

DISCOVERY OF HEPATITIS G VIRUS

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In 1995-96, the hepatitis G virus (HGV) was cloned and sequenced. This virus is from the group of new agents called GB viruses (GB virus A, GB virus B and GB virus C) and is also designated as GB virus C (GBV-C). HGV is a positive-stranded RNA virus, with a genome of 10 KB and appears, on the basis of genome length and organization, to be a member of the *Flaviviridae*, distinct from the hepatitis C virus (HCV). HGV infection appears to be transmitted following receipt of blood from HGV RNA-positive donors; however, these patients had only moderate liver enzyme (ALT) elevations. The strength of the association of HGV infection with acute hepatitis is unclear. Persons infected with the virus appear to remain persistently infected (HGV RNA-positive) for as long as nine years. Although the virus RNA can be detected with varying frequency in patients with various forms of chronic liver disease, an association of the infection with disease has not been demonstrated. The application of existing molecular techniques are likely to add at least one enterically transmitted agent and an undefined number of parenterally transmitted agents to the existing list (A to G) of hepatitis viruses. In this article, the author would like to focus on the following aspects of viral hepatitis: 1) the reasons which led to the belief that some viral hepatitis might be caused by as yet uncharacterized viruses; 2) newly characterized Flaviviruses thought to be associated with hepatitis, including HGV; 3) the impact of HGV virus on clinical disease; and 4) evidence that more hepatitis viruses may exist and may be cloned and sequenced in the near future.

Viral hepatitis is one of the most important global health problems, infecting hundreds of millions of individuals and responsible for more than a million deaths per year.¹ It is in the last three decades that the clinical disease and economic consequences of viral hepatitis have

been recognized. During the last two decades, there has been a dramatic improvement in the understanding of viral hepatitis, the consequences of which will affect hundreds of millions of people worldwide. Up until 1995, five distinct and unrelated hepatitis viruses had been molecularly characterized (Table 1), and the clinical impact of these agents has been the focus of extensive studies. In addition to the spectrum of acute and chronic liver disease, these agents can cause a number of systemic diseases (Table 2).

Non-A-E Agents

Over the years, considerable evidence has accumulated that some forms of viral hepatitis are not etiologically related to the five known hepatitis viruses (A-E) and thus another viral agent, as yet uncharacterized, may be the cause of viral hepatitis under these situations. Also, evidence points to the existence of an as yet unknown hepatitis viral agent causing hepatitis-associated aplastic anemia (Table 3).

Multiple Hepatitis Episodes

Some of the earliest evidence came from clinical observations of the occurrence of multiple episodes of

TABLE 1. Five human hepatitis viruses A-E and their clinical consequences.

Agent	Genome	Clinical consequences
Enteric		
HAV, picornavirus, 27 nm	4.5 kb, ssRNA	AH, FHF
HEV, calcivirus, 32 nm	7.5 kb, ssRNA (+)	AH, FHF*
Parenteral		
HBV, hepadnavirus, 42 nm	3.2 kb, dsDNA	AH, FHF, CH [†] , cirrhosis HCC
HCV, flavivirus, 30-60 nm	9.4 kb, ssRNA	AH, CH [‡] , cirrhosis, HCC
HDV, satellite, 35-40 nm	1.7 kb, ssRNA (-)	AH, FHF, CH ^{**} , cirrhosis, HCC

AH=acute hepatitis; FHF=fulminant hepatic failure; CH=chronic hepatitis; HCC=hepatocellular carcinoma; *>20% in pregnant women; †5% in adults and >90% in neonates; ‡50-80%; **5% in coinfection and >50% in super-infection.

