Prevalence of present and past hepatitis G virus infection in a French haemodialysis centre

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Abstract

Background. Previous studies, detecting GB virus-C (GBV-C) or hepatitis G virus (HGV) RNA by using reverse transcriptase polymerase chain reaction (RT-PCR), have shown that haemodialysis (HD) patients had a high risk of being infected and viraemic with this virus. A past GBV-C/HGV contact can now be detected by testing for antibodies directed against the GBV-C/HGV envelope protein E2 (anti-E2).

Methods. In order to evaluate GBV-C/HGV contact, 120 patients undergoing chronic HD were tested for GBV-C/HGV RNA by RT-PCR and anti-E2 antibodies by ELISA. GBV-C/HGV viraemic patients were followed prospectively for 18 months, and retrospectively when sera were stored. The total follow-up was between 18 and 78 months.

Results. GBV-C/HGV RNA was detected in 17 patients (14%), and 18 patients (15%) had a significant level of anti-E2 antibodies. No positive anti-E2 specimens were also positive for GBV-C/HGV RNA and vice versa. A total of 35 patients (29%) were contaminated with GBV-C/HGV. Sixteen of the 17 viraemic patients had a persistent viraemia (follow-up 18–78 months) and one cleared the virus during the study period. A past or present GBV-C/HGV contact was statistically correlated with the duration of HD and hepatitis C virus (HCV) infection, but was independent of age, hepatitis B virus (HBV) infection, and alanine aminotransferase (ALT) level.

Conclusions. Twenty-nine per cent of patients who underwent HD in our centre have been infected by GBV-C/HGV, 49% were still viraemic and 51% have developed anti-E2 antibodies, indicating a past contact with GBV-C/HGV. Our results demonstrate that the prevalence of GBV-C/HGV contact in HD was underestimated when only RT-PCR was used. Therefore GBV-C/HGV contact is probably much more frequent in HD than previous studies would suggest and is at this time not correlated with hepatotoxicity. Anti-HCV antibodies blood screening since 1990 and recent changes in managing HD patients have probably reduced GBV-C/HGV contact in the same way.

Key words: anti-E2 antibodies; GBV-C/HGV; haemodialysis; HCV; PCR

Introduction

Recently a new human virus belonging to the Flaviviridae family and sharing 30% homology with hepatitis C virus (HCV), has been identified in the serum of patients with non-A–non-E hepatitis. This virus was designated as GB virus-C (GBV-C) [1] or hepatitis G virus (HGV) [2]. GBV-C/HGV appears to share with HCV similar modes of transmission [3,4]. GBV-C/HGV is distributed worldwide. High prevalence of GBV-C/HGV RNA was detected in several at-risk populations: patients with acute and chronic hepatitis, multiple transfused patients, intravenous drug users, patients with clotting disorders [5–9]. A high prevalence of GBVC/HGV infection was also shown in patients undergoing haemodialysis (HD). According to the authors, 3–57.5% of HD patients had been viraemic for GBV-C/HGV 

The only available diagnostic method indicating an ongoing GBV-C/HGV infection is to demonstrate a viraemia in a patient sample by reverse transcriptase polymerase chain reaction (RT-PCR). An assay detecting antibodies to the envelope protein E2 (anti-E2) of GBV-C/HGV has been recently developed. This serological marker is considered as an indicator
of the virus clearance [25–27]. Thus, the presence of anti-E2 seems to testify a past GBV-C/HGV contact and is highly associated with protection from reinfection [28]. Prevalence of anti-E2 antibodies has been already established in several populations at risk or not. Indeed, these antibodies were found in 3–10.9% of blood donors [25,26], 8.9% in French unpaid blood donors [18], 41–85.2% of intravenous drug users [25,26], in 25.7% of patients with clotting disorders [9], in 12.9–29% of HD patients in Germany [14,29], in 22% of HD patients in Vienna, Austria [15], and in 14.2% of HD patients in Leuven, Belgium [16].

