

# Hepatitis G virus infection in fulminant hepatic failure

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## Abstract

**Background**—RNA sequences of the recently identified hepatitis GB virus C (HGBV-C), also named hepatitis G virus (HGV), have been detected in patients with idiopathic fulminant hepatic failure (FHF) but the role of this agent in the disease remains controversial.

**Aims**—To investigate the presence and implications of HGV infection in a large series of Spanish patients with FHF.

**Patients**—Sixty eight patients with FHF, including 19 with idiopathic disease, were studied. In 28 cases, studies were performed before and after liver transplantation. For comparison 200 volunteer blood donors and 22 patients transplanted for chronic liver disease were also studied.

**Methods**—HGV RNA was measured in serum by reverse transcriptase polymerase chain reaction of the 5' non-coding region.

**Results**—Evidence of HGV infection was found in 3% (6/200) of blood donors and in 19% (13/68) of patients with FHF. HGV infection was more frequent in patients with hepatitis B (24%, 6/25) or hepatitis D (42%, 5/12), than in patients with idiopathic disease (11%, 2/19). Half of the patients with HGV infection used illicit intravenous drugs. Specific clinical features associated with HGV infection were not identified. A very high rate of infection with HGV was observed in patients who underwent liver transplantation, either for FHF (60%, 15/24) or chronic liver disease (45%, 9/20).

**Conclusions**—In our geographical area, HGV infection is relatively frequent in FHF, but it does not seem to play a major role in idiopathic cases.

(Gut 1997; 41: 696-699)

Keywords: viral hepatitis; hepatitis G virus; fulminant hepatic failure; liver transplantation

Fulminant hepatic failure (FHF) is a dramatic condition resulting from severe impairment of the function of a previously normal liver.<sup>1</sup> Massive or submassive destruction of hepatocytes as a consequence of infection with hepatitis viruses A to E is the most frequently recognised cause of FHF worldwide, but the aetiology cannot be identified in approximately one third of patients.<sup>2</sup> The nature of the agent or agents causing idiopathic fulminant hepatic failure remains elusive and several studies have yielded conflicting results.<sup>3-7</sup>

Recently, a new transmissible agent, the hepatitis GB virus C (HGBV-C) has been identified.<sup>8</sup> This virus belongs to the *Flaviviridae* family and presents notable sequence similarity with another agent, the hepatitis G virus (HGV), identified in an independent laboratory.<sup>9</sup> HGBV-C and HGV are different isolates of the same virus.<sup>10</sup>

The role of this agent in human liver disease is currently under investigation. Preliminary data indicate that HGV/HGBV-C infection can be detected in a relatively high proportion of apparently healthy volunteer blood donors, in persons exposed to parenterally transmitted viruses such as recipients of blood transfusions, patients on haemodialysis, intravenous drug abusers, and institutionalised patients, and in patients with acute and chronic liver disease.<sup>8,9,11-18</sup> However, the information concerning the prevalence and the pathogenic role of HGV infection in these situations is still rather limited.<sup>19</sup>

The presence of HGBV-C RNA sequences has recently been demonstrated in serum from 50% of patients with idiopathic fulminant hepatitis,<sup>20,21</sup> suggesting that this virus may have a role in the aetiology of this disease. These findings, however, were not fully confirmed by others.<sup>18,22-31</sup>

Several surveys on the aetiology of FHF demonstrated remarkable differences between different geographical areas.<sup>32-36</sup> We therefore investigated the possible role of HGV infection in a relatively large series of Spanish patients with FHF of known aetiology and in a representative group of patients with idiopathic disease.

## Patients and Methods

### PATIENTS

Between January 1987 and December 1995, 108 patients with fulminant hepatic failure (FHF), according to the criteria of Trey and Davidson,<sup>1</sup> were admitted to the Liver Intensive Care Unit of the Hospital Clinic, Barcelona. Sixty four patients (60%) were admitted directly and 44 patients (40%) were transferred from other centres in Spain for specialised care. Well preserved serum samples taken at admission were available in 68 cases (65%) and these patients formed the basis of the present study. Recent exposure to hepatotoxic drugs and risk factors for transmission of hepatotropic viruses, including recent administration of blood or blood products, were recorded in every case. The aetiology of the disease was defined by standard clinical, serological, biochemical, and

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Accepted for publication  
29 May 1997

histopathological studies.<sup>2</sup> The clinical presentation of the disease as hyperacute, acute, or subacute was defined by the criteria of O'Grady *et al.*<sup>37</sup> Patients received standard supportive therapy<sup>2</sup> and an orthotopic liver transplantation was performed in 28 cases, according to criteria reported previously.<sup>38</sup> Twenty two randomly selected patients with chronic liver disease who received a liver transplant during the same period of time and 200 consecutive, first donation, volunteer blood donors were also studied for comparative purposes.