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TABLE 2. *Extrahepatic manifestations of hepatitis viruses.*

Condition	Virus
Polyarteritis nodosa	HBV
Glomerulonephritis	HCV, HBV
Essential mixed cryoglobulinemia	HCV
Porphyria cutanea tarda	HCV
Aplastic anaemia	Non-A-E

TABLE 3. *Clinical conditions in which novel agents may be identified and putative novel agents described in the past.*

Clinical condition	Putative agent
Acute hepatitis in surgeon (GB)	GB agent
Fulminant hepatitis non-A-E	Hepatitis F (toga virus)
Syncytial giant cell hepatitis	Paramyxoviridae
Non-A, non-B hepatitis (non-A-E type)	Chloroform-resistant non-tubule forming agent
Epidemic hepatitis (non-A-E type)	None
Hepatitis-associated aplastic anemia	None

hepatitis in the same individual.² One or more than one such episode was unrelated to the existing agents (A-E) and thus pointed to a non-A-E agent(s). Such observations were commonly documented in patients receiving transfusions, intravenous drug users, hemophiliacs and dialysis patients, suggesting that the non-A-E agent may be transmitted by parenteral route. Animal transmission studies with non-A, non-B hepatitis agents was another piece of strong evidence for a non-A-E agent.³ Chimpanzee transmission studies identified two infectious inocula, resulting in two types of disease with differences in incubation period, pattern of enzyme elevations, chronicity and ultrastructural changes (Table 4). Subsequent studies identified HCV in a chloroform-sensitive, tubule-forming, infectious inoculum, and as an etiologic cause of the disease caused by this inoculum. Unresolved was the nature of the second agent and the disease caused by it (non-A-E agent).

Transfusion-Associated Hepatitis

Transfusion-associated hepatitis has, for the first time, set the stage for the existence of a non-A, non-B agent and has led to the subsequent discovery of HCV. The same clinical syndrome has set another stage for the existence of a parenterally transmitted non-A-E agent. In the multicenter Transfusion Transmitted Virus Study, it was shown that only 60% of cases originally classified as non-A, non-B hepatitis were related to HCV. Therefore, by serologic exclusion, 40% of these cases might be classified

as non-A-E.⁴ In the prospective study, conducted at the National Institutes of Health in Bethesda, MD, a higher proportion of cases were HCV-related, but still, 12% were classified as being of unknown etiology.⁵ However, recent comparisons of incidence rates between suspected cases of non-A-E hepatitis and nontransfused or autologous transfused subjects have cast some doubt on the magnitude of transfusion-associated hepatitis of unknown etiology. In the controlled study, the incidence of hepatitis C was markedly different between transfused subjects and nontransfused controls (5.4% versus 0%), whereas the incidence of non-A-E did not differ significantly among transfused and nontransfused controls (3.5% versus 3.0%). This reflected, in part, lenient criteria for defining viral hepatitis in that study, such that many nontransfused subjects met the study criteria for viral hepatitis, but probably had low-level ALT elevations related to their surgery and hospitalization rather than to viral infection.⁴

Two additional studies have demonstrated low rates of transfusion-associated hepatitis of undetermined etiology, after the second-generation anti-HCV assay for donor screening has been instituted.^{6,7} Though the magnitude of transfusion-associated hepatitis of undetermined etiology may be a focus of controversy, there is no doubt that this is the strongest evidence for the existence of an agent(s) other than hepatitis A-E.

Community-Acquired Hepatitis

Excellent studies at the Centers for Disease Control (CDC) have been conducted into the causation of community-acquired hepatitis.⁸ The CDC has established four sentinel counties across the United States that continuously monitor acute hepatitis incidence and thus establish viral and epidemiologic cause in each case. In an analysis of 130 patients with non-A, non-B hepatitis, 82% were determined to be HCV-related based on the determination of anti-HCV, HCV RNA and HCV antigen in the liver tissue. Thus, 18% of community-acquired hepatitis in the USA might be due to the agent(s) of non-A-E origin. A study of community-acquired hepatitis of acute non-A, non-B in Greece revealed that only 53% were HCV-related; however, PCR was not utilized to detect HCV RNA in this study. With these results in mind, 47% of community-acquired hepatitis in Greece was presumed due to an infectious agent or agents other than HCV.⁹ Buti et al., in Barcelona, analyzed 341 patients presenting with acute hepatitis: 33% were due to HAV, 20% to HBV, 6% to HDV, 22% to HCV and 64 (19%) were negative for all viral markers, including HEV.¹⁰

Thus, the pattern emerges that 20% to 50% of community-acquired hepatitis might be due to an as yet undetermined agent in Western Europe and the USA.