The aim of this study was to assess the prevalence of present or past GBV-C/HGV contact in a cohort of French HD patients. We compared the presence of GBV-C/HGV with age, time on dialysis, alanine amino transferase (ALT) levels, co-infection with hepatitis B virus (HBV), HCV, and human immunodeficiency virus (HIV). Moreover, in order to determine the outcome of the infection, GBV-C/HGV viraemic patients were followed prospectively for 18 months, and retrospectively when sera were stored.

Subjects and methods

Patients

All 120 patients on maintenance HD in Edouard Rist Medical Center (Paris, France) were tested for GBV-C/HGV RT-PCR and anti-GBV-C/HGV envelope protein E2 antibodies. The population consisted of 75 males and 45 females. Mean age was 49 ± 21 years and mean HD duration was 85 ± 83 months. Sixty-five patients were from Europe, 38 from Africa, nine from Asia, and eight from America. All patients gave informed consent.

Data on time on HD, history of transfusion, ALT levels, presence of HBV markers (HBsAg, HBeAg, HBeAb), HCV serology (anti-HCV antibodies (HCV Ab)), HCV viraemia (HCV-RNA investigated with RT-PCR), and HCV genotype, as well as HIV infection and CD4 lymphocytes counts (T4), were obtained from individual patient files at the time of the study.

Methods

All serum samples were collected in January 1996, aliquoted and stored at −80°C. GBV-C/HGV RNAs were extracted from 100 µl of serum according to a guanidium isothiocyanate–phenol method (Trizol LS, Life Technologies, USA). cDNA synthesis of 10 µl RNA was performed using a random hexanucleotide mixture and a Mu-LV reverse transcriptase (First-Strand cDNA Synthesis kit, Pharmacia, Sweden). cDNA was amplified in a 50 µl volume using a commercial assay (HGV Primer and Capture Probe Set, Boehringer Mannheim, Germany) which includes two sets of primers located in the putative 5′ non-coding region (5′-NCR primer-I (101–120), 5′-CGG CCA AAA GGT GGT GGA TG-3′; primer-2 (285–267), 5′-CGA CGA GCC TGA CGT CGG G-3′) and NS5a region (NS5a primer-1 (77–101), 5′-CTC TTT GTG GTA GTG GCC GAG AGA T-3′; primer-2 (152–172), 5′-CGA ATG AGT CAG AGG ACG GGG TAT-3′) [6]. Forty-five cycles were performed (30 s at 94°C, 30 s at 55°C, 30 s at 72°C in a 9600 Perkin Elmer thermocycler). GBV-C/HGV RNA amplification products were detected by a hybridization with specific internal probes labelled with digoxigenin using the DIG-System (Boehringer Mannheim, Germany). Our laboratory has participated in a GBV-C/HGV-PCR quality control [30].

Positive and negative controls were included in each run and false positive results were avoided by application of contamination prevention measures. Samples were considered positive when positive results were obtained with both primer sets starting from two independent extractions. Anti-E2 were detected by an ELISA sandwich assay (µPlate Anti-HGenv, Boehringer Mannheim). According to the manufacturer’s recommendations, the positive results were assessed by a confirmatory test that excludes E2 antigen in the incubation step.

In order to define the duration of GBV-C/HGV carriage, we investigated GBV-C/HGV viraemia in some of the HGV-PCR-positive patients whose earlier available samples had been stored in adequate conditions to perform RT-PCR. Moreover, each HGV-PCR positive patient was also tested 6, 12 and 18 months after the beginning of the study for GBV-C/HGV viraemia and for anti-E2.

Statistical analysis was performed by Student–Fisher t-test, χ² test with Yates’ correction when necessary, and by the odds ratios. Differences were considered as significant when P < 0.05.

