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Hepatitis B and Chronic Kidney Diseases

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Published Date: June 07, 2016

Besides hepatic diseases, HBV (hepatitis B virus) affects multiple organ systems [1]. Kidney damage caused by HBV infection is common among all the diseases related to HBV. Since Combes et al. [2] discovered the relations between HBV infection and membranous nephropathy in the 1970s, various pathologic types of glomerular damage have been found to be associated with HBV infection, which are termed as hepatitis B virus associated-glomerulonephritis **(HBV-GN)** collectively [3]. Some will progress into chronic kidney insufficiency, and even kidney failure. With the accumulation of thorough study and clinical practice of HBV-GN in recent years, the recognition of this disease has been enhanced in a large scale. This chapter will elaborate on and summarize the research progress of its epidemiology, pathogenesis and treatment.

EPIDEMIOLOGY

There is a wide distribution of HBV infections across the world. According to the reports of World Health Organization **(WHO)**, about two billion people were affected by HBV, of whom 350 million are chronic. However, the distribution in different areas in the world is not even. The infection rate in developed countries is relatively low, such as that in the US and West Europe, where the infection rate is lower than 1% [4,5]. In these areas, parenteral and sexual transmissions play a bigger role in all the transmission pathways. While in developing countries such as those in Africa and Asia, the infection status is more serious, with a carrier rate of 10% to 20% according to reports of China and Southeastern countries [6]. The epidemiological study of hepatitis B in China in 2006 showed that there are approximately 93 million people chronically infected and about 20 millions of them are Chronic Hepatitis B **(CHB)** patients.

HBV-GN refers to a kind of glomerulonephritis directly or indirectly triggered by HBV, excluding other secondary glomerulonephritis relevant to liver or kidney disease and with an established etiology, such as lupus nephritis, after verification of sero-immunological and renal biopsy immune fluorescent experiments. The epidemiology of HBV-GN is basically parallel to the trend of HBV infection. The infection rate of HBV is relatively high in China, which has led to a much higher incidence of HBV-GN compared to other regions of the world [7]. HBV-GN accounts for 16.6%-32% of all kinds of glomerulonephritis, in which Membranous Nephropathy **(MN)** is the main type [8]. Male patients are about 1.5-2.0 times as many as the females. At the same time, the incidence rate of HBV-GN of children is significantly higher than that of adults, due to the immaturity of their immune systems.

The clinical presentations of HBV-GN in adults are kidney damage and extra renal manifestations [9]. Kidney damage is characterized by proteinuria or nephrotic syndrome, hematuria, edema and oliguria. Hypertension is also seen in 40% of the patients. Compared to children, adults are more prone to have aberrant kidney and liver functions. Nearly all patients are positive for serum HBsAg and 60%~80% cases are positive for HBeAg. Kidney injury can occur in 6 months to several years after infection. In children, the majority (73%) of HBV-GN patients present symptoms that are identical to nephrotic syndrome. On the contrary, gross hematuria, hypertension and renal insufficiency are rarely seen. Most children patients manifest no hepatic symptoms, but almost half have an elevated Alanine Aminotransferase **(ALT)**. Serum HBsAg, HBeAg and HBcAb are positive in 75% of the affected children. HBV-GN tends to resolve spontaneously in children and there is a low incidence of renal insufficiency afterwards. However, the prognosis of adult HBV-GN is poorer, in whom around 20% progress into End Stage Renal Diseases **(ESRD)**.

PATHOGENESIS

The mechanism of HBV-GN has not been fully understood yet. It is commonly agreed that HBV-GN is a process mediated by immune factors and a result of the interaction of the virus, host and environmental factors [10]. The possible mechanisms are expounded as follows.

Glomerular Deposition of Immune Complexes

The theory is widely approved at present and is the theoretical basis for its immune suppressive treatment. There are two type of immune complexes: Circulating Immune Complexes **(CICs)** and in situ immune complexes. Each of them alone is pathogenic and the two types can also exist at the same time. CICs are formed when anti-HBV antibodies, which are generated by the human body after HBV infection, meet corresponding antigens in the circulation. CICs are deposited in mesangial regions and sub-endothelial space when the blood flow through the areas. These complexes activate complements subsequently, causing immunologic injury. There are preclinical experiments showing that, with a small molecular weight and positive charge, HBeAg is able to be deposited in sub-endothelial space of the glomeruli via non-immunological mechanism and form in situ immune complexes with anti-HBe antibodies from the circulation.