#### SEROLOGICAL STUDIES

The presence of current infection with hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis D virus (HDV), or hepatitis C virus (HCV) was assessed with commercially available enzyme linked immunosorbent assay (ELISA) kits (HAVAB-M EIA, Auszyme II, Corzyme M, Anti-delta EIA, Abbott Laboratories, Chicago, Illinois, USA), for antihepatitis A IgM, hepatitis B surface antigen, antihepatitis B core IgM antibodies, and total antihepatitis D, respectively, and for antihepatitis C virus antibodies (second and third generation Anti-HCV ELISA test, Ortho Diagnostics Systems, Raritan, New Jersey, USA). HCV RNA was investigated in serum with a nested polymerase chain reaction (PCR) assay, using primers derived from the 5' non-coding region (5' NCR) of the HCV genome, as described previously.<sup>39</sup>

Hepatitis G virus RNA (HGV RNA) in serum was determined by a commercially available assay kit (Boehringer Mannheim, Mannheim, Germany) for PCR amplification of the 5' NCR of the HGV genome as described previously.<sup>15</sup> Briefly, nucleic acids were extracted from 140 µl of serum using QUIAMP-HCV extraction columns (Qiagen, Hilden, Germany). Eluted RNA was transcribed into cDNA with Moloney murine leukaemia virus retrotranscriptase in the presence of random primers and a ribonuclease inhibitor. PCR was carried out for 35 cycles (94°C, one minute; 55°C, one minute; 72°C, one minute) and five minutes at 72°C for final extension using 10 µl of a cDNA, dNTP mixture containing 200 µM

of dATP, dGTP, and dCTP, 190 µM of dUTP, 10 µM of digoxigenin-11-dUTP, 50 pmol of primers NCR1 (5'-CGGCCAAAAGGTGG-TGGATG-3') and NCR2 (5'-CGACGAGCC-TGACGTCGGG-3'), that encompass a 184 bp fragment of the 5' NCR, and 1.25 U of Taq DNA polymerase in a final volume of 50 µl. Digoxigenin labelled PCR products were detected by hybridisation for one hour at 37°C (DIG-ELISA detection kit, Boehringer Mannheim, Mannheim, Germany) with a capture probe (5'-biotin-CGTAGCCACTATAGGTGG-3') immobilised on streptavidin coated microtitre plates. After hybridisation, wells were incubated with digoxigenin peroxidase and washed. Absorbance was read at 405 nm (reference filter at 492 nm). Two negative and one positive control sera were included in PCR reactions and three blanks were included in each hybridisation reaction. All samples were tested at least twice in separate rounds. Samples were considered positive when the measured absorbance was greater than four times the mean absorbance obtained in negative controls, in which the signal ranged between 0.084 and 0.113. Results were accepted on agreement between at least two separate determinations.

The NS3 region of the HGBV-C genome was analysed in all the samples reactive for 5' NCR sequences of HGV RNA and in 15 non-reactive samples selected at random from patients with FHF. RT-PCR was performed as described by Yoshida *et al.*<sup>20</sup> with some modifications,<sup>12</sup> using primers deduced from the nucleotide sequence of HGBV-C described by Simons *et al.*<sup>8</sup>

#### STATISTICAL ANALYSIS

Differences in proportions between groups were analysed with the  $\chi^2$  test and Fisher's exact test. Quantitative variables were analysed with Student's *t* test or the Mann-Whitney test when appropriate.

#### Results

Table 1 shows the main features of the patients with FHF. Anti-HAV antibodies of the IgM class were detected in three cases, HBsAg and anti-HBc of the IgM class in 25, HBsAg and anti-HDV antibodies in 12, and anti-HCV and HCV RNA in two. These findings suggested that infection with hepatotropic viruses was the cause of FHF in 42 cases (62%). A recent history of potentially hepatotoxic drug intake was recorded in five patients (antituberculous drug therapy in three, ketoconazole in one, and halothane in one). Massive involvement of the liver by previously unrecognised lymphoma was found in one case and evidence of Wilson's disease was detected in another. A possible aetiological factor was not found in the remaining 19 cases (28%).