Studies in the Indian subcontinent have revealed HEV as the major etiologic agent for acute sporadic hepatitis. Of

the 42 patients with non-A, non-B, non-C hepatitis, 27 (64.2%) had acute markers of HEV, with the remaining 35% of patients classified as hepatitis non-A-E.¹¹

Fulminant Hepatitis

One of the most intriguing aspects of hepatitis epidemiology is defining the cause of fulminant hepatitis. In Western Europe and the USA, while some cases of fulminant hepatitis are clearly due to HAV and HBV, the majority of such cases lack markers of hepatitis A and B viruses and have been traditionally labeled as non-A, non-B hepatitis. Recent studies using anti-HCV, HCV RNA by PCR studies in sera and liver tissue have failed to incriminate HCV as an etiologic cause of fulminant hepatitis of non-A, non-B type. Overall, in five studies, samples from 81 such patients were analyzed and HCV markers were detected in only two.¹²⁻¹⁶ These data strongly suggest that the predominant cause of fulminant hepatitis in the West is an as yet uncharacterized agent of non-A-E type. Fagan and co-workers have described toga virus-like particles in hepatectomy specimens of seven of 18 patients engrafted for acute liver failure due to non-A, non-B hepatitis.¹⁷ The significance of these findings to the overall spectrum of fulminant hepatitis of non-A, non-B is currently unknown.¹⁸

Chronic Hepatitis

Does a possible novel agent exist in chronic hepatitis of non-A, non-B, non-C type? Diodati and co-workers in Padua, Italy, studied 172 consecutive patients of biopsy-proven chronic hepatitis of non-A, non-B type. Overall, 156 (91%) cases were caused by HCV; thus, the remaining 9% of such cases could be caused by a novel agent.¹⁹ Marcellin and co-workers in France studied 823 patients of histologically proven chronic hepatitis and found only 30 (3.6%) cases unrelated to HBV, HDV, HCV or autoimmune hepatitis, which were possibly related to a novel agent.²⁰

Syncytial Giant Cell Hepatitis

The criteria for diagnosis of syncytial giant cell hepatitis are threefold: 1) clinical features of subacute or chronic hepatitis, usually of greater than average severity or of fulminant hepatitis; 2) biopsy findings which include fusion of hepatocytes with syncytial giant cell transformation of the liver cell cords; bridging necrosis and cholestasis being also invariably present; and 3) demonstration by electron microscopy of cytoplasmic tubular/filamentous particles that resemble nucleocapsids of *Paramyxoviridae* in the syncytial giant cells. Since the original description of this disease, 30 additional cases have been observed in Canada that fulfill these three criteria, and there have also been cases referred from the United States, Mexico, Europe, Australia, and Asia. Many

TABLE 4. Evidence of two types of non-A, non-B hepatitis by reinjection and cross-challenge studies in chimpanzee.³

Infection inocula	Inoculum 1	Inoculum 2
Source	Healthy donor with ↑ ALT	Healthy donor with ↑ ALT
Incubation period	2 weeks	6 weeks
Enzyme elevation	Fluctuating	Monophasic
EM change	Tubular cytoplasmic particles	Granular nuclear particles
Chronicity	High	Low
Rechallenge	Immune	Immune
Cross challenge	Disease	Disease
Chloroform treatment	Sensitive	Resistant
Agent	HCV	Non A-E

other instances fulfill the first two criteria, but electron microscopy was not available or was not successful in demonstrating the cytoplasmic particles (candidate cases). The basic observations confirm that this is a serious disease, but there are exceptions in that some cases are not progressive, and in a few instances, response to antiviral treatment has been reported; in other cases, antiviral or other treatment has not been successful. The identification of the putative paramyxovirus associated with these cases has proven difficult to establish and the virus is still only partially characterized. A comparison between the ultrastructural appearance of the cytoplasmic particles seen in these cases with that of known paramyxovirus is also in progress.²¹

