Hepatitis C virus genotypes in patients on renal replacement therapy

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Abstract

Background. Chronic hepatitis C virus (HCV) infection is prevalent among patients on renal replacement therapy. Viral genomic differences can contribute to diversities in clinical manifestation. The distribution of HCV genotypes depends on the geographical region and risk factors unique to the patient population. We determined the HCV genotypes in patients on renal replacement therapy in order to define the genotypic profile and examine the relationship between genotype, mode of renal replacement therapy, and the prevalence as well as severity of liver disease.

Methods. HCV genotypes were determined by restriction fragment length polymorphism and sequencing of the 5'-untranslated region in 21 renal allograft recipients, 29 patients on dialysis, and 26 non-renal failure controls.

Results. The most prevalent genotype among patients with renal failure was 1b (78%), followed by 1a (10%) and 6a (8%). 2 renal allograft recipients with 6a infection probably acquired HCV from the same donor. The relative prevalence of HCV genotypes was similar to that of controls. While renal allograft recipients demonstrated more severe liver disease than dialysis patients, the prevalence and severity of chronic hepatitis were similar between patients with 1b and non-1b infection.

Conclusions. Resemblance of genotype distribution in Hong Kong to that of southern China and east Asia suggests common epidemiological evolution of HCV infection in these regions. Our results imply that in addition to viral characteristics, host factors such as the immunosuppressed state play an important role in the pathogenesis of liver disease in these patients.

Key words: dialysis; genotype; hepatitis C virus; transplantation

Introduction

The hepatitis C virus (HCV) is a major cause of chronic liver disease among patients on renal replacement therapy [1–3]. The majority of these patients acquire HCV through transfusion of unscreened blood products, while the renal allograft and nosocomial transmission during haemodialysis represent other modes of infection [4–7]. Once infected, spontaneous clearance of HCV is rare. The clinical consequences of chronic HCV infection in these patients are variable, ranging from a carrier state with minimal hepatic pathology to rapidly progressive chronic active hepatitis and cirrhosis [8–10]. There is accumulating evidence that viral factors may play a role in the pathogenesis of liver disease.

HCV can be classified into six major genotypic groups according to the nucleotide sequence in different regions of the genome [11]. Genotypic differences have been observed with regard to the virus load as depicted by the level of serum HCV RNA, the severity of liver disease, and the response to interferon therapy [12,13]. The relative prevalence of HCV genotypes shows marked geographical variation, with obvious clinical implications. In view of the distinctive risk factors in patients with renal failure, the genotypic distribution in these patients may not be identical to that of other subjects with post-transfusional HCV infection. Previous reports have demonstrated differences in genotypic distribution among patients with renal failure between some Asian countries [14,15]. The relationship between genotypes and the modes of renal replacement therapy, as well as clinical manifestations, remain to be established. We therefore determined the HCV genotypes in renal allograft recipients and dialysis patients, and compared them with non-renal failure subjects with post-transfusional HCV infection. The inter-relationship between genotypic differences, mode of renal replacement therapy, immunosuppression, and clinical manifestations of chronic liver disease was examined.

Subjects and methods

Patients and controls

Eight hundred and sixty patients on renal replacement therapy (330 renal allograft recipients, 130 on haemodialysis, 400 on peritoneal dialysis) were screened for chronic HCV infection.
infection by testing for anti-HCV; 50 (5.8%) patients who were seropositive for HCV RNA by the nested polymerase chain reaction (PCR) assay were included for genotype studies. Genotyping was also performed for 26 patients with post-transfusional chronic hepatitis C, without renal disease. None of the subjects was sero-positive for HBsAg, or had isolated anti-HBc.

Histological assessment

Histological assessment of percutaneous liver biopsy was done by the same pathologist (PCW) without knowledge of the patients’ clinical data. Liver pathology was scored according to ‘inflammatory activity’, ‘architectural abnormality’, and the degree of ‘bile duct damage’, adding up to a ‘total histological score’ [9].

Statistics

Results were expressed as mean ± SD. The median values were also given for some variables. Comparisons were made using the Mann-Whitney test, the Kruskal-Wallis test, the Chi-square test, and the Fisher’s exact test where appropriate. Two-tailed P values of < 0.05 were considered statistically significant.

Results

HCV RNA was detected in serum samples from 50 (5.8%) of 860 patients on renal replacement therapy. The group comprised 21 renal allograft recipients, 25 patients on haemodialysis, and four patients on peritoneal dialysis, giving seroprevalence rates of 6.4, 19.2, and 1% respectively. Among the 21 renal allograft recipients, 14 had the transplant operation performed in Hong Kong, while the remaining seven had received renal allografts in China. The age of renal allograft recipients, dialysis patients, and post-transfusional controls (40.3 ± 15.5) were similar (Table 1). Renal allograft recipients had shorter duration of dialysis before transplantation (32 ± 34 months vs 121 ± 63 months, P < 0.0001) and had received fewer blood transfusions [11]. Subtypes 1a/c and 1b were further differentiated by digestion with the restriction enzyme BstUI. Subtypes 2a/c and 2b, as well as subtypes 3a and 3b were further differentiated by digestion with the restriction enzyme ScrFI. Differentiation between genotypes 1 and 6 was confirmed by sequencing of the 5'UTR.

