REVIEW ARTICLE

HEPATITIS C VIRUS INFECTION IN PATIENTS WITH CHRONIC KIDNEY DISEASE - A REVIEW

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ABSTRACT

Viral infections contribute greatly to the high global burden of chronic kidney disease (CKD) especially in parts of the world where the prevalence of glomerulonephritis is high. These infections pose special challenges in the management of patients throughout the spectrum of chronic kidney disease. Hepatitis C Virus infection in patients with chronic kidney disease could be coincidental or be responsible for the CKD. The observance of universal principle against transmission of blood borne infections remain the single most effective tool to stop the tide of increasing HCV infection in CKD patients. Combination therapy using nucleoside analogue, ribavarin and interferon's offers the only real chance of treating HCV infected patients.

Keywords: *HCV infection, Chronic Kidney Disease, Dialysis, Transplantation*

INTRODUCTION

Hepatitis C virus (HCV) was first identified in 1989 and was recognized as the primary cause of non-A/non-B hepatitis and since then its existence in patients with kidney failure has been established.[1] This relationship could be causal, a complication or coincidental finding. Infection with HCV is a significant cause of membranoproliferative glomerulonephritis (MPGN), especially in countries where HCV is highly prevalent.[2] Hepatitis C virus infection could also be a complication of end-stage renal disease especially in those who have had transfusion with hepatitis C-infected blood, blood products or renal transplant.[3]

The spread of HCV in renal patients on haemodialysis has been reported not to occur via the haemodialysis machine but is presumably carried over by medical personnel in spite of preventive measures.[5,6] When every effort is made to reduce potential person-to-person transmission, the rate of new infection can be reduced to virtually nil.[7] It has also been reported that the rate of anti HCV positivity is related to the length of time on dialysis treatment and number of blood transfusions.[8]

The increasing use of third generation immunoassay for the determination of antibodies to hepatitis C virus in serum and plasma has reduced the rate of its transmission through blood and blood products to patients with kidney disease and the general population.[4] This third generation immunoassay has a sensitivity of 98% and specificity of about 99.8%.[4]

EPIDEMIOLOGY OF HEPATITIS C VIRUS INFECTION

There are about 150 million chronic HCV carriers throughout the world with an estimated prevalence of 3%.[9] In Africa epidemiological data are deficient but a prevalence of 6% has been documented.[10,11]

Following exposure to hepatitis C virus, approximately 85% of individuals develop chronic infection.[12] Transmission of HCV takes place most readily through serum.[13] Sexual transmission is rare because of the usually low level of viraemia. Vertical transmission is possible with marked viraemia.

Factors associated with poor prognosis for chronic HCV infection include male gender, age at HCV acquisition of more than 40 years, alcohol consumption, iron overload, high titres of viral ribonucleic acid (RNA), immuno-suppression and high serum gamma glutamyl transferase and bilirubin levels.[13,14] Hepatitis C viral infection is an important cause of membranoproliferative glomerulonephritis (MPGN), especially in countries where HCV is highly prevalent. The virus is present in about 60% of patients with MPGN in Japan and in 10 - 20% of patients with MPGN in the United States.[2] The greater prevalence of MPGN in some developing countries may be due to greater prevalence of chronic HCV infection.[2] HCV infection has also been reported to be present in about 7 - 9% of patients with kidney failure who have not undergone dialysis and who have no history of blood transfusions.[15] Nosocomial transmission of HCV during dialysis may occur, independent of blood transfusions.[15]

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PATHOGENESIS OF HCV INFECTION

It is postulated that HCV infects circulating B lymphocytes[16] and stimulates them to synthesize the polyclonal IgM rheumatoid factor (RF) responsible for type III mixed cryoglobulinemia. In some patients, additional factors such as superimposed infection with other viruses (eg hepatitis B virus, Epstein-Barr virus) might induce a shift to abnormal proliferation of a single clone of B cells that produces monoclonal IgM-Kappa RF, thus inducing type II mixed cryoglobulinemia. IgM-Kappa RF binds avidly to anti-HCV IgG or to the IgG-HCV immune complex. These circulating immune complexes concentrate in glomerular capillaries, where they are mostly deposited in the sub endothelium and mesangium and initiate cellular proliferation and leukocyte infiltration.

Chronic HCV infection may produce autoantibodies to native renal antigens, which may account for some of the immune mediated glomerular damage.