Hepatitis-Associated Aplastic Anemia

The association between aplastic anemia and viral hepatitis has been well documented. In Japan, where both hepatitis and aplastic anemia are more common than in the West, hepatitis has been associated with aplastic anemia in around 8% of the patients.²² In hepatitis-associated aplastic anemia, evaluation rarely reveals the presence of HAV and HBV, and most cases have been classified as non-A, non-B hepatitis based on serologic exclusion. Pol and co-workers compared 19 such patients to 23 patients of aplastic anemia of other or unknown etiology; anti-HCV and HCV RNA by PCR was detected in 16% and 21%, respectively, in patients with hepatitis-associated aplastic anemia, and 35% and 26% respectively in aplasia of other etiology.²³

Hibbs et al. studied 28 patients with hepatitis-associated aplastic anemia from the USA, Asia and Europe. HCV RNA was detected by PCR in 36% of patients; however, the viremia appeared to be associated with blood transfusions received after the development of aplastic

anemia, rather than being causally related to the development of the aplastic anemia.²⁴ Thus, the syndrome of hepatitis-associated aplastic anemia generally cannot be attributed to HAV, HBV or HCV, strongly suggesting the existence of an additional novel agent causing the syndrome.

Waterborne Epidemic Hepatitis

Waterborne epidemics of hepatitis occur in developing countries, involving hundreds and thousands of people. The disease occurs in the adult population, with a high mortality rate in pregnant women. The illness is acute self-limiting hepatitis with no evidence of a chronic carrier state or chronic liver disease. HEV is the etiologic cause of the majority of these epidemics. Over the last few decades, since these epidemics are being regularly tested for HEV, over 30 epidemics were studied and found to be serologically related to HEV.²⁵ Recently, however, two epidemics of presumed waterborne disease, which lacked acute markers of HEV, have been reported in the Indian subcontinent.²⁶ There was no clinical or epidemiological evidence of exposure to any hepatotoxin in this population. It is strongly suspected that such epidemics were caused by another, as yet uncharacterized, agent. In the absence of any solid information regarding the nature of the causative agent(s) of non-A-E hepatitis, all molecular "roads" remained open. Primate transmission studies suggested that as many as three separate non-A-E viruses might be responsible for the viral hepatitis, unrelated to known agents. In fact, application of such a molecular approach to presumed non-A-E hepatitis led to the discovery of the hepatitis G virus (HGV).

Discovery of Novel Agents

GB Agent

The first hint of a transmissible non-A-E hepatitis agent appeared over 30 years ago in the laboratory of the late Prof. F. Deinhardt. Blood serum from a surgeon (GB) induced acute hepatitis when inoculated into tamarins (small South American monkeys). In the 1970s, the sera were tested for HAV and HBV and found to lack acute markers of either infection. In the 1980s, new assays ruled out hepatitis C and hepatitis E viruses as causative agents.¹ Thus, the GB agent held promise for identifying a novel virus. However, the true origin of the GB agent remained questionable until the recent application of modern molecular virological techniques by the virus discovery group of Abbott Laboratories in North Chicago, headed by Dr. Isa Mushahwar.