Table 1. Characteristics of the 50 patients on renal replacement therapy who had chronic HCV infection

<table>
<thead>
<tr>
<th></th>
<th>Renal transplant patients</th>
<th>Dialysis patients</th>
<th>Total patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (year)</td>
<td>42.6 ± 9.3</td>
<td>44.2 ± 10.5</td>
<td>43.5 ± 10.0</td>
</tr>
<tr>
<td>Male:Female</td>
<td>15:6</td>
<td>19:10</td>
<td>34:16</td>
</tr>
<tr>
<td>Post-transplantation follow-up/ time on dialysis (month)</td>
<td>103.9 ± 56.6</td>
<td>121.2 ± 62.7</td>
<td>—</td>
</tr>
<tr>
<td>No. of blood transfusions* (unit)</td>
<td>10 ± 9</td>
<td>30 ± 42</td>
<td>22 ± 33</td>
</tr>
<tr>
<td>Chronic hepatitis</td>
<td>13 (62%)</td>
<td>14 (48%)</td>
<td>27 (54%)</td>
</tr>
<tr>
<td>No. of patients with liver biopsy</td>
<td>14 (67%)</td>
<td>14 (48%)</td>
<td>28 (56%)</td>
</tr>
<tr>
<td>Liver histological score</td>
<td>10.2 ± 8.6</td>
<td>3.9 ± 2.6</td>
<td>7.2 ± 7.1</td>
</tr>
<tr>
<td>Inflammatory activity*</td>
<td>7.8 ± 5.8</td>
<td>3.3 ± 1.9</td>
<td>5.7 ± 4.9</td>
</tr>
<tr>
<td>[6.2–27]</td>
<td>[3.1–8]</td>
<td>[5.1–27]</td>
<td></td>
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<tr>
<td>Bile duct damage</td>
<td>0.5 ± 0.5</td>
<td>0.2 ± 0.4</td>
<td>0.4 ± 0.5</td>
</tr>
<tr>
<td>Architectural abnormality</td>
<td>1.8 ± 3.0</td>
<td>0.6 ± 0.8</td>
<td>1.3 ± 2.2</td>
</tr>
</tbody>
</table>

Data represent mean ± SD. Value in square brackets represent median and range. *P < 0.05 for renal transplant patients vs dialysis patients.
Genotypes 1b and 2b. More on virus load than the genotype negative subjects were renal allograft recipients infected and that their response to interferon therapy depended on renal failure, and in all controls. The two anti-HCV among haemodialysis patients infected by genotype 1b, (96%) of the 50 HCV RNA seropositive patients with strated marked variations in the level of HCV RNA.

The two renal allograft recipients with genotype 6a who had received haemodialysis and renal transplanta- tion is not a major problem in this cohort. Differences in HCV genotype distribution between patients with or without renal failure in the same locality may suggest nosocomial transmission within the former group [20–22]. The similar prevalence of genotypes in the two groups in this study, together with a low incidence rate of <0.6%/year among patients with renal failure, suggest that nosocomial transmission is not a major problem in this cohort. That mixed infections were only noted in two patients who had received haemodialysis and renal transplanta- tion in China raises the suspicion of suboptimal precau- tionary measures or the coexistence of other risk factors leading to superinfections. The detection of identical genotype 6a in two renal allograft recipients with the same cadaveric donor strongly suggests transmission of HCV via the renal allograft.

Due to the predominance of genotype 1b, the geno- typic impact on clinical manifestations in patients with renal failure cannot be ascertained for some genotypes in the present study. Nevertheless, the prevalence of chronic hepatitis as well as the histological scores do not differ between patients infected by 1b and non-1b genotypes. In this context we have previously demonstrated marked variations in the level of HCV RNA among haemodialysis patients infected by genotype 1b, and that their response to interferon therapy depended more on virus load than the genotype per se [23]. Furthermore, although the prevalence of chronic hepatitis is similar between dialysis patients and renal allograft recipients, liver disease is more severe in the latter group as indicated by the higher histological scores. The host immune status thus assumes an important role in the pathogenesis of liver disease among patients infected by the same HCV genotypes.
We conclude that the distribution of HCV genotypes among patients on renal replacement therapy is similar to non-renal failure subjects with post-transfusional hepatitis C in Hong Kong. The predominance of genotype 1b suggests common epidemiological evolution of HCV infection in southern China and northeastern Asia. Genotype analysis can be helpful in tracing the source of infection. The more severe liver disease among renal allograft recipients and the similar clinical manifestations between 1b and non-1b infections suggest that host factors such as the immunosuppressed state also play an important role in disease pathogenesis.

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