REVIEW

DOES HEPATITIS G VIRUS CAUSE SIGNIFICANT CLINICAL LIVER DISEASE?

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Abstract. Regarding the newly discovered hepatitis G virus (HGV), little is known about its relation to the cause and clinical significance of acute and chronic liver disease and hepatocellular carcinoma. Lacking a reliable serum immunoassay, the only method available for detecting the viral RNA in patients consists of the rather costly and time consuming RT-PCR. HGV has a worldwide distribution with up to 5% voluntary and 12.9% commercial blood donors infected, yet it appears to be asymptomatic. Moreover, HGV is frequently found as a coinfection with HCV or, to a lesser extent, HBV with symptoms tending to follow the patterns known for HCV or HBV infection, respectively. Being a blood-borne virus, it is most prevalent among members of high risk groups, such as IVDUs, patients on hemodialysis, recipients of blood and blood products and patients infected with HCV, HBV, or HIV. HGV can be parenterally, vertically, or sexually transmitted and after prolonged exposure, the virus may be eliminated by the patient's immune response. As yet, no unambiguous evidence exists regarding HGV's role in causing acute or chronic liver disease and, apart from a few isolated reports to the contrary, the infections appear rather mild. Therefore, more studies are required before a decision can be made whether to routinely screen blood donors for the presence of HGV RNA.

INTRODUCTION

Based on epidemiological as well as clinical studies, the existence of additional, non-A-E hepatotropic viruses responsible for some cases of non-A-E human hepatitis has been proposed (Alter, 1994; Simons et al, 1995a). In 1995, two novel viruses designated GBV-A and GBV-B, respectively, were identified in the serum of a tamarin infected by the human GB hepatitis agent by means of a subtractive polymerase chain reaction (PCR) methodology (Simons et al, 1995b). Subsequently, a third virus named GBV-C and closely related to GBV-A was isolated by reverse-transcription PCR (RT-PCR) using degenerate oligonucleotide primers capable of amplifying a segment of the helicase gene of either GBV-A, GBV-B, or hepatitis C virus (HCV) (Leary et al, 1996). GBV-A, GBV-B, and GBV-C have been identified as members of the Flaviviridae family with their genome comprising single-stranded RNA of positive polarity and thus are clearly distinct from HCV (Muerhoff et al, 1995). Simultaneously, another virus was isolated from the plasma of a patient suffering from non-A-E chronic hepatitis and designated hepatitis G virus (HGV) (Linnen et al, 1996). Due to its close

relatedness to GBV-C, both viruses are now considered two independent isolates of the same virus (Zuckerman, 1996). Subsequently, numerous studies were performed confirming GBV-C/HGV, from here onwards designated HGV, to be capable of infecting humans acutely and chronically.

Epidemiology of HGV infection

HGV infection has a worldwide distribution and since no reliable serological test has been available, many studies were performed aimed at determining the prevalence of HGV infection among blood donors and healthy individuals by means of RT-PCR, which has been proven to be the most sensitive, though time consuming method for identifying HGV RNA in human serum. In the USA, the frequency of detection ranged from 0.79% in voluntary blood donors with normal plasma alanine aminotransferase (ALT) values to over 3.9% in voluntary blood donors with elevated ALT values to 12.9% among commercial blood donors (Dawson et al, 1996). In European countries, the prevalence was found to be between 1 and 4% (Heringlake et al, 1996; Schlueter et al, 1996; Stark et al, 1996; Wolff et al, 1996; Fiordalisi et al, 1996); in Aus-

tralia it was 4% (Moaven *et al*, 1996), and in Japan 0.9% (Masuko *et al*, 1996). A high frequency of 14% has been reported in sera obtained from West Africa (Dawson *et al*, 1996), supposedly due to the simultaneous prevalence of hepatitis B (HBV). Yet contrasting this, in Asia where HBV is endemic, HGV infection was found to range from 0.7-2% among voluntary blood donors (Lin and Jin, 1997; Wu *et al*, 1997) to 7.9% among commercial blood donors in China (Wu *et al*, 1997), and up to 5% in Thailand (Poovorawan *et al*, 1997b), respectively. Taken together, HGV infection is more prevalent in the population than HCV.