GBV-C Virus

A PCR method (representational difference analysis) was used to clone specific nucleotide sequences present in

the infectious plasma of a tamarin infected with the GB hepatitis agent. Extension of sequences found in the seven original clones revealed the presence of two related but unique Flaviviral-like RNA genomes. These two newly discovered viruses were provisionally named GB virus A (GBV-A) and GB virus B (GBV-B).²⁷ PCR studies indicate that GBV-A and GBV-B can be detected in tamarin serum after inoculation with the GB agent. However, GBV-B alone was found to be sufficient to cause hepatitis in the inoculated tamarins, while GBV-A did not appear to induce hepatitis in tamarins. In infected tamarins, there was transient but specific immune response to GBV-B proteins, but no detectable immune response to GBV-A proteins.²⁸ GBV-A-like sequences were detected in the sera of several different tamarins prior to their exposure to the GB agent. These data suggested that GBV-A may be a naturally occurring tamarin virus obtained during passage of the original GB agent in tamarins.²⁹ Degenerate oligonucleotide primers derived from regions highly conserved for GBV-A, GBV-B and HCV were utilized in PCR studies to determine if GBV-A and/or GBV-B could be detected in human sera. Although GBV-A and GBV-B were not found, a third novel flavi-like virus was identified, provisionally named GBV-C. Additional PCR studies indicated that GBV-C is identified in the sera of several different individuals with hepatitis. The novel virus, GBV-C, was subsequently sequenced.³⁰

HGV

Simultaneously with these studies in the Abbott Laboratories, researchers at Genelabs Technologies Inc., Redwood City, CA, cloned and sequenced a novel virus from a patient with post-transfusion chronic hepatitis and from another person with elevated ALT and no history of hepatitis. The new virus was called hepatitis G virus (HGV). The virus was transfusion-transmissible and was associated with acute and chronic hepatitis.³¹

Phylogenetics

The evolutionary relationship between the GB viruses (GBV-A, GBV-B, GBV-C), hepatitis G virus (HGV) and HCV was determined by phylogenetic analysis of the aligned viral polyprotein sequences. The data shows that none of the GB viruses possess more than 32% amino acid sequence identity with any HCV isolate. In contrast, the HCV isolates exhibit at least a 70% sequence identity with each other. The identity between GBV-A and GBV-C is 48%, while that between GBV-B and GBV-A/C is below 30%. In addition, GBV-C and HGV possess 95% identity, indicating that they are independent isolates of the same virus. Thus, the novel human hepatitis virus identified is designated as hepatitis G virus (HGV) or hepatitis GB virus-C (GBV-C).³²⁻³⁵

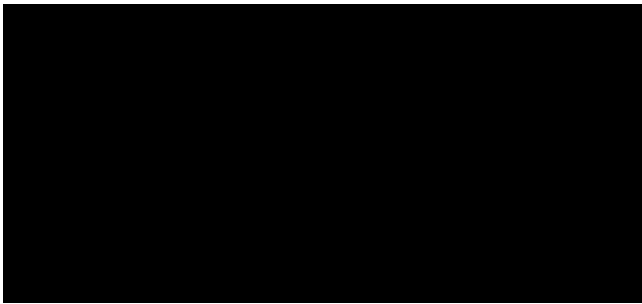


FIGURE 1. Genomic organization of HGV/GBV-C. The genome consists of at least 9125 nucleotides and has structural (C, E1 and E2) and nonstructural (NS2, NS3, NS4 and NS5) proteins located at 5' and 3' ends, respectively. 5'-untranslated end contains blocks of highly conserved sequences. The virus encodes a single polyprotein of 2900 aminoacids (NC=non-coding region; AA=amino-acids).³³

Genomes

The genomes of GB viruses are organized like those of other flavi- and pestiviruses, with genes predicted to encode the structural and nonstructural proteins located at the 5' and 3' ends respectively (Figure 1). These viruses encode for genes for a serine protease, a helicase and an RNA-dependent RNA polymerase, consistent with other pesti- and flaviviruses. Across their entire open reading frames, the GB agents exhibit less than 27% to 48% identity to each other, suggesting that GBV-A, GBV-B and GBV-C/HGV may be classified as three new separate genera within the *Flaviviridae*.^{30,31}

