

Review Article

Hepatitis B and Kidney Diseases

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Abstract

Renal disease associated with hepatitis B virus (HBV) infection most commonly occurs in endemic areas where chronicity with infection is high particularly when acquired in early childhood. The pathogenetic role of HBV infection in kidney diseases is demonstrated by presence of hepatitis B antigen-antibody complexes in the renal lesions. The commonly found HBV-related renal dysfunctions are due to membranoproliferative glomerulonephritis, membranous nephropathy and polyarteritis nodosa. A kidney biopsy is performed to confirm the presence of an underlying glomerular process, whereas a different tissue site (example: skin) is biopsied to confirm polyarteritis nodosa (PAN). Diagnosing HBV-associated renal disease is important because therapy with corticosteroids and cytotoxic agents, which are common therapies for idiopathic forms of the above disorders, may not be beneficial in patients with HBV-associated renal disease and may worsen the scenario due to reactivation of HBV replication.

Introduction

About 350 million people worldwide have chronic HBV infection. In South East Asia, the proportion of chronic HBV carriers exceeds 10% in the general population. Hepatitis B virus (HBV) infection is associated with a variety of renal pathologies [1,2]. Usually following types of renal disease results commonly from HBV infection:

- Membranous glomerulonephritis
- Membranoproliferative glomerulonephritis (MPGN)
- Polyarteritis nodosa (PAN)

In fewer cases, HBV infection is associated with IgA nephropathy, mesangial proliferative glomerulonephritis and amyloidosis.

Epidemiology

Renal disease associated with hepatitis B virus (HBV) infection most commonly occurs in endemic areas, particularly when infection occurs during infancy and early childhood, which increases the probability of becoming a chronic carrier [3]. In South East Asia, proportion of chronic HBV carriers can exceed 10% in the general population. In a recent series which included 390

patients with membranous nephropathy, HBV was the underlying cause in 12% of patients [4]. Hepatitis B vaccination has decreased the incidence of HBV-related renal diseases, providing evidence for probable pathogenetic role of HBV [5,6].

Pathogenesis

The pathogenetic role of HBV infection is demonstrated by presence of hepatitis B antigen-antibody complexes in the renal lesions on immunofluorescence microscopy, including deposition of HBeAg in membranous nephropathy [1,7,8]. Whether these immune complexes are formed *in situ* or are derived from circulating immune complexes being trapped in the glomerulus remains controversial. Immune deposition occurs predominantly in the subepithelial region but can also involve the mesangial and occasionally subendothelial areas, depending on the size of the antigens and immune complexes. It has been speculated that the low molecular weight of HBeAg might account for its ability to traverse the glomerular basement membrane and thus the formation of subepithelial immune deposits [7]. The immune complexes then activate complements and glomerular injury occurs via the formation of membrane attack complex and other downstream events such as the induction of proteases, oxidation injury, and disruption of cytoskeleton [9,10].

HBV-Related Glomerulonephritis

Membranous nephropathy

HBV-associated secondary membranous nephropathy usually presents with proteinuria, which can be in the subnephrotic or nephrotic range and microscopic hematuria. Compared with idiopathic membranous nephropathy, patients with HBV-associated membranous nephropathy are likely to have microscopic hematuria, lower complement levels, and a negative anti-phospholipase A2 receptor antibody (anti-PLA2R) [11,12]. The histologic presence of mesangial or subendothelial immune deposits, in addition to the typical subepithelial localization, provides a clue to secondary membranous nephropathy.

HBV-related membranous nephropathy is characterized by thickened capillary wall and glomerular basement membrane on light microscopy. Although this feature could be subtle in the early stage, the capillary wall can assume a rigid appearance in advanced disease. Immunofluorescent staining and electron microscopy demonstrate granular IgG, C3, and some IgM staining in the subepithelial region along the glomerular basement membrane accompanied by extensive effacement of the podocyte foot processes, and in some cases viral particles in various locations within the glomerulus. Electron microscopy shows subendothelial expansion and the formation of new basement membrane material, which accounts for the double-contour appearance on light microscopy. The subendothelial and mesangial immune deposits trigger complement activation and increased local expression of inflammatory and chemotactic mediators, leading to the infiltration of inflammatory cells. The natural history of HBV-related membranous nephropathy appears different between children and adults. In contrast to pediatric subjects, in whom spontaneous remission of proteinuria is common and the renal function is often well preserved, adult patients are more likely to have progressive disease and up to one third of patients might eventually develop renal failure [13,14,15].

