large and cationic. Owing to the dimension and charged immune complexes, these antigens could favor the mesangial or subendothelial deposition and facilitate the development of MPGN or IgA nephropathy. Indeed, immune complexes containing HBsAg have been eluted from a patient affected by HBV-MPGN (11). The low molecular weight of HBcAg (300 kilodalton) and its cationic charge could favor transmembrane migration and their deposition in the subepithelial space (12). The role of HBeAg in determining

membranous nephropathy is further documented by the fact that circulating HBeAg containing immune complexes correlate with the severity of the disease (13, 14).

After glomerular deposition or formation of immune complexes, the complement activation could justify glomerular damage (15, 16). Figure 1 explains the relationship between the antigens and the type of glomerular disease.

Direct viral effect

The expression of HBV-DNA in the glomeruli in the absence of antibodies could justify the direct effect of HBV in glomerular damage (17).

Diao et al. (18), putting in culture together with mesangial cells and HBV, documented cell proliferation and formation of extracellular matrix proteins.

Host and viral genetic factors

HBV-associated glomerular disease may be linked to specific major histocompatibility complex class II alleles such as DQB1*0603 for membranous nephropathy and DRB1*1502 for MPGN (19, 20).

We have mentioned the possible relationship between different genotypes of HBV and associated nephropathy. Further studies have found that mutations in HBV genes (*C1653T*, *A1726C*, *A1727T*, *C1730G*, *T1753C*, *A1762T*, and *G1764A*) are present in 84% of patients with membranous nephropathy (21).

Clinical Aspects

Membranous nephropathy

The natural history of HBV-related membranous nephropathy seems to differ in children and adults.

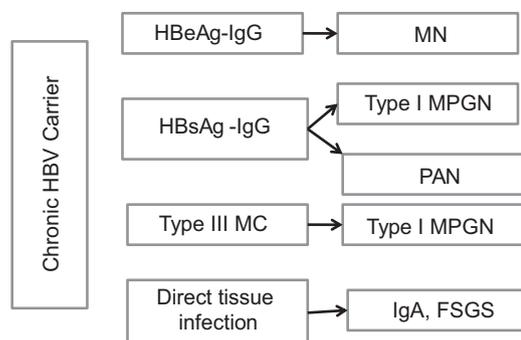


Figure 1: Glomerular syndromes associated with an HBV carrier state. MN: membranous nephropathy; MPGN: membranoproliferative glomerulonephritis; PAN: polyarteritis nodosa; MC: mixed cryoglobulinemia; FSGS: focal segmental glomerulonephritis.

Children often present with proteinuria in the nephrotic range with associated microematuria and hypertension. Kidney function as evaluated by estimated glomerular filtration rate (eGFR) is generally preserved. The natural history in children is often benign with a remission rate of 64% at 4 years (22). The disease prevails in males as idiopathic MN (23). HBV-MN in adults has a worse evolution in comparison to children. A declining eGFR has been observed in 29% of patients and one-third patients develop end-stage renal disease (ESRD) (24).

The deposition of immune complexes is typically in the subepithelial space because of their small size. Segmental glomerular damage and mesangial cell proliferation are more frequent in the idiopathic form (25). Some studies have documented the simultaneous presence of subendothelial and mesangial deposits in HBV-MN (26, 27).

Immune complexes may also be formed by implant antigens, and the presence of complement factors, platelet aggregation, and polymorphonuclear leukocytes may justify glomerular damage (28).

Finally, the direct effect of the virus has been suggested in HBV-MN also. Several studies have found HBV DNA in the nucleus and cytoplasm of epithelial and mesangial cells (29).

In the vast majority of patients, pathological basis is not possible to distinguish the HBV-related MN from the idiopathic MN. The only method available is based on the finding of circulating anti-phospholipase A2 receptor Ab (30, 31).

Membranoproliferative glomerulonephritis

MPGN is the second most common glomerulonephritis in HBV-positive patients. It is characterized by lobular aspects of the glomeruli because of mesangial proliferation. The splitting of glomerular basement membrane (GBM) is due to the infiltration of mesangial cells and their deposition in the subendothelial space of immune complexes containing HBsAg because of its size (32–34). Type 1 and type 3 MPGN have been observed in HBV-positive patients, while type 2 has been never observed (35).

Presence of mixed cryoglobulinemia (polyclonal IgM and IgG) has been described in HBV-positive patients. As cryoglobulinemia is mostly typical of HCV infection, a co-infection of HBV-HCV should be excluded.

HBV-positive patients with cryoglobulinemia have nephrotic syndrome, frequently with acute kidney injury (AKI) and vasculitis with low C3 and C5 levels in serum.

Polyarteritis nodosa

Although PAN is not strictly a renal disease, its evidence is high in HBV-positive patients with occurrence of a renal disease. PAN is a vasculitis with necrosis of medium size

vessels due to deposition of HBsAg antibodies immune complexes (36).