A positive signal for the 5' NCR of the HGV genome was detected in serum from 13/68 patients with FHF (19%) and in 6/200 blood donors (3%) tested (Fisher's exact test,  $p < 0.001$ ). Sequences of the NS3 region of the HGBV-C genome were detected in the 13 serum samples positive for the 5' NCR of HGV but in none of 15 samples negative for HGV RNA.

TABLE 1 Main features of patients with fulminant hepatic failure according to the presence or absence of HGV RNA sequences in serum

	Total (n=68)	HGV RNA	
		Present (n=13)	Absent (n=55)
Age (y)	30 (13)	29 (11)	30 (14)
Sex (M/F)	32/36	8/5	24/31
<i>Presumed source of infection</i>			
Intravenous drug abuse	18	6 (33%)	12 (66%)
Sexual	11	3 (27%)	8 (73%)
Unknown	39	4 (10%)	35 (90%)
<i>Presumed aetiology</i>			
HAV	3	0	3 (100%)
HBV	25	6 (24%)	19 (76%)
HBV/HDV	12	5 (42%)	7 (58%)
HCV	2	0	2 (100%)
Miscellaneous non-viral	7	0	7 (100%)
Idiopathic	19	2 (11%)	17 (89%)
<i>Clinical presentation</i>			
Hyperacute	26	4 (15%)	22 (85%)
Acute	30	4 (13%)	26 (87%)
Subacute	12	5 (42%)	7 (58%)
<i>Final outcome</i>			
Recovery	9	4 (44%)	5 (56%)
Death	21	5 (24%)	16 (76%)
Liver transplantation	38	4 (11%)	34 (89%)

The presence of HGV RNA in serum from patients with FHF did not seem to be related to previous administration of frozen plasma as supportive therapy for coagulation disorders. This therapy was administered within two days prior to collection of serum for HGV RNA testing in 17 cases. HGV RNA was found in 3/17 treated patients (21%) and in 10/41 (24%) who did not receive supportive therapy.

HGV RNA was detected with greater frequency in patients with a history of intravenous use of illicit drugs (6/18, 33%) than in patients with no risk factors (4/39, 10%) (Fisher's exact test,  $p=0.04$ ) (table 1).

The presence of HGV RNA sequences in serum was more frequent in patients with HBV infection, with (5/12, 42%) or without (6/25, 32%) evidence of HDV infection, than in patients with idiopathic disease (2/19, 11%). However, this difference did not reach statistical significance (Fisher's exact test,  $p=0.058$ ). HGV RNA was not detected in patients with HAV or HCV infection nor in those with miscellaneous conditions other than viral infection (table 1).

Neither the clinical presentation of the diseases as hyperacute, acute, or subacute, nor the final outcome of the disease seemed to be related to the presence in serum of HGV RNA sequences (table 1). The proportion of patients presenting with HGV RNA among those who recovered with conventional measures (4/9, 44%) was somewhat greater than among patients who died (5/21, 24%) or underwent liver transplantation (4/38, 9%). None of these differences reached statistical significance.

Liver transplantation was performed in 38 patients with FHF. Six of them died shortly after the operation and four were not followed at our institution. Serum samples obtained six months after transplantation were available for the remaining 28 patients. HGV RNA was detected in pretransplant samples in four of these patients.

Twenty two randomly selected patients transplanted for chronic liver disease (16 males, six females; mean age 50 years, range 36–59) were also studied. The indication for transplantation was hepatic cirrhosis in 21 cases (related to hepatitis C virus infection in 13, of alcoholic type in five, primary biliary cirrhosis in one, and cryptogenic in two), and advanced primary sclerosing cholangitis in one. HGV RNA was detected in pretransplant serum samples in two of these patients. After transplantation, HGV RNA was detected in 19 (68%) patients with FHF and in 11 (50%) with chronic liver disease. No patient cleared HGV RNA after transplantation. HGV RNA thus emerged after transplantation in 15/24 (60%) patients transplanted for FHF and in 9/20 (45%) of those transplanted for chronic liver disease.

The number of donors of blood, platelets, or other blood components involved in the transplantation procedure was greater in patients transplanted for FHF (61 (50)) than in patients transplanted for chronic liver disease (36 (24)), but the difference was not statistically significant.