MOLECULAR BIOLOGY OF HCV

Molecular studies of the HCV genome have shown that it is a virus with a single RNA chain,[17] and similar organization to that of the flavivirus family, to which it belongs. Other viruses in the group include dengue virus, yellow fever virus and Japanese encephalitis virus. Viral structure is spherical, with a lipo-protein capsule and a diameter between 35 and 50nm.[18] Currently more than 10 variants of the virus, which share from 55 - 72% of their amino acids, have been described. These variants are pooled in accordance with the classification by Simonds, *et al*[19] into six different genotypes (1-6), which are subdivided into various subtypes according to how they were described (a,b,c, etc.). In Nigeria, a pilot survey in healthy adult donors and children of pre-school age showed genotypes 1a, 4, and 1d to be the dominant subtypes.[20] The important fact is that there are remarkable differences in HCV subtype pathogenicity, as well as in the response to interferon treatment.[21]

HCV is constituted by an RNA genome of approximately 9400 nucleotides. The translator region codes for a protein of 3010 or 3011 amino acids, suggesting that the non-transcribed regions at the 5' end and 3' end are very short. Region 5' varies from 324 to 341 nucleotides and has conservation greater than 97%.[22] Slight differences in this region, however, have been used to determine the virus genotype by the polymerase chain reaction (PCR).[19] This region is important in virus transcription control and pathogenesis.[23]

LABORATORY FINDINGS

Mixed cryoglobulins containing polyclonal IgG and monoclonal IgM rheumatoid factor (RF) (usually IgM-Kappa RF) are present in the serum. These elements are measured as cryocrit. The amount of circulating cryoglobulins varies among patients as well as in individual patients at different times (range, 20 - 70%). Mixed cryoglobulinaemias may be temporarily undetectable during the course of the disease. A weak correlation exists between the amount of circulating cryoglobulins and the severity of renal disease.

Very low levels of early components, including C4, C1q, and CH50, characterize serum complement pattern; C3 levels are in the normal range or only slightly lower. Serum complement pattern, which does not vary much in relation to changes in clinical activity, is characteristic of cryoglobulinaemic glomerulonephritis.[24]

Serum levels of anti-HCV and HCV RNA are detected by reverse transcriptase polymerase chain reaction. These components are found in high concentration in cryoprecipitate as well. Classic membranous glomerulonephritis usually is associated with normal complement levels, normal liver function, absence of RF, and cryoglobulinaemia.

HCV antibody detection and viral RNA qualitative amplification are currently used to diagnose HCV infection. The detection of antibodies against the virus is performed through the Enzyme-Linked immunosorbent Assay (ELISA), which allows identification of antibodies to the viral proteins. The first-generation assays (ELISA I) [25] detects antibodies to the protein NS4, ELISA II detects antibodies to core protein and NS3,[26] and ELISA III detects NS5.[27] The low sensitivity and specificity of the first generation assays led to the evolution of better ELISA tests.[28] In this way, the addition of antigens increases the sensitivity and specificity of the assays. ELISA I, for example has sensitivity ranging from 46 to 89%, taking PCR as the gold standard. In contrast, ELISA II has sensitivity of 93% and specificity of 92%.[28]

Another way of determining the presence of HCV-Ab is the recombinant immunologic bioassay (RIBA) which detects antibodies to antigens NS4 ($_c$ 100-3 and 511), NS3 ($_c$ 33), core ($_c$ 22-3) and NS5. The reaction is only positive, however, when there are two or more antigens. It is indeterminate if there is only one, and with none, it is negative. This results in a very specific test (94%), but with low sensitivity (86%), thus it is mainly used to confirm positive result of ELISA, because false positives are very frequent especially in patients with autoimmune hepatopathies.[28]

The most important diagnostic problem of hepatitis C virus infection derives from the viral structure, since the RNA genome makes it difficult to determine its presence directly. This is possible, however, using molecular biology as a diagnostic tool. In this way, the combination of serum RNA extraction, reverse transcription and PCR (RT PCR) allow the identification of

the virus by amplifying an HCV genome region, which is usually the non-transcribed zone 5, since it is the best conserved.[29]

RENAL INVOLVEMENT IN HEPATITIS C VIRAL INFECTION

Although renal involvement is common in hepatitis C, absence of clinical manifestations means it may go undiagnosed in the majority of patients. Renal involvement can occur early in the course of the disease and occasionally is the presenting symptom of HCV infection.[30] Cryoglobulinaemic glomerulonephritis is diagnosed between the fifth and sixth decades of life in most patients, and it occurs slightly more often in women than in men.[30] Only about 20% of patients with cryoglobulinemia have physical signs of liver disease at the time of presentation, but the majority of patients (about 70%) have mildly elevated aminotransferase levels and evidence of liver involvement on biopsy.[31]