Results

Prevalence of GBV-C/HGV RNA and anti-E2 envelope protein

Clinical and serological data from the studied patients are reported in Table 1. Seventeen of the 120 patients (14%) were HGV-PCR positive and 18 (15%) had anti-E2. None of the patients were simultaneously positive for GBV-C/HGV-RNA and anti-E2. Therefore 35 (29%) of our patients had been contaminated with GBV-C/HGV.

Clinical correlation

No significant difference was observed between the 17 GBV-C/HGV-viraemic and the 15 anti-E2-positive patients concerning duration of haemodialysis or clinical and serological markers. Therefore the group of 35 GBV-C/HGV patients has been compared with negative patients. GBV-C/HGV contact was statistically correlated with the duration of dialysis: 114 ± 76 months compared with 73 ± 83 months for patients without GBV-C/HGV infection (Fischer’s exact test P < 0.01), but not with the age.

The number of patients with an increased ALT level was so low (4/120), that we could not statistically compare the two groups for this marker. Among these four patients with a high ALT level (range 81–100), only one was GBV-C/HGV viraemic. This patient was also infected with HIV, one was free of any virus, one was HCV viraemic and was treated for hepatocellular carcinoma, and the last one had an active hepatitis B. The two last patients had anti-E2.
Table 1. Comparison of patients with and without HGV infection

<table>
<thead>
<tr>
<th></th>
<th>All patients</th>
<th>HGV-RNA +</th>
<th>Anti-E2 +</th>
<th>Contact HGV</th>
<th>Total HGV−</th>
<th>PHGV+/HGV−a</th>
<th>Odds ratio (IC 95%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>120</td>
<td>17</td>
<td>18</td>
<td>35</td>
<td>85</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>49 ± 11</td>
<td>38 ± 13</td>
<td>58 ± 18</td>
<td>48 ± 18</td>
<td>49 ± 22</td>
<td>NS</td>
<td></td>
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<tr>
<td>Time on HD (months)</td>
<td>85 ± 83</td>
<td>133 ± 84</td>
<td>96 ± 65</td>
<td>114 ± 76</td>
<td>73 ± 83</td>
<td>&lt;0.01</td>
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<tr>
<td>ALT &gt; 2N (N = 40)</td>
<td>4 (3%)</td>
<td>1 (6%)</td>
<td>2 (11%)</td>
<td>3 (9%)</td>
<td>1 (1%)</td>
<td>NT</td>
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<td>IU/ml</td>
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<tr>
<td>HBsAg+</td>
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<td>HBeAg+/HBsAg−</td>
<td></td>
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<tr>
<td>Contact HBV</td>
<td>45 (38%)</td>
<td>9 (53%)</td>
<td>8 (44%)</td>
<td>17 (49%)</td>
<td>28 (33%)</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>HCV Ab+</td>
<td>43 (36%)</td>
<td>8 (47%)</td>
<td>11 (61%)</td>
<td>19 (54%)</td>
<td>24 (28%)</td>
<td>&lt;0.01</td>
<td>3.02 (1.3–6.9)</td>
</tr>
<tr>
<td>HCV-RNA+</td>
<td>35 (29%)</td>
<td>8 (47%)</td>
<td>9 (50%)</td>
<td>17 (49%)</td>
<td>18 (21%)</td>
<td>&lt;0.01</td>
<td>3.51 (1.6–7.7)</td>
</tr>
<tr>
<td>HIV Ab+</td>
<td>8 (7%)</td>
<td>5 (29%)</td>
<td>1 (6%)</td>
<td>6 (17%)</td>
<td>2 (2%)</td>
<td>&lt;0.01</td>
<td>8.58 (1.6–43.6)</td>
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<tr>
<td>Contact with ≥1 virus</td>
<td></td>
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<tr>
<td>(HBV/HCV/HIV)</td>
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</table>

*aStudent–Fisher t-test, χ² test with Yates’ correction when necessary.

Co-infection with other viruses

Twenty four of the 35 GBV-C/HGV-positive patients (69%) were found to be coinfect with HBV and/or HCV and/or HIV (see Table 1 and Figure 1).