## Discussion

Despite intensive investigation, the cause of the disease remains obscure in a considerable proportion of patients with FHF. Hidden viral infection, not identifiable with ordinary serological techniques, may be responsible in some cases of idiopathic FHF.<sup>3,4</sup> Infection with a previously unrecognised virus, such as HCV in the East<sup>33,34</sup> or HEV in developing countries<sup>37</sup> may be involved in others. However, despite the use of complex molecular biology techniques to identify viral nucleic acid in liver or serum, the aetiology of FHF cannot be reliably identified in many patients. Idiopathic FHF is therefore often referred as non-A, non-E fulminant hepatitis.

The HGBV-C or HGV is a recently identified transmissible agent that can cause hepatitis in man.<sup>8,9</sup> HGBV-C genome sequences have been detected in serum from patients with non-A, non-E fulminant hepatitis, and this finding suggested that HGBV-C might be involved in the pathogenesis of this disease.<sup>20,21</sup> However, other groups did not share this opinion.<sup>22,31</sup>

In the current study HGV RNA sequences were detected in 19% of Spanish patients with FHF. The specificity of this finding is supported by the highly concordant results obtained by reverse transcriptase PCR amplification of viral RNA using primers derived from the 5' NCR of HGV and the NS3 region of HGBV-C.

In comparison with other studies,<sup>20,21</sup> the large number of HGV RNA negative cases of FHF found in this study may be related to inadequate preservation of RNA in serum samples or to low sensitivity of the reverse transcriptase PCR assay. This is, however, unlikely because the frequency of HGV infection observed in our patients with chronic liver disease, and in blood donors, was in the range observed in previous studies<sup>8,9,11–18</sup> or even higher. In addition, low prevalence of HGV infection has also been reported by others.<sup>30</sup>

Patients with fulminant viral hepatitis characteristically have low levels of viraemia, which may escape detection<sup>35,40</sup> unless very sensitive techniques are used for detection. Theoretically, hidden viral infection might become apparent if patients are transplanted and treated with immunosuppressive drugs, as has been reported in patients transplanted for chronic liver disease.<sup>41</sup> In the present study, HGV infection became apparent after transplantation in as many as 60% of the patients with FHF. Hidden HGV infection might thus be present in many more patients than indicated by pretransplant studies. This is not likely, however, as HGV infection became apparent in a similar proportion of patients transplanted for chronic liver disease. The high rate of post-transplant HGV infection observed in this study can be explained by the large number of blood donors involved in the transplantation procedure, in whom the estimated prevalence of HGV infection was as high as 3%.

On the other hand, it is possible that detection of HGV RNA by reverse transcriptase PCR in patients with FHF may not be

due to a current infection with this agent but simply reflect passive transmission of HGV material present in fresh frozen plasma or other blood products administered as treatment for clotting disorders. In this study, however, HGV RNA sequences were detected with a similar frequency in treated and untreated patients.

Eleven of the 13 patients with FHF in whom HGV RNA was detected in serum also presented evidence of infection with HBV or with HBV and HDV. The majority of these patients were intravenous drug abusers or had a recent history of sexual contact with drug addicts (data not shown). HGV RNA was detected in approximately one third of FHF patients with HBV, in agreement with recent observations indicating that the majority of patients with FHF infected with HGV are also infected with HBV.<sup>18 21 31</sup> In contrast, HGV RNA was detected at a lower frequency in patients with idiopathic disease and was not found at all in patients with hepatitis A or hepatitis C, or in those with miscellaneous conditions.

It has recently been recognised that multiple viral infection, involving well known, readily identifiable viruses such as HBV, HDV, and HCV, can be detected in many patients with fulminant hepatitis.<sup>35</sup> Our data suggest that a role for HGV infection as a cofactor in patients with fulminant hepatitis infected with HBV or HDV cannot be disregarded. Infection with HGV alone, however, does not seem to be a major cause of idiopathic fulminant hepatitis in our geographical area.

Supported in part by grants 94/0848 from FIS of the Ministerio de Sanidad and SFA-97/0103 from DGICYT of the Ministerio de Educacion y Ciencia. E Olmedo, F Forns, F X López-Labrador, M Guilera, and S Ampurdanés were supported by Fundació Privada Clinic.

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*Gut* 1997 41: 696-699

doi: 10.1136/gut.41.5.696

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