Direct Kidney Infection by HBV

HBV can affect not only the liver but also the kidney and replicate and express itself in renal tissues. With the development of molecular biological techniques in recent years, a great many scholars have found HBV-DNA or HBV antigens in the renal tissues of HBV-GN patients. Clinically, it was also found via renal needle biopsy that there are HBV antigen deposits in renal tissues in patients with nephrotic syndrome whose serum HBV markers are all negative (including HBsAg, HBsAb, HBeAg, HBeAb, HBcAb and HBV-DNA). Moreover, as HBV-DNA and HBV antigens disappear from the serum, clinical symptoms also resolve. All of the above suggest that there might be HBV-GN caused by direct HBV infection of the kidney [11-13].

Autoimmune Response

After HBV infects the hepatic cells, the antigens might undergo changes in the replication and be released into the blood with hepatic cells being destroyed, triggering auto-immune reactions. This leads to a production of multiple autoantibodies such as anti-DNA antibodies, anti-cytoskeleton antibodies, anti-smooth muscle antibodies and anti-hepatocyte membrane Lipoprotein Complex **(LSP)** antibodies. Meanwhile, there might be cross-reacting antigens in hepatic tissues and renal tissue [14]. Some researchers have also found that some aberrant immunologic phenomena are similar to those in lupus nephritis, while HBV antigens are often found via renal needle biopsy in the renal tissues of lupus nephritis patients. These indicate the potential auto-immune factors in the pathogenesis of HBV-GN.

Immunodeficiency

Immunologic abnormality is a common complication in HBV-GN patients. In general, the immune system is unable to eradicate HBV and clear some immune substances in the circulation. Moreover, HBV can attack lymph nodes at the same time and deteriorate the immunologic function, thus triggering or exacerbating HBV-GN.

Genetic Factors

Human Leukocyte Antigen **(HLA)** is the first genetic system found to be in clear association with disease. It is polymorphic, polygenic and highly specific. In recent years, the correlation of HLA genes and HBV-GN has been found, which has indicated the participation of genetic factors in the pathogenesis [15]. Until now, the research on the correlation is focused mainly on HLA-II genes together with HLA-A1, A3, A10 and HLA-B13 [16-19]. Gene frequency of HLA-A1, -A3, -A10 and HLA-II is markedly higher than that in the comparison group. In contrast, HLA-B13 as a protective gene against HBV-GN is lower.

TREATMENT

The treatment for HBV-GN consists of two main aspects: immune suppression and anti-virus therapy.

Immune Suppressive Agents

Corticosteroids Corticosteroids have been widely used for primary glomerular nephritis and have shown definite curative effect. Abundant experience has been gained from the clinical use. However, it is more complicated to treat HBV-GN with corticosteroids. In 1980s, Lai began to apply steroids to HBV-GN patients [9]. Proteinuria was alleviated and even resolved. But some scholars believe that although steroids can achieve short-term remission in some patients, they weaken the ability of the body to clear HBV in the long term and lead to massive replication of HBV in hepatic cells, resulting in more severe liver damage and even life-threatening liver failure. Nevertheless, some studies point out that the stimulation of the viral replication is mostly temporary—after reducing the doses of steroids or discontinuing the use in the late stages, the immunity of the body is gradually restored. This brings down the concentration of seral HBV-DNA and even eradicates it.

It was found in a meta-analysis study that for adult HBV-GN patients, when controlling proteinuria, there is no statistical significance in the curative effect of large doses and small doses of steroids[20]. Moreover, it is safer to adopt small doses. Thus, the majority of scholars hold the opinion that the combination of small doses of corticosteroids and immune suppressive agents and (or) anti-virus therapy can be considered in HBV-GN patients who are seral HBeAg negative, have relatively normal liver functions and negative or low HBV DNA titers. But the course of corticosteroids should not be too long, and the liver function, the kidney function, HBV DNA, hepatitis B markers should be monitored regularly when administering steroids in these patients. For patients on immune suppression therapies who are HBsAg positive, nucleosides should be taken as the anti-virus therapy one week prior to treatment even in those who are HBV DNA negative and have normal ALT levels. For patients negative for HBsAg and positive for HBcAb, the levels of HBV DNA and HBsAg should be closely monitored when administering long-term or large doses of immune suppressive agents. Anti-virus treatment should be adopted in time once

there is seroconversion [21]. In recent years, it has been much rarer to use steroids alone in the treatment of HBV-GN. More commonly seen is the combination of steroids with other immune suppressive agents and anti-HBV drugs.