With respect to idiopathic PAN, HBV patients have a more severe disease with frequent evolution to AKI due to renal ischemia and infarction. Arthralgia, fever, and cutaneous lesions are present. Additionally, elevated hypertension and renal infarctions of the cortex are also present. A case of HBV-positive patient with associated PAN and membranous nephropathy has been described by Mouthon et al. (37).

Other glomerulonephritis

The first description of mesangial proliferative glomerulonephritis with mesangial deposition of IgA and HBsAg or HBcAg has been made by Nagy et al. (38). Lai et al. (39) described a larger series of patients with HBV-associated mesangial proliferative glomerulonephritis. Approximately 20% of patients developed progressive renal failure within 4 years of follow-up, but this finding was not confirmed by others (40).

Relationship between FSGS and HBV is debated. Two cases have been described by Khaira et al. (41). The finding of HBsAg or HBcAg in the glomeruli in the absence of immunoglobulins suggests the role of a direct pathogenic effect of the virus.

MCD and diffused proliferative glomerulonephritis have been described in HBV-positive patients (42), but because of few cases reported, more confirmative studies are needed.

Diagnosis

The diagnosis of an HBV-related renal disease should be suspected for any HBV-positive patient with an abnormal urine analysis or a reduced renal function.

Patients with proteinuria, higher than 1 g (24 h), and microematuria are suspected for glomerular lesions. In such cases, a renal biopsy is necessary to confirm the suspected diagnosis (Figure 2). The diagnosis of HBV-related glomerular disease is confirmed by finding monoclonal antibodies and one or more HBV antigens (HBsAg, HBcAg, or HBeAg), although in one study only 39% of biopsies were positive (43). In the case of HBV-related PAN, urine-analysis may be negative, and a definitive diagnosis should be made by angiography (44).

Treatment

The vast majority of our knowledge on the treatment of HBV-related GNs relies on studies on membranous nephropathy, while data on MPGN or other glomerular diseases principally refer to case reports.

The main goal of the treatment is to reduce viral load. Antiviral treatment is effective in inducing HBV clearance

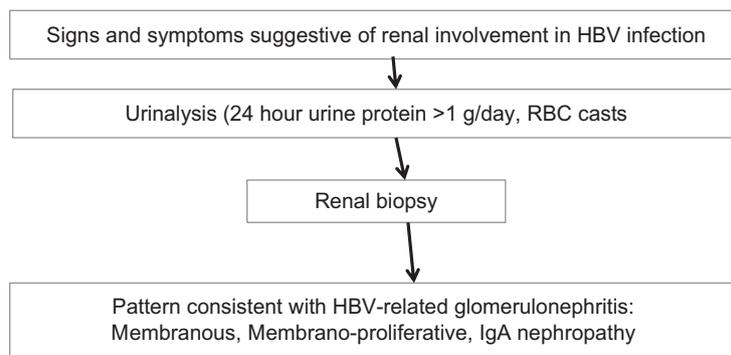


Figure 2: Diagnostic steps for diagnosing HBV-related glomerulonephritis.

and proteinuria remission (45, 46). In 2012, the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines on glomerulonephritis recommended interferon alpha ($\text{IFN}\alpha$) with nucleos(t)ide analogs (NAs) as the treatment of choice for HBV-GN (47).

Initially, the antiviral treatment was based on $\text{IFN}\alpha$ and lamivudine (LMV). Their use was effective in reducing proteinuria, principally in children with membranous nephropathy (48, 49). According to these studies the renal prognosis was different in children and adults. Indeed, the occurrence of ESRD was 3% in children and 30% in adults.

Main drawback of LMV was the appearance of mutants resistant to therapy (50).

The peginterferon (PEG- IFN) alpha-2a is a more powerful treatment because it has both immune regulatory and antiviral action (51).

$\text{IFN}\alpha$ could induce proliferation of T lymphocytes and helper T cells (52).

Patients affected with HBV-related MN have a reduced TCD28-related cytotoxic activity, and $\text{IFN}\alpha$ treatment has an effective activity in 30–40% of patients with clearance of HBeAg (53).

Other NAs, in addition to LMV, used to date are entecavir (ETV), adefovir (ADV), telbivudine (TBV), and tenofovir (TAF), although LMV, ADV, and TBV are not recommended for treating chronic HBV infection (54).

ETV is effective with low resistance (55). Its dosage should be reduced according to renal function (56). ADV is effective for liver improvement, viral suppression, and biochemical improvement in patients resistant to LMV (57, 58). A major drawback of ADV is dose-dependent nephrotoxicity that could be avoided by maintaining a dose of 10 mg/daily (59, 60).

Use of TBV is limited due to the emergence of drug resistance that may reach 25.1% in 2 years of treatment (61, 62). Additionally, TBV may cause myopathy and peripheral neuropathy (63).

