REVIEW ARTICLE

HEPATITIS VIRUS AND KIDNEY

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ABSTRACT

Hepatitis A, B and C viruses are major causes of viral hepatitis in human. These infectious agents not only damage liver parenchyma but can also affect renal parenchyma. Hepatitis A virus could produce acute renal failure in a similar fashion to hepatorenal syndrome. Several lines of evidence have shown that chronic hepatitis B virus-infected patients could develop immune complex glomerulopathy. There are convincing data which incriminate hepatitis C virus as the proximate aetiology of certain forms of glomerulonephritis. In post-renal transplanted patients, hepatitis B and C virus could cause increased morbidity and mortality from chronic viral hepatitis. Whether renal transplantation should be performed, either as a donor or as a recipient, in subjects infected with hepatitis B or C virus, is still an issue of controversy.

Keywords: hepatitis A, hepatitis B, hepatitis C, renal failure, glomerulonephritis, post-renal transplantation

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INTRODUCTION

Hepatitis A, B, C, D and E virus are well established hepatotropic viruses. In the field of nephrology, hepatitis A, B, and C virus (HAV, HBV, and HCV respectively) can cause a variety of pathological changes in the kidney, including abnormal renal function and various pathological lesions in the glomerular structure. HAV may cause acute renal failure, which can occur irrespective of the degree of liver damage injury caused by the viral agent. There are scarce data regarding glomerulonephritis caused by HAV. Liver abnormalities caused by HBV and HCV infection in renal transplanted patient are one of the most important complications in post-transplantation period and can cause a significant loss of graft function[1]. An increased death rate becomes apparent in 8 to 10 years after renal transplantation in patients with chronic viral hepatitis[1]. Progression of HBV-induced liver disease is more than that of HCV after transplantation.

Hepatitis A

Hepatitis A virus (HAV) which belongs to the Picorna virus family, is a non-enveloped 27 nm RNA virus, and is resistant to heat, acid, and ether. The incubation period of HAV infection is approximately 4 weeks. The virus is present in the liver, bile, stool, and blood during the late incubation period and during the acute preicteric phase of illness. Viremia and infectivity of HAV infection diminish rapidly once jaundice becomes apparent. These occur despite the persistence of virus in the liver and viral shedding in the faeces. HAV infection has a more benign course as compared to that of HBV infection[2]. Regarding HAV-related renal disorders, fulminant hepatitis A could produce renal failure in a similar fashion to hepatorenal syndrome. There have been, however, several reports of acute renal failure developing in the patients with non-fulminant form of hepatitis A infection[3-5]. In addition, HAV infection accompanied by G6PD deficiency may cause massive intravascular haemolysis and acute renal failure[6]. Pathological studies have shown no apparent renal histological changes in some patients while tubular necrosis is detected in others. At present, the mechanism of HAV-induced renal failure is still not well-established. Various non-specific factors in inflammation which lead to renal ischaemia superimposing on hepatic dysfunction might produce renal failure.

An association between HAV and glomerulonephritis has not been demonstrated. Recently, there was a case report of a 9-year-old boy who simultaneously developed inapparent HAV infection and glomerulonephritis. The diagnosis of HAV infection was confirmed by the finding of serum anti HAV IgM. Recovery of both HAV infection and glomerulonephritis was uneventful[7].

Hepatitis B

Hepatitis B virus (HBV) is a 42 nm virion which can be disrupted by mild detergent, leading to isolation of 27 nm nucleocapsid core particle. Naked core particle does not circulate in the serum but resides in the liver cell. The antigen expressed on the surface of the nucleocapsid core particle is designated as hepatitis B core antigen (HBcAg). Hepatitis surface antigen (HBsAg) is a soluble antigen, 27 nm in diameter, and is constituted as a marker for chronic HBV infection. The third antigen associated with hepatitis is hepatitis B "e" antigen (HBeAg). HBeAg is a soluble, nonparticulate antigen which is found only in HBsAg-positive serum. This antigen is immunologically and biochemically different from HBsAg and HBcAg but appears to be an internal component or a degradation product of the core of HBV. It appears that HBsAg-positive serum containing HBeAg has the higher infectivity and is more likely to be associated with the presence of hepatitis virion (DNA polymerase and HBV-DNA) when compared to HBeAg negative serum[8].