There was no relationship between GBV-C/HGV positivity and ongoing (HBsAg-positive individuals) or past (patients with HBeAg and HBsAb) HBV infection. HBV contact was found in 45 patients (38%); 13 (11%) were positive for HBs antigen. Among these 45 subjects, 17 (14%) had contact with HBV-C/HGV and HBV. Among the 43 patients with anti-HCV antibodies, 35 were viraemic (29% of the total) with a known genotype, but there were no associations with various HCV genotypes (data not shown). On the other hand, the frequency of HCV carriage was significantly different (OD = 3.02, IC 95% 1.3–6.9) between the group of GBV-C/HGV-positive patients (54% had anti-HCV) and individuals without GBV-C/HGV markers (28% had anti-HCV). Among the eight HIV patients present in the unit during the study period (T4 = 334 ± 253/mM³), six have been in contact with GBV-C/HGV, five were viraemic (T4 = 302 ± 30 1/mm³), and one has developed anti-E2 (T4 = 244/3 mm³). The GBV-C/HGV-positive patients were more often infected with HIV (17%) than GBV-C/HGV-negative subjects (2%) (OD = 8.58, IC 95% = 1.6–43.6%). Seventy-five patients (62.5%) have been in contact with GBV-C/HGV or HCV or HBV or HIV and were under HD since 113 ± 89 months. Forty-five (37.5%) patients were free of the four studied viruses, they had been under HD for 38 ± 39 months (P < 0.001).

Blood transfusion

Sixty-four of the 120 patients had had blood transfusions in the HD unit. The transfusion history for the
56 remaining patients was not available; thus, this group of 56 patients was excluded from further analysis. Twenty-three (36%) of the 64 transfused subjects were infected with GBV-C/HGV. There was no significant difference between the group of GBV-C/HGV viraemic patients and the group of individuals with anti-E2 (Table 2).

Because HCV systematic screening was established in March 1990 in France, we looked for GBV-C/HGV contact in patients transfused before 1991. In the group of 23 GBV-C/HGV-infected patient, we observed more patients ($P$<0.01) with a transfusion history prior to 1991 (19/23) than after 1991 (4/23).

Duration of GBV-C/HGV viraemia

The results obtained from the detection of GBV-C/HGV viraemia and anti-E2 antibodies in sequential samples involving the 17 RT-PCR GBV-C/HGV-positive individuals during a follow-up retrospective and prospective study are given in Table 3. A persistent viraemia was observed at the end of the study period in 16/17 HGV-RNA-positive patients with a mean follow-up of 46 months (range 18–78).

For 12 of the 17 GBV-C/HGV RNA-positive patients, one or more samples were available for GBV-C/HGV RNA investigation. All of them were already GBV-C/HGV infected before the date of the first studied specimen. Two patients (nos 68 and 108) had transient GBV-C/HGV viraemia. One (no. 101) was GBV-C/HGV-RNA negative at the end of the study without developing anti-E2. None was anti-E2 positive at baseline (January 1996), but one patient (no. 68) developed these antibodies in June 1997, with persistent viraemia.

Persistent GBV-C/HGV viraemia without anti-E2 was observed for all the five HIV/HGV RNA-positive subjects (nos 1, 14, 24, 35 and 99). The follow-up for these patients were 18 months (2 patients), 47 months (1 patient), and 54 months (2 patients).

During the observation period (between January 1996 and June 1997), none of the GBV-C/HGV-infected patients developed biochemical or clinical signs of hepatitis or other symptoms not attributable to the underlying disease.