Mycophenolate Mofetil (MMF) MMF is a new immune suppressive agent in recent years. It is hydrolyzed into Mycophenolic Acid **(MPA)** in vivo which can cut off the de novo synthesis pathway of guanylic acid by inhibiting inosine Monophosphate Dehydrogenase **(IMPDH)** and suppress immune reaction by inhibiting the proliferation of lymphocytes, glycosylation of Cell Adhesion Molecules **(CAMs)** and the production of specific antibodies and cytokines. MMF has been used in the therapy for refractory nephropathy and has achieved favorable effects [22], but there are few reports on its effect on HBV-GN. It has been reported that MMF combined with steroids in treating HBV-GN can effectively lower urine protein levels and raise seral albumin levels without causing HBV to replicate or aggravate liver damage. The advantages of MMF lie in the immune suppressive effect without obvious complications. It exhibits no obvious liver or kidney toxicity and relatively mild myelosuppression. No hypertension, osteoporosis or gonadal suppression is observed and the rate of infection is low. Currently, there have been some small-scale preliminary clinical trials showing the curative effect of MMF. However, further research is warranted about the course, efficacy, the occurrence of a relapse after withdrawal and the safety in long-term application.

Anti-Virus Treatment

The overall goal of treatment for secondary renal diseases is to manage the primary diseases which give rise to nephropathy rather than nephropathy alone. Secondary renal diseases are resolved with either the spontaneous clearance of HBV or clearance after using anti-virus drugs. This suggests that the core of the treatment is to terminate HBV infection. As a consequence, the emphasis of HBV-GN treatment is anti-HBV treatment with drugs such as Interferon **(IFN)** and nucleoside analogs.

Interferon (IFN) With immunomodulatory, anti-proliferation, and anti-virus effects, IFN is one of the most commonly used drugs in treating hepatitis B and HBV-GN currently. IFN-α inhibits the replication of HBV and alleviates IC-induced damage by reducing the glomerular deposition of HBeAg as well, thus achieving the goal of treatment. Researchers have shown an efficacy rate of 30% ~40% in treating HBV-related membranous nephropathy with IFNa-2b [23]. Bhimma et al. have proved that IFN-α can inhibit viral replication of HBV and decrease urine proteins [24]. However, there are various side effects of IFN which are relative to the dosage and administration time. The side effects increase along with the increased dosage or the prolonged administration time. Thus, this needs to be closely monitored when IFN is put into clinical use. In summary, though certain effects have been achieved in treating HBV-GN with IFN, more trials with large sample size and strict control are needed for further research.

Nucleoside analogs

(1) **Lamivudine** Lamivudine is the first nucleoside analog used for HBV infection. It mainly inhibits DNA synthesis and viral replication by inhibiting DNA polymerases and exhibits excellent anti-virus effect. Extensive reports domestically and abroad have shown that the clinical symptoms of HBV-GN are completely or partially resolved with administration of Lamivudine. It is one of the main anti-virus agents at present. Khedmat et al. believe that Lamivudine can effectively prevent the progress of HBV-GN. However, the drug resistance is increasing year by year and the rate of HBV gene mutation as a result of treatment is proportional to the administration time. Therefore, it is no longer recommended as a first choice, unless in a planned short-term administration. The C domain of the P gene on the negative-sense strand of HBV nucleotide sequence contains tyrosine-methionine-aspartate-aspartate (YMDD), which is the active site of reverse transcriptase encoding in the polymerase gene. Mutation of this domain is the principal reason for the appearance of lamivudine-resistant strains. Once resistance is formed, viral breakthrough occurs, and the condition of HBV-GN patients deteriorates subsequently. Adefovir, dipivoxil or entecavir should be the substitute or be used in combination with the existing treatment to control resistance.

(2) **Adefovir** The main advantages of Adefovir are that it has an inhibitory effect towards wild type HBV and mutated Lamivudine-resistant HBV as well. There are relatively less clinical reports on Adefovir treatment for HBV-GN due to the consideration of its potential renal toxicity. Thus, caution must be given in applying the drug.