HBV infection is worldwide in distribution with low carrier rates in the Western countries. The prevalence of the HBsAg carrier varies from 0.3% to 1% in North America to 1% in Western Europe; 5% in South America, Eastern Europe, Japan and Western Asia; 7% in Africa; and 10% to 20% in China, Taiwan, and South East Asia[9].

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HBV-associated glomerulopathy

The pathogenetic role of HBV in glomerulonephritis is the topic of great interest. The observation of a high incidence of HBsAg carriers among the patients with various forms of glomerulonephritis when compared with the general population tends to support the role of HBV in the pathogenesis of glomerulonephritis.

The association between chronic HBV infection, characterised by persistent HBV antigenemia, and renal disease was first reported in 1971[10]. A case of a 53-year-old man with persistent HBV antigenemia, known at that time as Australia (Au) antigen, developed nephrotic range proteinuria. Subsequent renal biopsy revealed membranous glomerulonephritis. Immunofluorescent staining showed glomerular deposits of IgG, complement C_3, and Au antigen in a pattern characteristic of immune complex deposition. Since then, various morphological patterns of HBV-related renal diseases including membranous nephropathy, membranoproliferative glomerulonephritis, and mesangial proliferative glomerulonephritis have been described [11-13]. Among various glomerular lesions described in HBV-associated glomerulopathy, membranous nephropathy is the most recognised pathology. The clinical renal manifestations of this HBV-associated glomerulopathy include nephrotic syndrome, proteinuria, or chronic renal failure[13].

An association between HBV and macroscopic polyarteritis nodosa (PAN) also is well documented. Macroscopic PAN is an immune complex-mediated disease involving medium-sized arteries. The disease can lead to renal infarction and microaneurysm. A case of HBV-related PAN with nephrotic syndrome has been reported, and membranous nephropathy has been subsequently diagnosed by renal biopsy. From literature review, however, HBV-related PAN rarely occurs simultaneously with HBV-associated glomerulopathy[14].

Pathogenesis of HBV-associated glomerulopathy

Several lines of evidence have shown that HBV-associated glomerulopathy is an immune complex glomerular disease. By immunofluorescene study, granular immune deposits with HBV-related antigen-antibody complex have been demonstrated. Several HBV antigens including HBsAg, HBcAg and HBeAg have been detected in the circulating immune complexes and in the granular immune deposits in the kidneys of patients with HBV-associated glomerulonephritis[15]. Among three different HBV antigens identified, HBeAg has been shown to have the most important role in subjects with chronic HBV infection who have membranous nephropathy. The accumulation of HBeAg-anti HBe immune complex has been demonstrated in the glomeruli of HBV-associated glomerulopathy. Thus, HBV infected person with high viral replication may have a higher risk to develop HBV-associated glomerulopathy. Moreover, electron-microscopic examination identifies spherical virus-like particle located within subepithelial deposit in HBV-associated membranous nephropathy.

A recent in situ hybridization study has shown the presence of HBV-DNA in the kidney glomeruli and tubular epithelia. The detectable rate is correlated with the time-course of the disease, the duration of proteinuria. The rate of detection also is higher in the patients who progress to end-stage renal disease (ESRD). It appears that the persistent existence of HBV-DNA in the tubular epithelium would be the potential risk of viral DNA replication of HBV and, thus, could enhance tubular interstitial damage, leading to progression of renal disease[16].