Discussion

A past or present GBV-C/HGV infection was found in 29% of the 120 patients on chronic HD in our centre. One-half of the GBV-C/HGV-exposed patients have resolved their infection as judged by the presence of anti-E2 in the serum with negative HGV-RNA detection. These results are in accordance with the reports of Szabo et al. [14], Schulte-Frohlinde et al. [29], Tribl et al. [15] and Sheng et al. [17], who

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Table 2. Relationship between transfusion history and HGV infection in 64 patients transfused in the HD unit

<table>
<thead>
<tr>
<th>Transfusions</th>
<th>n</th>
<th>HGV-RNA+</th>
<th>Anti-E2+</th>
<th>Total HGV+</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1991</td>
<td>36</td>
<td>10 (28%)</td>
<td>9 (25%)</td>
<td>19 (53%)</td>
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<tr>
<td>$\geq$1991</td>
<td>28</td>
<td>2* (7%)</td>
<td>2* (7%)</td>
<td>4 (14)%</td>
</tr>
<tr>
<td>Total</td>
<td>64</td>
<td>12 (19%)</td>
<td>11 (17%)</td>
<td>23 (36%)</td>
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</tbody>
</table>

*1/2 in each group was also anti-HCV Ab positive.

$^aP$ (HGV+ patients transfused before 1991/HGV+ patients transfused after 1991)<0.01.

Table 3. Follow-up results of 17 HGV RT-PCR positive patients

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<td>14*</td>
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<td>24*</td>
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<td>+</td>
<td>+</td>
<td>neg</td>
<td>neg</td>
<td>47</td>
</tr>
</tbody>
</table>

*HIV positive.

+ HGV RT-PCR positive; neg, HGV RT-PCR negative; without result, serum not available for PCR testing.

Anti-E2 antibodies were tested for all these patients in:

- June 1996, all tested negative;
- June 1997, one specimen (no. 68) tested positive.
found a contact rate for GBV-C/HGV in HD patients of 23% (7/31), 35% (25/72), 34% (40/119), and 28.6% (32/112) respectively.

In our study, 14% of HD patients were found to be GBV-C/HGV viraemic. This prevalence is comparable with most European data reported in similar populations (Kallinowski et al. 7.9% [16], Schulte-Frohlinde et al. 10% [29], Szabo et al. 12.9% [14], Tribl et al. 13% [15], Cornu et al. 16% [10], Sampietro et al. 19% [12], Sheng et al. 17% [16], Forns et al. 26% [11]), but less than those found in a previous French study [13], which reported a HGV-RNA-positive rate of 57.5%.

It can be assumed that these discrepancies are caused by the nucleic acid amplification method applied. However, altogether these data confirm that the prevalence of GBV-C/HGV infection is higher in HD patients than in healthy individuals like blood donors (14% of HD studied subjects were GBV-C/HGV RNA positive vs 3.3% of 2548 unpaid blood donors in France [18]).

On the contrary, a similar prevalence of anti-E2 is observed in this HD population when compared to healthy controls (15 vs 8.9% in blood donors [18]). This observation suggests that the resolution of GBV-C/HGV infection in immunosuppressed HD patients might be less efficient than in healthy subjects. In accordance with this hypothesis, we can point out that 16 of 17 GBV-C/HGV-viraemic patients were still GBV-C/HGV RT-PCR positive after 18 months follow up. One became GBV-C/HGV-RNA negative, but in the absence of anti-E2, we cannot differentiate a resolved infection from a transient viraemia.

Twelve of 17 patients in whom earlier serum samples were available were also GBV-C/HGV RNA positive for the first tested serum. Thus, the minimal duration was between 18 and 78 months. This high level of GBV-C/HGV chronic carriers would be partly imputed to a centre effect due to the presence of five HIV GBV-C/HGV-viraemic patients, in regards to the epidemiology of HIV infection in HD patients in France [31].

However, the average of follow-up delay for HIV patients was not higher than that observed in non-HIV population (38.2 vs 48.7 months), and long, chronic GBV C/HGV infection in HD patients has been described [4,10] in a period over 16 years [4].