Virus

HGV/GBV-C is a positive-strand RNA virus with sequence identity with various flaviviruses. The genome consists of at least 9125 nucleotides and has structural and nonstructural proteins located at the 5' and 3' ends, respectively. Sequence analysis of PCR products obtained from specimens found to contain the virus indicate that the sequences were fairly divergent (83% to 99% identical). Multiple sequence alignments demonstrated that the 5'-untranslated region (UTR) contains blocks of highly conserved sequences. The conserved deletions/insertions shifts in the reading frame resulted in the observation of three different sizes of the putative capsid protein in different isolates. Also, sequences analysis suggests that the virus encodes a single polyprotein of 2900 amino acids, which includes highly conserved motifs in NS2, NS3 and NS5. Antigen regions were identified in the putative NS3, NS4 and NS5 proteins from the virus. Epitope mapping with smaller expressed regions have identified at least four epitopes in HGV/GBV-C. Until now, five distinct genotypes of virus have been identified.^{30,31}

Diagnosis

GBV-C was originally identified by molecular assay

utilizing degenerate oligonucleotide primers derived from the putative NS3 region of the genome and serum-derived DNA as the template. This primer pair has been used to demonstrate the presence of GBV-C sequence in cases of non-A-E hepatitis, HCV sero indeterminants and intravenous drug users.³⁰ The second molecular assay utilized oligonucleotide primer pairs from the 5'-end sequences of GBV-C, presumably in the untranslated region of the virus. Extensive studies have been done using these primers in RT-PCR to detect GBV-C RNA in a normal blood donor, intravenous drug users and acute/chronic non-A, non-B hepatitis.³⁴ Automated probe-based assays have been established for the detection of GBV-C (Abbott Lcx probe system). Researchers at the Genelabs, USA, have published data on HGV epidemiology using two independent primers from the NS5 region in RT-PCT to detect HGV RNA.³¹ Studies at Abbott Laboratories have developed an ELISA for detection of GBV-C-specific antibodies and attempts are being made to optimize the technique.³⁶

Prevalence

HGV/GBV-C is detected in about 1% of volunteer blood donors with normal ALT values and in approximately 4% of blood donors with elevated ALT values. This data illustrate that the virus is present in the blood supply. It is detected in 15% of intravenous drug users, suggesting a parenteral route of transmission. HGV/GBV-C can be detected in 13% of paid plasma donors. Potentially, the virus is being transmitted through the use of contaminated blood and blood products. Approximately 20% of those individuals with acute or chronic hepatitis C virus infection are HGV/GBV-C RNA positive. The virus establishes a persistent viremia in many individuals, with viral RNA being detected for a year after infection. The virus is detected in only 7% of non-A-E hepatitis cases, including cases of fulminant hepatitis and hepatocellular carcinoma. Eighteen percent of a random population from West Africa were positive for HGV/GBV-C. This region is endemic for HBV.^{30,31}

Sequence of Events

Krawczynski et al. performed transmission experiments with HGV containing plasma specimens from two patients with chronic hepatitis (PNF 2161 and R 10291).³⁷ Inoculation of the infectious inocula were done into chimpanzees, tamarins and cynomolgus monkeys. In chimpanzees inoculated, HGV RNA was detected in serum samples 74 to 84 days after inoculation and persisted up to 20 months after inoculation. The liver enzyme values were in the normal range throughout the observation period and no pathogenic changes were detected in liver biopsy

specimens. In tamarins, liver enzyme activity was elevated beginning 30 days after inoculation and was accompanied by necroinflammatory lobular changes and portal infiltrates in the liver. Among inoculated cynomolgus monkeys, HGV RNA was detected in the serum specimen of one macaque 39 and 47 days after inoculation. These experiments provide evidence that HGV can be transmitted experimentally to nonhuman primates and cause persistent viremia. The lack of evidence of liver damage in the chimpanzee model of HGV infection may be related to the biologic characteristic of the virus replication in the liver and/or extrahepatic locations.

The natural history of HGV/GBV-C in humans was studied by Gallagher et al.³⁸ The authors examined serial serum samples from patients with community-acquired viral hepatitis for HGV RNA by RT-PCR. Of 12 patients evaluated, all had evidence of persistent viremia over a follow-up period extending from three to nine years. Four patterns of viremia were observed. HGV RNA persistence and titer were not associated with the presence or absence of HCV co-infection.