Natural course and treatment of HBV-associated glomerulopathy

Despite a good documentation of the pathological features of HBV-associated glomerulopathy, the natural history of this disorder and the role of therapy with antiviral agents have not been fully delineated. In paediatrics group, retrospective data from 6 studies of a total of 66 boys and 16 girls have shown that spontaneous regression of the nephrotic syndrome can occur in 60% of patients within 12 months after diagnosis[13,17,18]. The remaining patients have persistent proteinuria, 6 (7.3%) have chronic renal failure, and 2 (2.4%) have end-stage renal failure. Analysis of the data in these studies has demonstrated that HBeAg plays an important role in the development of HBV-associated membranous nephropathy. HBeAg-anti HBe antibody immune complexes can produce subepithelial deposition in the kidney, the deposition of which is correlated with the aggressiveness of the disease. Spontaneous remission of nephrotic syndrome is associated with the clearance of HBeAg[19].

In adult group, the natural course is different[13]. In contradistinction to the finding in children, spontaneous remission of proteinuria or nephrotic syndrome does not occur in adult patients. There are some reports showing that proteinuria tends to decrease with time, though[20]. Furthermore, complications related to overt nephrotic syndrome such as thromboembolic disorders are common. Data show a slow and relentless progression to chronic renal failure in 29% of patients with HBV-associated glomerulopathy and 10% of such cases after an average duration of 6 years may require dialysis therapy[21,22]. Treatment of HBV-associated glomerulopathy with prednisolone has been shown to be deleterious, inducing viral replication in the liver[17,20]. This could cause acute viral hepatitis, chronic active hepatitis or even fatal fulminating viral hepatitis. The attenuation of progression to chronic azotemia and the anecdotal observation of improved renal and liver function after the successful treatment of HBV infection with interferon have been recently reported[21-23]. Earlier studies have shown therapeutic benefit from using interferon in inducing remission in HBV-associated glomerulopathy[23-25]. Subsequent studies, however, have shown a reverse effect, occurring particularly in patients in HBV-endemic areas[26]. The discrepancy of clinical responses between patients with HBV-associated glomerulopathy living in HBV-endemic areas and those residing in non-endemic areas might be due to the difference in duration of integration of HBV-DNA into host-cell chromosomal DNA. Patients in the former group have acquired the infection since early childhood, thus, interferon therapy is likely to be less effective. The doses of interferon used in various studies range from 5 to 10 milliunits, subcutaneously, thrice weekly, with a duration of 6-12 months. The effectiveness of treatment in the responded cases is usually associated with the seroconversion of HBeAg and/or HBsAg. Further clinical assessments of therapy with higher dose interferon with and longer duration are strongly indicated in patients in HBV-endemic areas.

Hepatitis C

Prior to 1975, only HAV and HBV have been recognised as infectious causes of viral hepatitis[27]. Non-A, and non-B hepatitis was first described in 1975 when a substantial number of post transfusion hepatitis cases could not be ascribed to HAV or HBV infection. After more than a decade of uncertainty regarding the causal agent of parenteral hepatitis or non-A, non-B (NANB) hepatitis virus, hepatitis C virus (HCV) was cloned in 1988 from a copy DNA extracted from infectious chimpanzee plasma. HCV was subsequently shown to be the cause of NANB hepatitis in over 90% of cases[28].

Virology of HCV[29]

HCV, a 30-38 nm single-stranded DNA virus of the Flaviridae family, is encircled with lipid structure around inner core. The

genome of the virus consists of 9379-9481 nucleotides (Fig 1). HCV genome can be divided into 2 regions, a constant 5' terminal region (329-341 nucleotides) named "conserved region" and a variable 3' terminal region which can transcribe structural and nonstructural proteins. Structural region will transcribe core glycoprotein p21 and envelope glycoprotein gp31 and gp70. Non-structural region (NS_2, NS_3, NS_4, NS_5) will code replication enzymes such as protease, helicase, replicase, and polymerase. Certain genomes between structural and nonstructural region, called "hypervariable region (HVR)", are sensitive to sequential mutation and thus could cause viral escape phenomenon. This phenomenon might explain the persistence of HCV infection and the ineffectiveness of humoral antibody to eliminate the virus.