Hypertension is present some of the patients at the onset of renal disease; it is often severe and difficult to control. It may have an accelerated course in patients who are predisposed to cardiovascular and cerebrovascular events.[31]

Renal disease occurs in about half of patients with mixed cryoglobulinemia associated with HCV infection.[32] These patients present with palpable purpura, arthralgia, neuropathy, and abdominal pain secondary to mesenteric vasculitis. Such symptoms of mixed cryoglobulinaemia often manifest years before a diagnosis of renal disease is made, but in some patients, renal and extra renal manifestations appear concurrently. In a few patients, symptoms of mixed cryoglobulinaemia are absent.[33]

The most common presenting clinical syndrome is an isolated proteinuria with microscopic haematuria, which is associated with moderate renal insufficiency in about 50% of cases.[24,34] About 25% of affected patients present with nephrotic syndrome. These patients do not have circulating cryoglobulins. Acute nephritis characterized by rapid deterioration of renal function, proteinuria in the non-nephrotic range (protein, <3.5 gm/24 hr), and haematuria is present at onset in 20 - 25% of patients. This acute nephritic syndrome usually occurs concurrently with acute flare-ups of systemic signs of mixed cryoglobulinemia. Massive precipitation of cryoglobulins in the glomerular capillary lumen with consequent severe monocyte infiltration, often with signs of systemic and renal vasculitis, is responsible for this syndrome. Acute nephritis is often complicated by oliguric renal failure, which is reversible with timely treatment using corticosteroids and cyclophosphamide.

The course of renal disease is variable. Partial or complete remission of renal symptoms is seen in nearly one third of patients even in patients who present with acute renal failure or severe nephrotic syndrome.[35] In another 30% of cases, renal disease has a rather indolent course and does not progress to renal failure for several years, despite the persistence of urinary abnormalities and mild renal dysfunction. In the remainder of patients, multiple reversible clinical exacerbations, such as acute nephritis and nephrotic syndrome, occur during the course of the disease. These acute flare-ups are usually associated with intensification of the systemic signs of the disease.[24]

Progression to end-stage renal failure that requires dialysis is relatively rare (about 10% of cases), even many years after the onset of renal disease.[35] The majority of these patients die of cardiovascular disease, systemic vasculitis, or infection before they reach end-stage renal failure. End-stage renal disease is more likely to develop in older patients and in patients with recurrent purpura, renal biopsy finding of marked monocytic infiltration, a high serum cryocrit (the amount of cryoglobulins circulating in the bloodstream), viraemia, proteinuria, and a high serum creatinine level at presentation.[36]

Most patients with HCV associated membranous nephropathy present with overt nephrotic syndrome; while a few have isolated proteinuria in the non-nephrotic range. Periodic monitoring of renal function and proteinuria should be performed in all patients with HCV infection. Once renal disease manifests, renal biopsy is needed to identify the type of glomerular lesion present and define management modalities.

HCV INFECTION IN PATIENTS WITH KIDNEY FAILURE

The development of haemodialysis, peritoneal dialysis and renal transplantation has considerably improved the life expectancy of patients with chronic kidney failure, a situation that has however, led to the emergence of various diseases, including viral hepatitis B and C. This seems to be a consequence of blood transfusion and, in the case of patients undergoing haemodialysis; there is an additional risk due to blood handling in the haemodialysis unit.

The prevalence of hepatitis C viral infection in haemodialysis units varies from 8-51%.[37-39] Agbaji, in Jos Nigeria, found a prevalence of 22% among haemodialysis patients.[40] This variation results from the region in which the haemodialysis unit is located, the number of blood transfusions and the duration of haemodialysis. A higher prevalence of HCV infection has been reported in patients on both haemodialysis and peritoneal dialysis than in the general population.[41]

HCV GENOTYPES OF PATIENTS WITH CHRONIC KIDNEY FAILURE

The distribution of genotypes among patients on dialysis is very similar to that found in the non-nephropathic

population infected with HCV, and related to the place where the patients live. In most countries of the world including the United States of America and Europe,[19] the most common viral genotype is 1b (50%), followed by 1a and 2a each in 16% of the patients and eventually 2b and 2c in 8.3% each.[47] In Nigeria, a pilot survey in healthy adult donors and children of pre-school age showed genotypes 1a, 4, and 1d to be the dominant subtypes.[20] It has been reported that the genotype distribution by dialysis types is similar.[42]

HCV LOAD IN PATIENTS WITH CHRONIC KIDNEY FAILURE

RNA quantification has been used to estimate the hepatic prognosis and to assess the response to treatment with interferon alpha.[43,44] In patients on dialysis, the viral load correlates with the degree of hepatic inflammation and transmission mode.[44,45]

