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Hepatitis C Virus (HCV) and chronic renal disease

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Summary
Recent epidemiological evidence suggests an association between HCV infections and immunologically mediated renal disease. A high seroprevalence of anti-HCV has been observed in patients with glomerulonephritis in several countries including, Japan, Italy, America and Spain. However, a study in France did not show such association but increased seroprevalence of anti-HCV has been reported in patients with end-stage renal disease (ESRD) on chronic haemodialysis when compared with normal population suggesting that dialysis patients might be at higher risk of acquiring this infection. Anti-HCV seroprevalence has been found to increase with the duration of dialysis and the number of units of blood transfused raising the possibility of both transfusion and nosocomial transmission of HCV. A greater seroprevalence of anti-HCV has also been reported in predialytic chronic renal failure (CRF) patients independent of blood transfusion when compared with patients without renal disease and the normal population. The mechanism underlying hepatitis C induced renal damage is not certain. However, most evidence suggests that glomerular injury results from the deposition of circulating immune complexes (CICs) containing hepatitis C antibodies, hepatitis C antigens and complement mainly C3 within the sub -endothelium and mesangium. The optimal treatment strategy for hepatitis C –associated renal diseases remains to be defined but treatment has been associated with improvement in the level of proteinuria and variable response in serum creatinine levels using some antiviral agents.

Keywords: *Hepatitis C: chronic; renal; disease*

Résumé
Une évidence épidemiologique recente suggére que une association entre l 'infection du HCV et la maladie rénale immunilogiquement médié. Une élevation du taux d'anti-HVC a été observé chez les patients ayant la glomérulonephritite dans plusieurs pays inclus le Japon , l'Italie ; L'amerique l'Espagne. Cependant, une étude en France n' a montré aucune association, suggérant que les patients ayant la dyalise pourraient etre au grand risque d'acquérir cette infection.L'augmentation de la prevalence de l'anti-HCV a cte repote chez les patients ayant l'étape finale de la maladie rénale sur hémodyalise chronique quand compare avec la population a seroprevalence normale de l'HCV a été enregistré augmentant avec la durée de la dyalise et le taux de sang transfusé élevant la possibilité de transfusion sanguine et de transmission nococomale du HCV. Un taux elevé de séroprevalence de l anti-HCV a été reportée chez des patients ayant l echec renal chronique prédyalittique indépendent de la transfusion sanguine comparé avec les patients sans maladie rénale et une population saine. Ce méchanisme relevant que l'hépatite C induit la destruction renale n' est pas certain. Cependant, plus d'évidence suggére que la blessure glomérulaire résulte du dépot des complexes immunitaire circulant en péripherie contenant lesanticorps de l'hépatite C, les antigens de l'hépatite C et les systemes complémentaires spéciaux tels que C3, dans les tissues endothéliales et mésangiales. La podologie optimale de l'hépatite C et les maladies rénales associées, reste à définir mais le traitement a été associé l'amélioration du taux de protein dans les urines et les taux variables de creatinine utilisant certains produits retriviraux.

Introduction

In 1989, Hepatitis C virus was cloned and identified as the major cause of parenterally transmitted non- A, non-B hepatitis (NANBH) [1]. Recent prevalence estimates by the World Health Organization (WHO) suggests that 3% of the world population (170 million people) are currently infected with HCV [2]. There is a high prevalence in Japan, the Mediterranean countries of Europe, the Middle East and Africa [3,4]. Reported prevalence rates in Africa varies between 0.41-12% [5-8].