Diagnosis of HCV infection[29,30]

Antibody screening test

HCV antibody screening tests have been sequentially developed from anti HCV immunoassay (enzyme-linked immunosorbent assay or ELISA) to assay various recombinant polypeptides encoded from different parts of HCV genome. On developmental basis, HCV antibody screening tests can be categorised into 3 groups:

1) First generation ELISA. The test detects antibody to C-100-3 polypeptide encoded from genome NS_4.
2) Second generation ELISA. The test detects antibody to C-200 polypeptide encoded from NS_3, NS_4, and core protein.
3) Third generation ELISA. The test detects antibody to protein encoded from NS_3, NS_4, NS_5, and core region.

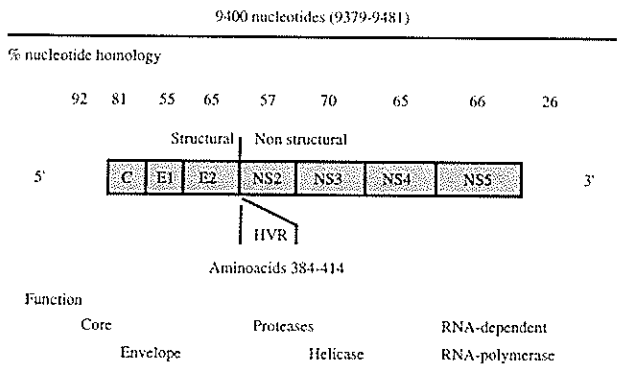
In general, seroconversion of anti HCV occurs 3-6 months after exposure to the virus. Under immunosuppression state, however, the seroconversion will be delayed or cannot even be found. The second and third generation tests are generally more sensitive than the first. It should be noted that IgMAb has no role in the diagnosis of acute HCV infection.

Confirmatory test

For confirmation of the positive results of anti HCV ELISA tests, recombinant immunoblot assay (RIBA) has been developed. HCV antigens are applied separately on nitrocellulose stripes and, after incubation with patient's serum, the anti-HCV antibody recognition patterns are made visible. RIBA test is indicated when screening Ab tests show indeterminated results. The test, however, can give false positive results in patients with positive rheumatoid factor, positive superoxide dismutase antibody, and hyperglobulinemic state.

The other confirmatory test is polymerase chain reaction (PCR). The application of PCR technique to amplify reverse transcribed cDNA has provided a sensitive assay capable of detecting small number of viral RNA molecules in blood or tissue specimens. PCR is used to diagnose early HCV infection and to study the viral load response to antiviral drugs.

Fig 1 – Virology of hepatitis C virus.



C = core glycoprotein p 21, E_1 = envelope glycoprotein gp 31, E_2 = envelope glycoprotein gp 70, NS = nonstructural region, HVR = hypervariable domain

Epidemiology

HCV infection is encountered worldwide with high prevalence in Japan, Africa, and Middle East where 0.5%-1.5% of blood donors are anti HCV positive. The incidence, however, is lower in USA and Canada, ranging from 0.01%-0.05%. The incidence of anti HCV positive by second generation ELISA in Thai blood donors studied in 1992 was 2%-3.3%[29].

The main route of HCV transmission is parenteral, and most HCV infected individuals are either intravenous drug users or recipients of blood products that in the past had not been screened for anti HCV[31]. Other parenteral risk factors include tattoo and needle-stick accidents among healthcare workers. Needle-stick accidents from patients with HCV viremia lead to HCV transmission in only 3%-10% of cases, the magnitude to which is much lower when compared to 67% in the case of HBV transmission (HBeAg positive)[29]. Vertical transmission of HCV infection has never been proven[32]. Sexual transmission of HCV is probably absent or rare[33].

Intervention with either passive or active immunisation for prophylaxis of HCV infection is not available. At present, there are no data regarding the effectiveness of early treatment with interferon in patients infected by blood products. Precaution to prevent HCV infection in risky situations should be emphasised.