Membranoproliferative glomerulonephritis (MPGN)

HBV-associated MPGN presents with hypertension, hematuria (often with dysmorphic red blood cells), proteinuria and reduced glomerular filtration rate. The histologic deposition of circulating antigen-antibody complexes in the mesangium and subendothelial space characterizes the MPGN associated with HBV. Both HBeAg and hepatitis B surface antigen (HBsAg) deposition have been implicated in this disorder, although their exact role remains uncertain [7].

Polyarteritis nodosa (PAN)

PAN is a necrotizing vasculitis affecting small- and medi-

um-sized blood vessels that produces multi-organ involvement; renal involvement usually presents with hypertension and reduced glomerular filtration rate. The presence of HBV-associated disease is suggested by the findings of HBsAg, HBeAg, and HBV DNA in the serum. The deposition of circulating antigen-antibody immune complexes in the vessel wall triggers downstream inflammatory processes [1,2].

Diagnosis

A kidney biopsy is performed to confirm the presence of an underlying glomerular process, whereas a different tissue site (example: skin) is biopsied to confirm polyarteritis nodosa (PAN). The detection of viral antigen deposition in the kidney requires special techniques that may not be available in usual clinical setting. Also, the presence of viral antigens in the renal tissue can be coincidental rather than causative of a disease [7]. However, a presumptive diagnosis can be made in patients whose renal biopsy findings are consistent with an HBV-associated disease especially when the patient is a child from an HBV-endemic region or an adult whose serologic tests show circulating hepatitis B surface antigen (HBs Ag) and hepatitis B e antigen (HBeAg) [1,2].

Diagnosing HBV-associated renal disease is important because therapy with corticosteroids and cytotoxic agents, which are common therapies for idiopathic forms of the above disorders, may not be beneficial in patients with HBV-associated renal disease and may worsen the scenario due to reactivation of HBV replication.

Treatment

The limited data on the treatment of HBV-associated renal diseases are based upon small case series and uncontrolled observations. There are no randomized trials. Moreover, the treatment of children and adults with HBV-associated renal disease differs because of different natural history.

Much of the data on the treatment of HBV-related glomerular diseases came from patients with membranous nephropathy, the most common histologic presentation, whereas the data on membranoproliferative glomerulonephritis or focal segmental glomerulosclerosis remain largely anecdotal.

Antiviral Therapy

Indications for antiviral therapy

In patients with HBV-associated renal disease and positive hepatitis B e antigen (HBeAg) or detectable serum HBV DNA, antiviral therapy is recommended [2,8].

Treatment options

There are two options for antiviral therapy: interferon alfa

(usually pegylated interferon alfa) and nucleoside/nucleotide analogs. Interferon has an immunomodulatory effect in addition to its ability to suppress HBV replication. Interferon- α activates cellular pathways that lead to breakdown of viral RNA and enhances cell-mediated immune response toward hepatocytes infected with HBV. Interferon treatment given for 4-12 months was associated with sustained remission of proteinuria in 20% to 100% of patients, clearance of HBeAg in 20% to 80%, and a drop-out rate of 10% to 15%. Resolution of proteinuria was often associated with clearance of HBeAg and/or HBsAg, and usually occurred within 6 months of seroconversion [13,16,17].

However, most of the reported data were anecdotal reports or data from small series. Bias from selective publication of positive results remains possible. Interferon is less well tolerated but is more likely to induce a sustained remission. Thus, it should be considered in children and young adults who can better tolerate interferon or who do not want to be on prolonged nucleoside/nucleotide therapy. Interferon is not recommended in patients with cirrhosis.