All 18 patients found positive for anti-E2 at the beginning of the study were GBV-C/HGV RT-PCR negative. One of the 17 initially GBV-C/HGV RT-PCR-positive patient has developed anti-E2 while keeping a positive GBV-C/HGV RT-PCR. It might well be that this patient is going to resolve GBV-C/HGV infection during further follow up. These data confirm that the presence of anti-E2 is associated with recovery from GBV-C/HGV infection.

One initially GBV-C/HGV-viraemic patient became GBV-C/HGV RNA negative without appearance of anti-E2 antibodies, suggesting that a combined detection of GBV-C/HGV RNA and anti-E2 can miss a few patients that have been exposed to GBV-C/HGV. Similarly, Tribl et al. [15] and Sheng et al. [9] identified a few serum GBV-C/HGV RT-PCR negative patients in whom GBV-C/HGV RNA could be demonstrated in peripheral blood mononuclear cells. Thus, the described prevalence of GBV-C/HGV contact may be actually at least partly underestimated.

Contrary to the studies on GBV-C/HGV viraemic HD patients [12,16], our study, in agreement to Tribl [15], has been able to find a significant association between GBV-C/HGV and HCV contact (odds ratio 3.03 and 3.51 for respectively HCV Ab- and HCV-RNA-positive patients). The application of the universal rules of prevention of HCV contact in dialysis units should allow a reduction of GBV-C/HGV transmission in HD patients. Thirty eight per cent of the patients in this study were free of HCV, HBV, GBV-C/HGV, and HIV contact and were yet haemodialysed for more than 3 years, suggesting that these rules are efficient. Moreover, the screening and elimination of anti-HCV positive donations since March 1990 in France has reduced not only transfusion-transmitted HCV infection, but probably also concomitant GBV-C/HGV transmission. Indeed, patients transfused in our centre before 1991 were more frequently contaminated by GBV-C/HGV than patients who were transfused after 1991 (P<0.01). Similar observations have been made in a Belgium HD unit [32]. Blood transfusion might be incriminated in transmission of GBV/C/HGV infection in our study. Indeed, at least 66% (23/35) GBV-C/HGV-positive patients received transfusions. Unfortunately, for the 56 patients who did not receive transfusions, we have no information concerning a transfusion history before their arrival at the centre. Consequently, it was not possible to compare the transfused and not transfused populations. Transmission of GBV/C/HGV by blood transfusion is not supported by the findings of Schulte-Frohlinde [29] who did not show correlation between GBV-C/HGV contact and history of blood transfusions. In fact, other parenteral routes of transmission may contribute to the higher rates of GBV-C/HGV infection in HD patients.

Time on HD appears to be a statistically significant factor for being exposed to GBV-C/HGV in our study. This result is in accordance with some reports [13,14,29], but not in others [10,12,15,16]. It must be stressed that, as shown by of Szabo et al. [14], GBV-C/HGV RNA-positive patients were on haemodialysis for a longer time. All these data are in accordance with the hypothesis that the incidence of GBV-C/HGV infection is decreasing, thanks to the combined effects of a better selection of blood donors, the elimination of HCV-positive blood products, the extensive use of erythropoietin, and the application of the universal rules of prevention of parenteral contact in dialysis units.

Only one out of the 17 patients GBV-C/HGV viraemic from our centre had a high ALT level, this patient was HIV positive. This suggests that GBV-C/HGV is poorly or not hepatotoxic. GBV-C/HGV has been implicated in the aetiology of hepatitis [33] and aplastic anaemia [34,35], but more recent epidemiological studies suggested that GBV-C/HGV has only a limited disease-inducing potential [4,20,36].
Prevalence of HGV infection in a French haemodialysis centre

In conclusion, prevalence of exposure to GBV-C/HGV is high in HD patients, and correlated to HCV contact and time on HD. RT-PCR alone underestimates the rate of exposure to GBV-C/HGV and needs to be combined with information about anti-E2 prevalence. GBV-C/HGV infection does not induce hepatitis in HD patients but chronic infection is a frequent finding. Recent changes in the way of managing patients on HD have probably reduced GBV-C/HGV contact.

References


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