Structure and Routes of Transmission of Hepatitis C Virus (HCV)

HCV is a lipid-enveloped, single stranded ribonucleic acid (RNA) virus in the family Flaviviridae and the genus hepacivirus see figure 1 (schematic diagram of hepatitis C virus taken from the internet). It is 30-60 nm in diameter and its genome, which

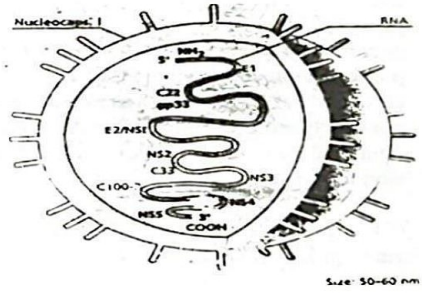

Fig. 1:

is approximately 9600 nucleotides in length, encodes for a single protein of about 3000 amino acids that undergoes proteolytic processing to form structural and non-structural viral proteins [3,4]. The N-terminus encodes the basic nucleocapsid (C) followed by two glycoprotein domains, the envelope (E1) and second envelope/non-structural-1 (E2/NS1) regions. Downstream to this region are the non-structural genes NS2, NS3, NS4, and NS5 respectively. The envelope glycoproteins E1 and E2 act as membrane anchors [3]. The E2 protein contains a hypervariable region 1 (HVR 1) in the N terminus, which mutates rapidly under immune pressure resulting in escape from neutralization and thus facilitating viral persistence.

The polymerase enzyme of HCV lacks proofreading ability and is therefore unable to correct copying errors made during viral replication leading to tremendous viral diversity. This viral heterogeneity prevents the development of conventional vaccines, allows the virus to escape eradication by the host's immune system and affects the completeness of the response to antiviral therapy. Genotype 1 is common in devel-

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oped countries (U.S.A., Japan and Europe), genotype 4 is predominant in the Middle East and North Africa, and genotype 6 is prevalent in Asia and genotype 5 in South Africa. Genotypes 1 and 4 have been described in Nigeria [9].

Hepatitis C virus is transmitted primarily through blood and blood products. Other routes of HCV transmission include sexual, vertical, tissue/ organ transplantation and via household contacts [3,4]. In 20 – 40% of cases, the route of infection is obscured. In most of these cases, infection is associated with high-risk lifestyles or particular demographic groups rather than a specific route of transmission.

Clinical Manifestations and Natural Course of Hepatitis C Virus Infection

Most cases of acute hepatitis C are anicteric and asymptomatic with fewer than 25% being clinically apparent. Fulminant hepatitis C is rare. The most remarkable and alarming aspects of HCV infection are its high rate of persistence and its ability to induce chronic liver disease. The infection persists in about 80% of cases leading to chronic hepatitis [3,4]. Approximately 20 to 30% of those chronically infected will develop cirrhosis and a proportion of these will develop hepatocellular carcinoma. Several extra-hepatic diseases have been associated with chronic HCV infection. These include:

- haematological diseases such as essential mixed cryoglobulinaemia, B-cell lymphoma and monoclonal gammopathies; [10-12].
- autoimmune disorders such as thyroiditis, sialoadenitis and autoimmune idiopathic thrombocytopenic pur pura; [13,14].
- dermatological conditions such as lichen planus and porphyria cutanea tarda; [11,12,15].
- chronic renal diseases such as membranoproliferative glomerulonephritis (MPGN) and membranous glom erulonephritis (MGN) which is the subject of discus sion in this write up [16,17].

Hepatitis C Virus and Chronic Renal Disease

Accumulating epidemiological evidence suggests an association between HCV infections and immunologically mediated renal disease, most commonly cryoglobulinaemic and non-cryoglobulinaemic MPGN, MGN and proliferative GN [16-17]. A high seroprevalence of anti-HCV has been observed in patients with glomerulonephritis in Japan, Italy, America and Spain. Prior hepatitis C infection is noted in 60% and 20% of patients with MPGN selected randomly in Japan and U.S.A. respectively [16,18]. However, a study in France did not show such association [19]. An increased seroprevalence of anti – HCV has been reported in patients with end- stage renal disease (ESRD) on chronic haemodialysis when compared with normal population suggesting that dialysis patients may be at higher risk of acquiring this infection. The reported prevalence in haemodialysis patients varies according to the type of laboratory assay used and the geographical location. Reported prevalence rates vary from 2 to 75% in different centers [20-22]. Agbaji in Jos found anti-HCV seroprevalence of 22.2% in patients on chronic haemodialysis compared to 6.4% in the normal control group [23]. Anti-HCV seroprevalence has been found to increase with the duration of dialysis and the number of units of blood transfused (raising the possibility of both transfusion and nosocomial transmission of HCV), the mode of dialysis (being higher in haemodialysis compared to peritoneal dialysis) and the prevalence of HCV infection in the dialysis unit (being higher in HD units with higher prevalence rates) [20-24].