Nucleos(t)ide analogues such as lamivudine, telbivudine, adefovir, entecavir, or tenofovir suppress HBV replication through their inhibitory effect on viral DNA polymerase. Because the deposition of immune complexes within the glomerulus is perceived to play a pivotal role in the pathogenesis of HBV-related nephropathy, reducing the quantity of viral antigens and thereby reducing immune complex deposition in the kidneys. Ameliorate kidney damage. Compared with interferon, nucleos (t) ide analogues offer the advantages of convenient administration and high tolerability, but often require longterm administration and could result in the selection of drug-resistant HBV strains. Adefovir should be used with caution in patients with renal impairment in view of its nephrotoxicity, which is mediated through inhibition of mitochondrial DNA replication resulting in disruption of normal mitochondrial respiratory function in proximal renal tubular epithelial cells. There are also uncommon reports of renal tubular toxicity with tenofovir [18]. Even fewer data exist regarding nucleos(t) ide analogues than interferon on HBV-related nephropathy. The factors predictive of treatment efficacy and the selection criteria for treatment also remain undefined. Data from an report on 10 patients with HBV-related membranous nephropathy showed that lamivudine treatment was associated with complete resolution of proteinuria in six patients [19]. However, the concomitant use of angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, and antihypertensive medications precluded definitive conclusions on the renal effect of antiviral treatment. Future studies on the effect of antiviral therapy on proteinuria or renal survival should thus include concurrent controls with comparable exposure to these potential confounders.

Nucleoside/nucleotide analogs rather than interferon are preferred in older adults and in children who are not candidates for interferon therapy. When a nucleoside/nucleotide analog is used, entecavir is preferred in view of its antiviral efficacy and low propensity for drug resistance. In view of the nephrotoxicity of adefovir and tenofovir, these two drugs are not preferred unless required in patients who have developed resistance to other agents.

The renal prognosis is distinctly different between pediatric and adult patients, with the incidence of chronic kidney disease reported as less than 3% in children and up to 30% in adult patients [13,14]. The overall data suggest that a favorable renal response to antiviral treatment seems more likely in pediatric patients than adults and in patients when renal manifestations are accompanied by increased viral replication, a high HBV DNA level, and hepatitis flare.

Duration of therapy

The optimal duration of antiviral treatment is not clear. Many patients treated with nucleoside/nucleotide analogs will require prolonged treatment except for those who achieve rapid HBeAg conversion to anti-HBe.

The duration of therapy depends upon the type of drug used: Interferon is given for a finite duration. Pegylated interferon is given for 48 weeks in both HBeAg-positive and HBeAg-negative patients.

If a nucleoside/nucleotide analog is used, treatment is continued for at least 12 months after seroconversion of HBeAg (to anti-HBe).

Treatment Target

The goal of antiviral therapy depends upon the presence or absence of HBeAg at baseline. HBeAg is considered to be a marker of HBV replication and infectivity. HBeAg seroconversion (disappearance of HBeAg and appearance of anti-HBe antibodies) is usually associated with a decrease in HBV DNA and remission. In patients who are initially HBeAg seropositive, the therapeutic goal is HBeAg seroconversion to anti-HBe. In patients who are initially HBeAg negative, the therapeutic goal is suppression of viremia, which requires monitoring of HBV DNA levels to ensure that therapy is effective. In patients treated with a nucleoside/nucleotide analog, lifelong therapy may be required. However, if the HBsAg becomes negative in a patient without cirrhosis, discontinuation of the nucleoside/nucleotide analog can be attempted [24-27].

Immunosuppression (with or without plasmapheresis) in combination with antiviral therapy should be considered in patients who have rapidly progressive glomerulonephritis (RPGN)

and PAN with severe manifestations. Except for these two indications, data from observational studies suggest that immunosuppressive therapy with corticosteroids or cytotoxic agents and plasmapheresis are of little benefit and are potentially harmful. This is particularly true among children with membranous nephropathy in whom spontaneous recovery over 6 to 24 months is common [1,2,20]. Antiviral monotherapy may also be sufficient to treat HBV-associated PAN in patients who do not have severe or life-threatening disease [21-23]. In addition, immunosuppressive therapy can trigger an increase in viral replication and possibly lead to exacerbation of chronic hepatitis [31-33].

RPGN

In patients with rapidly progressive (crescentic) glomerulonephritis due to HBV infection, treatment can be tried with antiviral medication (preferably a nucleoside/nucleotide analog) and a short course of glucocorticoids with or without an immunosuppressant, such as cyclophosphamide or rituximab (the latter must be accompanied by antiviral therapy since it may lead to increased viral replication and a flare of hepatitis [27]).