Various studies have shown that a smaller viral load occurs in patients on dialysis compared to non-nephropathic HCV-infected patients.[42,46-48] There is no clear explanation for this phenomenon. But Rampino *et al* recently proposed that it might be related to the fact that haemodialysis (HD) significantly increases the production of hepatocyte growth factor in such a way that it mimics the administration of this factor as a drug.[49] Some studies have shown that the exogenous administration of hepatocyte growth factor hastens hepatic regeneration and protects the liver from the toxicity of some compounds.[50,51]

On the other hand, it has been noticed that the viral load analysis is smaller when the infected patients are on continuous ambulatory peritoneal dialysis (CAPD) (0.20 ± 0.12 copies x 10^6/mL) than on HD (2.04 ± 0.88 copies x10^6/mL).[46] This finding may be explained by the hypothesis that HD induces certain degree of immunosuppression, since it affects phagocytosis, decreases granulocyte mobility and chemotaxis. It also inhibits T cell proliferation, reduces the IL-2 synthesis and decreases the activity of Natural Killer T cells.[52] In contrast, an alteration in the immune response occurs in patients on CAPD, but only at peritoneal level because of the contact with the peritoneal dialysis solution.[53]

HCV INFECTION IN HAEMODIALYSIS PATIENTS

Hepatitis associated with HCV was identified in HD patients some years ago.[37,41] Its clinical course is similar, although it seems that the hepatic enzymes remain elevated for longer periods in relation to the non-nephropathic population.[54] It also has greater prevalence than in the general population despite control measures for hepatitis transmission such as the routine identification of the B and C viral markers in blood donors and patients. The use of dialysis machines exclusive for patients with hepatitis B and C viruses, the implementation of vaccination programs for hepatitis B the implementation of vaccination programs for hepatitis B both the implementation of vaccination programs for hepatitis B both in patients, medical and paramedical staff, and the prohibition of dialysis material reuse in positive patients are other control measures employed to reduce the transmission of viruses.

Transmission of hepatitis C is mainly through blood transfusion. However, a high inter-patient transmission within haemodialysis unit has been demonstrated.[55,56] This is corroborated by the fact that nephropathic patients on CAPD and those on home haemodialysis, and who receive the same number of blood transfusion as those at the HD units, have less prevalence of HCV infection.

HCV INFECTION IN PERITONEAL DIALYSIS PATIENTS

The prevalence of HCV-Ab in the population on CAPD treatment has been reported to be about 15% [38] higher than in the general population (~1%),[57] but lower than in the population in HD unit [37-39] This difference probably results from the absence of vascular access in CAPD and the fact that dialysis is performed at home and not in a hospital. It is important to mention that, when the patients on CAPD that were previously on HD are excluded, the prevalence decreased significantly from 15% to 5.9%,[58] emphasizing the fact that vascular access and the haemodialysis unit are of primary importance in HCV transmission and infection of nephropathic patients. In addition, it is probable that the patients on CAPD with HD history were exposed during longer periods they were on haemodialysis to HCV infection risk factors.

HCV INFECTION IN TRANSPLANT PATIENTS

The deleterious impact of HCV infection extends to the kidney transplant recipients who have reduced patient and allograft survivals when compared uninfected controls.

TREATMENT OF HCV INFECTION

In 2002 the prevalence of HCV infection in the US haemodialysis population was greater than 7% but centres that had significantly lower blood transfusion rate had tendency for lower HCV rates.[59] Evidence based guidelines on the use of antiviral agents in the treatment of HCV infected CKD patients are non existent. Two categories of agents are useful in treating HCV namely; interferons and the nucleoside analogue ribavarin. Sustained virological response (SVR) was achieved in 26-39% of American CKD patients that received interferon monotherapy for HCV infection though same study indicated high drop out rate from treatment as a result of intolerable side effects.[60,61] In a number of small sized studies, treatment HCV infected

dialysis patients with pegylated interferon's have yielded higher SVR than in non pegylated interferon's presumably due to the sustained higher interferon levels in the former.[62,63] The addition of ribavarin to the standard interferon or the pegylated interferon treatments lead to higher SVRs than of the interferon is alone. Treatment of HCV infected renal transplant recipients pose special challenges since the use of interferons significantly reduce allograft survival whereas ribavarin monotherapy is not effective.[64]

CONCLUSION

Hepatitis C infection presents special management problems to health care providers and patients at any stage of the spectrum of chronic kidney disease. The time-tested application of universal caution in use of blood products in this group of patients remains the best control measure. Treatment in well-selected patients with a combination of ribavarin and interferon's remains the mainstay of treatment of HCV infected CKD patients.

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