HCV is related to various renal abnormalities. Chronic haemodialysis and continuous ambulatory peritoneal dialysis (CAPD) patients have high incidence of HCV infection[27]. A body of evidence also has shown that HCV plays an important role in liver dysfunction detected in post-renal transplanted recipients[28]. Furthermore, HCV infection may be the proximate aetiology of certain types of glomerulonephritis.

HCV in chronic dialysis

The incidence of anti HCV positivity in chronic haemodialysis patient ranges from 5% to 54%, depending on studies[27]. Two major factors contributing to this high incidence are blood transfusions and duration of dialysis. Numerous studies have reported a direct association between the number of blood transfusions and the prevalence of anti-HCV among haemodialysis patients. The prevalence of anti-HCV detection declines after the blood products are routinely screened for this antibody by the blood bank.

The association between the duration of dialysis and the increased prevalence of anti-HCV has been confirmed. If the length of time on dialysis is an independent predictor of anti-HCV status, then nosocomial transmission of HCV in dialysis setting should be considered as the proximate cause of the infection. Studies of genotype of HCV have shown the same genotype among patients in the same dialysis unit[34]. It is believed that the process of reused dialyzer or that of preparation of blood line equipment may be responsible for this nosocomial transmission. There is still no specific recommendation from the center of disease control (CDC) for dialysis unit regarding to haemodialysis procedure in caring of patients with anti-HCV positivity. Generally, HCV positive haemodialysis patients should be dialysed with precautions as for hepatitis B positive patients.

HCV and renal transplantation

HCV is an important cause of liver disease, a major complication in renal transplant patients[35]. Several studies have shown that approximately 60% of renal transplanted recipients with

abnormal liver function test (LFT) have positive anti-HCV[1].

Pathologic studies of the liver in renal transplanted recipients with positive anti-HCV have demonstrated several hepatic pathologies including cirrhosis, chronic active hepatitis, chronic persistent hepatitis in 74% cases[36]. In studies comparing the severity of liver pathology in HBV and HCV infections of post-renal transplanted patients, HBV infected patients have chronic persistent hepatitis at 17%, chronic active hepatitis at 14%, and cirrhosis at 19%; whereas HCV infected patients have chronic progressive hepatitis at 38%, chronic active hepatitis at 38%, and cirrhosis at 42%[37-39]. These data suggest that progression of HBV-induced liver disease is greater than that of HCV after transplantation. Despite the potential nature of progression observed in these studies, most cases of serious liver diseases in transplanted recipients are caused by HCV[39]. At present, there are no available data to explain the underlying mechanism of this observation.

The incidence of HCV infection in post-renal transplanted recipients is equal to that in chronic haemodialysis patients[27,28]. The seroprevalence and anti-HCV titer, however, decline with time post-transplantation. The possible explanations for these observations are the simultaneously decreased frequency in both blood transfusion and administration of immunosuppressive drug.

Anti-HCV titre, thus, is not a sensitive marker to follow the activity of HCV infection. In anti-HCV-positive patients, liver biopsy is recommended in defining liver prognosis and in adjustment of the use of immunosuppressive drugs which may cause viral replication and exacerbation of liver parenchyma injury[27]. Because of the markedly immunosuppressive effect of the drug, anti-lymphocyte globulin (ALG)[28] should be avoided in renal transplanted recipients with HCV infection. HBV and HCV coinfections can occasionally occur in renal transplanted recipients. Previous studies have shown that severe morbidity from liver function abnormalities and mortality from liver cirrhosis are increased in the coinfection when compared to either HBV or HCV infection alone.

Potential recipient or donor with positive anti-HCV

Although HCV infection could cause increased morbidity and acute rejection in post renal transplanted recipients, most of the studies have shown similar renal graft survival between those with and without infection. End-stage renal disease with HCV infection, therefore, is not an absolute contraindication for renal transplantation. It is, however, necessary to balance between the risk and benefit of each immunosuppressive drug which may affect liver function. For example, azathioprine at dose of 2-4 mg/kg body wt/day may cause hepatic occlusive disease, peliosis hepatitis, perisinusoidal fibrosis, and nodular regenerative hyperplasia. In multiple drug therapy regimen, using a lower dose of azathioprine also is effective and can minimise the above side effects of this drug[40].