TAF is a better-known NA and is used as two variants: tenofovir disoproxil fumarate (TDF) and tenofovir alafenamide (TAF).

TDF is effective on HBV, but is nephrotoxic because of tubular injury (63). Because of this fact, TDF should be avoided in the treatment of HBV-related GN. More promising is TAF, which seems to have a reduced nephrotoxicity with a similar antiviral action (64, 65). TAF seems to have a higher antiviral activity and reduced nephrotoxicity than TDF, though few studies have compared the two drugs.

The WHO (56) recommends the dose reduction of TAF and ETV according to renal function (*creatinine clearance*) as shown in Table 1.

Although the aim of this study was to review principal treatments for HBV-related GN, briefly we report the conclusions of the Swedish guidelines (66) for the use of PEG- IFN and NAs.

PEG- IFN has a weak antiviral effect compared to NAs. A small number of HBeAg-positive and negative patients obtained HBsAg clearance. In addition, PEG- IFN is poorly tolerated and necessitates parenteral administration.

NAs have a major potency in elimination of virus. ETV, TDF, and TAF are recommended because these drugs have a higher barrier to drug resistance. On the contrary, LMV, ADV, and TBV with low barrier to drug resistance are not recommended.

ETV, whose dose should be reduced according to eGFR, is the preferred treatment for naïve, non-cirrhotic HBeAg-positive patients. Attention should be paid to cross-resistance with LMV.

TDF is a highly effective treatment and has been approved as a monotherapy for the treatment of HBV. Risks of renal side effects do exist; hence, renal function should be monitored frequently.

TAF has the same mode of action as that of TDF, with fewer side effects on the kidney, and does not need to be

Table 1: Recommended dose reduction or dosing interval for tenofovir and entecavir.

	CrCl (mL/min)			
	50	30–49	10–29	Hemodialysis
Tenofovir (TAF)	300 mg every 24 h	300 mg every 48 h	300 mg every 72 h	Every 7 days
Entecavir (ETV)	1 mg once daily	0.5 mg once daily	0.3 mg once daily	0.1 mg once daily

CrCl: creatinine clearance.

Table 2: Outcomes from treatment of HBeAg-positive and negative patients, 6-month and after 1-year treatment with PEG-IFN, and after 1-year treatment with nucleos(t)ide analogs (NAs).

	PEG-IFN alpha 2a	LMV	TBV	ETV	ADV	TDF	TAF
Dose	180 µg	100 mg	600 mg	0.5 mg	10 mg	245 mg	25 mg
HBeAg-positive							
Anti-HBe seroconversion	32%	16–18%	22%	21%	12–18%	21%	10%
HBV DNA < 60–80 IU/mL	14%	36–44%	60%	67%	13–21%	76%	64%
ALT > ULN	41%	41–72%	77%	68%	48–54%	68%	72%
Loss of HBsAg	3%	0–1%	0.5%	2%	0%	3%	1%
HBeAg-negative							
HBV DNA < 60–80 IU/mL	19%	72–73%	88%	90%	51–63%	93%	94%
ALT < normal upper limit	59%	71–79%	74%	78%	72–77%	76%	83%
Loss of HBsAg	4%	0%	0%	0%	0%	0%	0%

PEG-IFN: peginterferon; LMV: lamivudine; TBV: telbivudine; ETV: entecavir; ADV: adefovir; TDF: tenofovir disoproxil fumarate; TAF: tenofovir.

LAM, TBV, and ETV are nucleoside analogues; and ADV, TDF, and TAF are nucleotide analogues.

monitored, although not recommended for patients with a very low eGFR.

The Swedish guidelines (66) report the outcomes of different NAs in HBeAg-positive and HBeAg-negative patients (Table 2).

Summarizing, the wider experience of the effects of antiviral treatments in HBV-GN is based on the studies conducted with LMV and IFN α therapy. Studies comparing the efficacy of new NAs and IFN α are still lacking. Anyway, HBV-GN goes into remission with the elimination of viral antigen (67–69). This fact favors the use of NAs with high potency. However, more studies are needed to confirm this point.

Immunosuppressants are also used frequently in the treatment of HBV-GN.

The usefulness of steroids is debated because the inhibition of the immune system may favor HBV replication (70). In a

meta-analysis study, the steroid efficacy is not proved (45). In this study, both proteinuria remission and HBeAg clearance were obtained with the use of antiviral agents.

Administration of steroids is not recommended principally in patients with high viral load.

Similarly, the use of rituximab and cytotoxic agents may cause fatal complications (71, 72).

Only in the treatment of HBV-PAN, the association of steroids and plasmapheresis has been used successfully (73).

Conflict of interest

The authors declare no potential conflict of interest with respect to the research, authorship, and/or publication of this article.

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