The glucocorticoid regimen consists of intravenous methylprednisolone, 500 to 1000 mg/day for three days, followed by prednisone, 0.7 to 1 mg/kg per day, tapered over four to six months. Antiviral therapy and monitoring of HBV DNA levels are continued for at least six months after cessation of immunosuppressive therapy (or up to 12 months if an anti-CD20 antibody is used) or until the therapeutic goal is achieved.

PAN

Immunosuppression and plasma exchange are part of many published treatment protocols for HBV-associated PAN [21-23,28-32]. Glucocorticoids suppress the inflammatory component of the vasculitis [20] and may improve survival [33], although they can enhance viral replication and lead to exacerbation of chronic hepatitis. Plasmapheresis removes circulating immune complexes, which may be beneficial in patients with severe disease manifestations. However, in patients with PAN and severe manifestations (defined by the presence of acute kidney injury, ulcerative or gangrenous lesions of the extremities, polyneuropathy, central nervous system involvement or myocardial ischemia), treatment can be attempted with both glucocorticoids and plasmapheresis in addition to antiviral therapy (preferably a nucleoside/nucleotide analog), although the data supporting the use of plasma exchange are weak.

The benefits of combination therapy were shown in a retrospective series of 80 patients with HBV-associated PAN who were treated with an antiviral agent (vidarabine, interferon alfa or

lamivudine, depending upon the era), a two-week course of corticosteroids, and an intensive schedule of plasma exchange [34]. Their course and outcomes were compared with 35 historic controls (before the antiviral era) treated with corticosteroids with or without cyclophosphamide, with most receiving plasma exchange. The following observations were made:

Remission was attained by 81 percent of all patients; patients who did not achieve remission died within a mean of 178 days. Overall five-year survival was 73 percent.

At a median follow-up of 237 months, combination therapy with antivirals, immunosuppression, and plasmapheresis was associated with lower rates of relapse (4 versus 14 percent) and death (30 versus 49 percent), although the differences did not reach statistical significance.

Combination therapy was associated with a significantly higher rate of HBeAg seroconversion to anti-HBe (49 versus 15 percent), which predicted a sustained remission. Seroconversion rates were similar for interferon and lamivudine (both over 60 percent) but lower for vidarabine (41 percent), which is no longer used due to neurotoxicity.

The addition of cyclophosphamide to glucocorticoids and plasma exchange does not appear to improve long-term outcomes in HBV-associated PAN, although initial disease control may be better [28,34].

There are no data on the role of other immunosuppressive agents, including mycophenolate mofetil and rituximab, in the treatment of HBV-associated PAN [35,36].

Vidarabine is no longer used for hepatitis B because of neurologic side effects and low antiviral efficacy.

Although data on entecavir or tenofovir in HBV-associated PAN are lacking, these newer nucleoside/nucleotide analogs are preferred to lamivudine because of low risk of drug resistance.

Summary

Renal disease associated with hepatitis B virus (HBV) infection most commonly occurs in endemic areas, particularly when infection occurs during infancy and early childhood, which increases the probability of becoming a chronic carrier.

The pathogenetic role of HBV infection has been documented primarily by the demonstration of hepatitis B antigen-antibody complexes in the renal lesions via immunofluorescence microscopy. The renal diseases most commonly associated with HBV infection include: membranous nephropathy, membranoproliferative glomerulonephritis, and polyarteritis nodosa.

A kidney biopsy is required to confirm the presence of an underlying glomerular process, although a different tissue site may be biopsied to confirm PAN.

There are two options for antiviral therapy: interferon alfa (usually pegylated interferon alfa) and nucleoside/nucleotide analogs, such as lamivudine, entecavir, adefovir, tenofovir, and telbivudine.

In children and young adults, initial therapy with interferon alfa (usually pegylated interferon alfa) rather than nucleoside/nucleotide analogs is preferred. Interferon is less well tolerated and is more likely to induce a sustained remission.

In older adults and in patients with cirrhosis, initial therapy with nucleoside/nucleotide analogs rather than interferon is preferred.

In patients with RPGN due to HBV infection, treatment is made with immunosuppression in addition to antiviral medication (preferably anucleoside/nucleotide analog).

In patients with PAN and severe manifestations, treatment with plasmapheresis and immunosuppression in addition to antiviral medication (preferably a nucleoside/nucleotide analog) is made.

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