To further minimise the morbidity in potential recipients who have HCV infection, liver biopsy should be examined. Severe liver pathology, particularly chronic active hepatitis, should be treated with interferon before undergoing renal transplantation[38].

The use of interferon, 2.5-3 million unit subcutaneously thrice per week, in chronic haemodialysis has been shown to be safe and effective to halt parenchymal liver lesion, leading to improvement in liver function. Pharmacokinetic studies have demonstrated that the half life of interferon in chronic renal failure is not different from that in normal renal function patients[41].

Whether the kidney from anti-HCV positive donor should be transplanted or not is still unestablished[42-44]. Incidence of donors with anti-HCV positivity ranges from 0.5% to 6%, depending on studies[45]. Cadaveric donors have a higher incidence of HCV infection than living related ones. Follow-up studies in recipients who obtain anti-HCV positive donors have shown conflicting results. Some reports have shown no liver diseases complications in transplanted recipients whereas the incidence of liver abnormalities can be 48% in one study[46]. Further well-designed prospective studies using appropriate methodology should be encouraged to delineate this bewildered issue.

According to recent surveys conducted in the United States of America, most renal transplantation centres have not used kidneys from anti-HCV positive donor[43,46]. In Europe, it is advisable to use anti-HCV positive kidney only for seropositive recipients. Considering the shortage of allograft kidney, the anti-HCV positive kidney may be transplanted to the anti-HCV positive recipient, or to the recipient who has been in the waiting list for longer than 5 years and has the full house HLA match (A, B, and DR antigen)[43].

HCV-associated glomerulonephritis

A line of evidence has shown that HCV may cause various renal abnormalities including glomerulonephritis and essential mixed cryoglobulinaemia (EMC)[47].

Recent studies have demonstrated that membranoproliferative glomerulonephritis (MPGN) type I and membranous nephropathy (MN) may be related to HCV infection[48,49]. Membranoproliferative glomerulonephritis type I is a primary glomerular disease characterised by mesangial cell proliferation, and depositions of IgM, IgG, and C_3 in capillary wall. By electron microscope study, these depositions are located in subendothelial area.

Incidence of anti-HCV positivity in EMC patients is as high as 69% in some reports[27,28]. The clinical syndrome of EMC is characterised by weakness, arthralgia and purpura. "Cryoglobulinaemic glomerulonephritis", an immune complex-mediated condition, may occur in some patients.

Pathogenesis of HCV-associated glomerulonephritis

The pathogenesis of HCV-associated glomerulonephritis has been widely believed to be due to the deposition of circulating immune complex. Indirect evidence suggests that HCV-associated MPGN and HCV-associated cryoglobulinemic glomerulonephritis are caused by the deposition of circulating immune complexes containing HCV, anti-HCV IgG, and rheumatoid factor[50]. Circulating cryoglobulin consisting of HCV-RNA and anti-HCV has been demonstrated[51]. Cryoglobulin-like structures have been observed in glomeruli from some patients with HCV-associated glomerulonephritis. Demonstration of HCV-RNA in the glomeruli, however, has remained elusive. Analysis of immune complex has shown the absence of HCV-RNA in antigen-antibody deposition. It is postulated that the antigen detected in immune complex may be tissue antigen synthesised from cytopathic effect of HCV[27,28].

The role of auto-antibodies to glomerular antigen is recently postulated[50]. Auto-antibodies are frequently demonstrated in chronic HCV-infected patients[52]. These antibodies may play an important role in the pathogenesis of HCV-associated membranous glomerulopathy that is not associated with cryoglobulinaemia or with the presence of rheumatoid factor[48].

There are no effective modalities of treatment for HCV-associated glomerulonephritis. Anecdotal case reports of treatment with interferon in various doses and various durations with promising results have been reported[53]. Significant alleviation of proteinuria and resolution of renal pathology have been demonstrated although relapse of HCV-related MPGN can occur.

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