HGV/GBV-C and Clinical Disease

HGB/GBV-C appears to be transmitted following receipt of blood from the infected donors. Persons infected with the virus appear to remain persistently infected (HGV/GBV-C RNA positive) for up to nine years. Although infection is documented in humans in many clinical situations, the strength of association of HGV/GBV-C infections with acute hepatitis and chronic liver disease is unclear and has not been fully demonstrated.

Transfusion-Associated Hepatitis

Alter et al. studied 13 cases of transfusion-associated non-A-E hepatitis from the NIH series for HGV RNA by PCR and three (23%) demonstrated the *de novo* appearance of the viral RNA.³⁹ The clinical course of these three cases was variable, one showing rapid recovery, another, delayed recovery and the third, chronic hepatitis. HGV RNA persisted in all cases for at least one year and in one case for at least four years.

Further analysis of the sera from the NIH cohort showed that the novel agent was present in 11% of 100 recipients, with minimal ALT elevations, in 10% of 62 patients with HCV-related hepatitis, nine (6%) of 152 recipients with no ALT elevations, and one (0.6%) of 157 nontransfused controls. Among HGV-RNA-positive patients, 5% met criteria of non-A-E hepatitis, 20% had minimal ALT elevations, 10% were co-infected with HCV and 65% had no biochemical evidence of liver disease. The authors concluded that HGV infection was transmitted

by transfusions, caused persistent viremia and was commonly co-infected with HCV; however, the infection was commonly asymptomatic and a clear association between transfusion-associated non-A-E hepatitis and HGV could not be documented.³⁹

Wang et al. conducted a prospective study of transfusion-transmitted GBV-C infection in Taipei, Taiwan.⁴⁰ Among the 400 adults who had undergone cardiac surgery, 40 were positive for GBV-C RNA and seven patients were co-infected with HCV. The risk of transmission of GBV-C was estimated to be approximately 0.46% per donor. GBV-C RNA was detectable one week after transfusion and persisted for eight years with a chronicity rate of 36%. However, no evident symptoms or signs were noted in the 25 patients infected by GBV-C alone and the average peak ALT was 31 (u/L range 12-123), with persistently normal values in 20 patients. In the seven patients co-infected with HCV, the clinical course of hepatitis was similar to those infected with HCV alone. Of the eight patients with transfusion-associated non-A-E hepatitis, only one was positive for GBV-C RNA. These data further strengthened the belief that this novel agent does not seem to cause clinical hepatitis in most instances.⁴⁰

Community-Acquired Viral Hepatitis

Alter et al. conducted epidemiological studies of GBV viruses on community-acquired acute viral hepatitis reported to four county health departments at the CDC in Atlanta, GA. An average of 17% of viral hepatitis was due to HCV and 2% were non-A-E type. GBV-A and GBV-B were detected in none of the sera; however, GBV-C RNA was detected in 20% of the HCV and 14% of the non-A-E hepatitis.⁴¹

The clinical and demographic data of subjects infected with HGV alone, HCV alone and HCV/HGV did not differ. All HGV-infected persons had persistent viremia but none had evidence of chronic hepatitis. Chronic hepatitis developed in >60% of the HCV alone and HCV/HGV groups and in 26% of the non-A-G group. The authors concluded that HGV accounted for only 0.3% of community-acquired acute viral hepatitis in the USA. Persistent viremia is common, but clinical disease and chronic hepatitis do not occur.