(3) **Telbivudine** Telbivudine is an artificially synthesized thymidine analog which can effectively inhibit HBV replication and increase seroconversion rate of HBeAg. Moreover, the preservation time of seroconversion is longer after withdrawal of telbivudine. Many studies indicate that the performance of telbivudine regarding both the overall efficacy in inhibiting HBV replication and the occurrence of resistance outdoes Lamivudine [25-28]. However, there is cross resistance in these two drugs. Telbivudine is not allowed in patients who have developed lamivudine resistance. With the clinical application of telbivudine in recent years, researches show that it elevates Glomerular Filtration Rate **(GFR)** in chronic hepatitis B patients and improves the kidney functions as a result [29-34]. Therefore, telbivudine can be used in HBV-GN treatment. Due to the scarcity of relevant studies, more researches are warranted for further verification. The incidence rate of overall adverse events of telbivudine is similar to lamivudine, but the former is more likely to increase Creatine Kinase **(CK)** levels. Attention must be paid to the occurrence of myopathies.

(4) **Entecavir** Entecavir is a new type of anti-virus drug in recent years. It effectively inhibits the replication of viral DNA and has shown favorable curative effect clinically in controlling and treating various HBV-induced diseases including hepatitis B and HBV-GN. Entecavir is less likely to result in viral resistance and performs rather well in controlling viral mutation rate. Moreover, it has been used as one of the first-line drugs for hepatitis B as well as multiple HBV-induced

diseases in that it has low and even no renal toxicity. In recent years, there have been large amounts of clinical researches showing the favorable effect of entecavir in treating HBV-GN. The positive anti-HBV effect of entecavir and its anti-mutation effect without renal toxicity have been widely recognized in clinical fields, and the efficacy and safety are definite.

(5) **Tenofovir disoproxil fumarate** This is a new type of Nucleoside Reverse Transcriptase Inhibitor **(NRTIs)**. Tenofovir diphosphate, the active ingredient of tenofovir, can competitively inhibit the polymerase of the virus by directly binding to the substrate natural deoxyribose, and terminate the synthesis of DNA strain by inserting itself into it. Clinical studies show that tenofovir has encouraging anti-virus effect on HBV infection, combined HBV and HIV infection and on patients who are lamivudine-resistant [38]. The latest research also shows that when applied alone, tenofovir exhibits a high efficacy and performs well in inhibiting the virus as well. Tenofovir disoproxil fumarate resembles adefovir dipivoxil in structure, but has stronger effect in inhibiting HBV and less renal toxicity compared to the latter. No drug resistance mutation has been found to be relevant to tenofovir disoproxil fumarate yet. It can be used in combined or alternative treatment if other nucleosides prove to be ineffective due to resistance. However, this drug is not commonly used in clinical settings at present.

Combined Treatment

Generally, the treatment for HBV-GN involves the treatment for liver diseases and renal diseases at the same time. Extensive studies have proven the limitation of single drug treatment. Moreover, recrudesce is more likely to occur in single drug treatment. Therefore, combined treatment with two or more than two drugs has been the hotspot of study in recent years. The most commonly used drug combination for treatment now includes anti-virus treatment with steroids and other immune suppressive agents. In a recent meta-analysis study on combined anti-virus and immune suppressive treatment in adult HBV-GN patients, it was found that this combination can improve proteinuria in HBV-GN patients without altering HBV replication or causing liver and renal damage[20]. The combined treatment with anti-virus drugs and immune suppressive agents has demonstrated high efficacy as well as reliable safety. Symptomatic treatment including diuresis, detumescence, function preservation and anti-coagulation can also be given when necessary.

SUMMARY

Although HBV-GN is a common disease in clinical settings, the mechanism is not clear yet. Controversies over the therapeutic regimen still exist. Currently, IFN, nucleoside analogs, steroids, immune suppressive agents and other drugs are mostly used in combination. Symptomatic treatment such as liver preservation, diuresis and anti-coagulation are adopted and relevant physiologic or biochemical indices are closely monitored at the same time. Further research and observation with randomized controlled and multi-center trials are needed to elucidate the mechanism and pave the way for novel treatment approaches in the future.

ACKNOWLEDGEMENT

This work was supported National High Technology Research and Development Program of China (863 Program) (2012AA021008) and the Guangdong Provincial Key Laboratory on Organ Donation and Transplant Immunology (2013A 061401007).

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