A greater seroprevalence of anti-HCV has also been reported in predialytic chronic renal failure (CRF) patients independent of blood transfusion when compared with patients without renal disease and the normal population [25-27]. The reported seroprevalence rates in predialytic CRF patients ranged from 0 to 18% in different units with most studies reporting rates between 3 and 9%. A recent study in our center, found a prevalence of 9 % in pre-dialytic CRF patients. Patients who were anti-HCV positive had a statistically significant higher diastolic blood pressure compared with anti-HCV seronegative patients and a higher, though non-significant serum creatinine level [28]. In another study Garcia-Valdecasas et al also found a statistically significant association between anti-HCV and creatinine clearance. Thirteen percent (13%) of the patients with creatinine clearance less than 30ml/minute have anti-HCV positivity while 2.7% of the patients with clearance above 30ml/minute were anti-HCV positive [27]. These data suggest that HCV may be involved in the pathogenesis of CRF or that advanced CRF predisposes to the acquisition of the virus from exposure to blood transfusions during frequent dialysis.

Possible Pathogenesis of Hepatitis C – Associated Renal Disease

The mechanism underlying hepatitis C induced renal damage is not certain. Suggested mechanisms include:

- deposition of circulating immune complexes (CICs): most evidence suggests that glomerular injury results from the deposition of CICs containing hepatitis C antibodies, hepatitis C antigens, complement mainly C3 (and rheumatoid factor in essential mixed cryoglobulinaemia) within the sub -endothelium and mesangium. The above mechanism is believed to underlie the pathogenesis of HCV-associated MPGN.
- induction of auto-antibodies directed against glomeru lar antigens with consequent glomerular injury. The mechanism underlying auto-antibody formation is unknown but may involve a direct effect of HCV on â cells with subsequent abnormal proliferation of the â cell clones and subsequent production of auto-anti bodies. The auto-antibody hypothesis appears to be more relevant in the pathogenesis of HCV-associated membraneous glomerulonephritis (HCV-MGN) though it may result in MPGN.
- reduced clearance of CICs as a result of reduced reticu loendothelial cell function or porto-systemic shunt ing secondary to chronic liver disease. This enhances systemic circulation of immune complexes with sub sequent deposition in the glomeruli. This may con tribute directly to the pathogenesis of MPGN or pro liferative glomerulonephritis [29,30].

Clinical manifestations of hepatitis C Virus– associated renal disease

Often the renal involvement is silent. Patient may present with essential mixed cryoglobulinaemia (EMC) with kidney affectation, non-cryoglobulinaemic membranoproliferative glomerulonephritis, and membranous glomerulonephritis. Essential mixed cryoglobulinaemia is a multisytemic syndrome characterized by palpable purpura from leucocytoclastic vasculitis, Raynaud's phenomenon, leg ulcers, arthralgia and/or arthritis, peripheral neuropathy and renal dis-

ease. In severe cases cardiomyopathy or abdominal pain from vasculitis occurs. The clinical manifestations of the renal disease include haematuria, proteinuria that is often in the nephrotic range and a variable degree of renal insufficiency. Involvement of the kidneys carries the worst prognosis. The frequency of HCV infection with essential mixed cryoglobulinaemia (EMC) varies from 20 – 90% according to geographical regions. Circulating HCV RNA is concentrated (10 to 100 fold) in the cryoprecipitate obtained from LMC [29,30].

Patients with noncryoglobulinaemic MPGN may present with acute nephritic syndrome typically manifesting as microscopic haematuria and hypertension or with microscopic haematuria and proteinuria in the nephrotic or subnephrotic range. On the average about 50% of patients will present with mild to moderate renal insufficiency. Majority (more than 80%) of patients with HCV-MGN present with nephrotic syndrome while the rest present with isolated proteinuria in the subnephrotic range [29,30]. In HCV associated MPGN, the rheumatoid factor is elevated, the serum complement (mainly C3) is low and the C1q binding assay is elevated. Many of the patients have circulating cryoglobulins though one half of these patients are only symptomatic. The serum complements are normal in HCV-MGN and there is no circulating cryoglobulins or rheumatoid factor [29,30].