Yashima et al. studied the role of HGV infection in the etiology of acute non-A-E hepatitis from Moscow, Russia. Of the 3511 acute viral hepatitis patients studied, 40 (1.1%) lacked markers of hepatitis viruses A-E. HGV RNA was detected in 1/28 (3%) of non-A-E patients, 9/22 (41%) of HCV patients and 0/11 (0%) of control subjects. The authors concluded that HGV was not the etiological agent of community-acute non-A-E hepatitis in Moscow, Russia.⁴²

Fulminant Hepatitis

Moaven et al. studied the possible role of HGV in the etiology of fulminant hepatitis of non-A-E type.⁴³ None of the nine such patients with fulminant hepatitis had HGV RNA detected by RT-PCR; however, two of the eight controls with HCV (n=1) and Wilson's disease (n=1) were positive for HGV RNA. Following liver transplantation, six of the nine fulminant and four of the eight controls were HGV RNA positive. The authors concluded no apparent association of HGV with non-A-E fulminant hepatitis.⁴³ Thomas et al. found that two of the 17 patients with fulminant non-A-E type were HGV RNA positive.⁴⁴

In contrast to the above data, Riffelman et al. studied six patients with fulminant hepatitis of non-A-E type: five patients had HGV RNA detected in their acute phase sera. These data demonstrate that GBV-C was possibly associated with fulminant hepatitis of non-A-E type in Europe.⁴⁵ Similar data of association of HGV/GBV-C with fulminant hepatitis of non-A-E type have been published from Japan. Mishiro and Okamoto found GBV-C RNA in 11 out of the 22 patients with hepatitis non-A-E type in Japan.⁴⁶

Apart from the above data, preliminary data are available in which HGV/GBV-C has been investigated as an etiological agent in chronic liver disease, hepatocellular carcinoma, aplastic anemia and even thrombocytopenic purpura. The GBV-C genome was detected in around 10% of patients with chronic liver disease in Japan, suggesting GBV-C contribution to chronic liver disease is less significant than other known viruses. In another study from Japan, Kiyosawa et al. detected GBV-C RNA in four of the 25 patients with chronic liver disease of non-A-E type. Of four patients, one was positive for HBV DNA.⁴⁷

Mantero et al. studied GBV-C detection in severe aplastic anemia patients. Of the 12 patients with aplastic anemia, six patients (all severe type) had GBV-C RNA detected in sera. Among the six patients with positive GBV-C RNA, two had been co-infected with HCV. One child with positive GBV-C RNA had hepatitis-associated aplastic anemia syndrome. The authors concluded that there is a strong association between GBV-C and severe aplastic anemia in children.⁴⁸ Further data in this area shall be watched with great interest. Data also have been published implying a possible role of GBV-C in the onset of idiopathic thrombocytopenic purpura in asymptomatic HIV+ patients.

No data are currently available about the role of HGV/GBV-C in the causation of a number of clinical situations of acute and chronic liver disease of undetermined origin; these data shall be available in due course.

Addendum

Since this paper was submitted for publication, further data have been reported on the epidemiology of HGV/GBV-C. A specific mutant strain of GBV-C was detected in German patients with fulminant hepatic failure (Lancet 1996;348:1626-9). Patients on hemodialysis were found to be at increased risk of GBV-C infection, which could be transmitted by transfusion and patient-to-patient routes (N Eng J Med 1996;334:1485-90; J Med Virol 1996;49:248-52). GBV-C infection was common in Japanese patients with leprosy (J Med Virol 1996;49:110-4). Italian patients with acute or chronic hepatitis of unknown etiology had high prevalence (35%-39%) of GBV-C RNA in their sera (J Inf Dis 1996;174:181-3). HGV infection was frequent with end-stage HCV disease undergoing transplantation and there was no association between the presence of HGV coinfection and the severity of liver disease post-transplantation, graft or patient survival (Gastroenterology 1996;111:569-75).

The clinical implications of GBV-C/HGV infection are as yet a matter of intense debate. Does this agent cause acute liver injury and can it lead to chronic liver disease? By including GBV-C/HGV in the family of hepatitis viruses, it is understood that it can cause acute and/or chronic liver disease. Most of the investigators feel that this appellation has been given to this agent rather prematurely (N Engl J Med 1996;334:1536-7). This agent as of today is in search for a candidate disease, and the search is on....

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