Significance of Prior Hepatitis C Virus Infection in Renal Transplantation.

Patients who are anti HCV positive before transplantation have a significantly increased risk of developing liver disease such as chronic active hepatitis and its sequalae, subfulminant hepatic failure and fibrosing cholestatic hepatitis which is characterised by severe cholestatis, extensive fibrosis and progressive liver failure.[31,32] Kidney transplantation in the patient previously infected with HCV is associated with increased proliferation of the virus resulting in a 1.8 to 30.3-fold increase in serum viral titre. However, there is a poor correlation between viral titre and risk of post- transplantation liver disease.[31] Conflicting results surround the issue of patients' survival following renal transplantation. While some studies have failed to detect significant differences in patient survival between recipients with and without anti- HCV prior to renal transplantation,[33,34] others have shown lower survival with pre-transplant evidence of hepatitis C infection [31,35]. For example, data from the New England Organ Bank revealed that recipients with pre-transplantation anti-HCV had a 3.3-fold higher risk of death and a 9.9-fold higher risk of death due to sepsis [31].

Treatment of Hepatitis C associated Renal Disease

The treatment of persons with chronic HCV infection is based largely on consensus guidelines [36,37]. The 1999 recommendations suggest that previously untreated persons without contraindications to treatment with interferon or Ribavirin (table 1) should receive combination therapy [37]. Treatment consists of Ribavirin in doses of 1.0-1.2 g daily in divided doses combined with interferon alpha 2b in a dose of 3MU three times weekly for six months. The virologic response to combination therapy should be assessed at week 24. Persons with positive PCR assay for HCV RNA at week 24 should be considered to have had no response to treatment and therapy should be discontinued. Those infected with HCV genotype 2 or 3 who have a negative PCR assay for HCV RNA can also usually stop therapy at this time but an additional 24 weeks of treatment is suggested for patients with other genotypes and a negative PCR [37].

Table 1: Contraindication to therapy with Interferon and Ribavirin

Severe psychiatric illness
Seizure disorder
Poorly controlled diabetes mellitus
Autoimmune disease
Haemoglobin <12g/dl in women and <13g/dl in men
White cell count <1500/min3
Platelet count < 100,000/mm3
Pregnancy or unable to practice contraception
Decompensated cirrhosis

The optimal treatment strategy for hepatitis C –associated renal diseases remains to be defined. Ribavirin is not recommended for patients with creatinine clearance below 50mls/min. Treatment has been associated with improvement in the level of proteinuria and variable response in serum creatinine level. Unfortunately, patients suffer from relapse of viraemia and renal disease after cessation of therapy [39,40]. Though higher doses of interferon-alpha and longer duration of treatment seem to be associated with higher response rates in haemodialysis patients, such regimens frequently result in more adverse effects. This increased risk may be due to the pharmacokinetics of IFN alpha in patients with impaired renal functions compared with non-uraemic patients. Haemodialysis patients have one-half the clearance of IFN-alpha, significantly higher half-lives of IFN-alpha 2b and markedly larger areas under the serum IFN concentration curve [41].

Conclusion

Chronic renal diseases associated with hepatitis C virus infection include membranoproliferative and membranous glomerulonephritides. The mechanisms underlying the pathogenesis of HCV-associated renal disease remain incompletely defined but evidence suggests deposition of circulating immune complexes and induction of auto-antibodies directed against glomerular antigens with consequent glomerular damage. Treatment has been limited by the high cost of therapy and relapse of renal disease following cessation of therapy.

Further studies are needed in elucidating the pathogenesis of HCV-associated renal disease, in improving current therapy and in defining optimal therapy. Until then the only effective method of preventing HCV infection is by instituting public health interventions such as screening of blood and blood products, effective use of universal precautions, adequate sterilizations of reusable materials, promotion of health education on HCV infection and identification of high risk patients.

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