HGV infection in high risk groups

Since HGV has been shown to be a parenterally transmissible agent (Linnen *et al*, 1996) it can be expected to be encountered more frequently among members of high risk groups, as for example IVDUs, patients on hemodialysis, and the recipients of blood and blood products, as well as individuals harboring some other blood-borne virus, such as HBV, HCV, or HIV. Accordingly, a German study detected HGV RNA in 33% of IVDUs and 11% of homosexual and bisexual men (Schlueter *et al*, 1996; Stark *et al*, 1996). Another group of investigators examined the sera obtained from patients with chronic hepatitis C for the presence of HGV RNA and found 19% positive. Analysis of HGV prevalence rates revealed dual infections related to shared parenteral risk factors, such as intravenous drug abuse (Stark *et al*, 1996) and multiple transfusions (Poovorawan *et al*, 1997b). Apart from this, patients with dual infections had a statistically significant lower mean age compared to those patients infected solely by HCV (Schleicher *et al*, 1996). A study performed with the aim to elucidate the impact of HGV infections on immunosuppressed patients revealed that HGV infections, first, were clinically insignificant and, second, not correlated with the duration of immunosuppression, but correlated closely with transfusion frequency (Wolff *et al*, 1996). These observations have been confirmed by various studies conducted on non-immunodepressed patients multiply transfused for thalassemia or sickle cell disease (Lefrere *et al*, 1996; Poovorawan *et al*, 1997b).

HGV infection and liver disease

The prevalence of HGV among various liver disease groups exhibits considerable variation. For example, it was found to reach 10% in patients suffering from conditions such as alcoholic liver disease, autoimmune hepatitis, primary biliary cirrhosis and chronic HBV infection, and interestingly, it amounted to 21% in the chronic HCV infection group (Hadziyannis *et al*, 1995). Actually, in most cases investigated to date HGV infection is found as a coinfection with HCV, without having any effect on the severity of coexisting HCV infection (Alter *et al*, 1997), and to a lesser extent with HBV (Bralet *et al*, 1997). However unlike HCV, HGV might be eliminated more easily by the host's immune system, at least in immunocompetent patients, as the prevalence of HGV RNA was shown to be much higher in immunosuppressed patients than that in the non-suppressed immunocompetent patients (Kudo *et al*, 1996). HGV has also been found to exist in an asymptomatic carrier state, for example, retrospective testing of stored sera from HGV positive patients has shown that viremia can persist for up to 17 years (Masuko *et al*, 1996; Kao *et al*, 1996a). As to the association of HGV infection with raised ALT levels, those patients infected with HGV alone had normal ALT levels and of those with raised levels, about half had enzyme elevations just above the upper limit of normal.

Contrasting this apparently rather mild course of infection are the results reported from Italy where HGV RNA could be demonstrated in 35% of acute and 39% of chronic hepatitis patients, respectively (Fiordalisi *et al*, 1996). A report originating from Karachi, Pakistan, also claims having identified HGV infection as the underlying cause of chronic liver disease (Moatter *et al*, 1996). Similarly in southern China, HGV infection has been claimed responsible for liver disease, specifically, acute or chronic hepatitis, liver cirrhosis, or HCC (Wu *et al*, 1997). The role of HGV in fulminant hepatitis remains also somewhat controversial, especially since studies conducted subsequently to the reports from Germany (Heringlake *et al*, 1996), Japan (Yoshiba *et al*, 1994, 1995), and India (Panda *et al*, 1996), respectively, have not been able to confirm those findings (Kuroki *et al*, 1996; Sallie *et al*, 1996). Regarding the potential of HGV to cause clinical hepatitis, it usually accounts for only a minority of cases of acute non-A-E hepatitis, and

there is no evidence yet of progression over time to chronic hepatitis, cirrhosis, or HCC, as occurs with HBV and HCV (Kew and Kassianides, 1996).

Post-hepatitis aplastic anemia

In few cases, aplastic anemia can be observed as a consequence of overt hepatitis. Yet, the conclusion arrived at independently by various research groups, who had detected only HGV RNA in the respective patient's sera at initial presentation, that HGV could be responsible for both hepatitis and aplastic anemia should be cautiously interpreted because of the small case numbers and the insufficient seroconversion data (Zaidi et al, 1996; Byrnes et al, 1996; Kao et al, 1996b). Here it is worth mentioning that our own observations made on two cases of post-hepatitis aplastic anemia contradict the above mentioned findings in that we could not detect any of the known hepatitis viruses A to G in the patient's sera (Poovorawan et al, 1997a).

Transmission of HGV

In addition to the parenteral transmission of HGV which has been proven by many different researchers worldwide (Linnen et al, 1996; Stark et al, 1996; Jarvis et al, 1996; Masuko et al, 1996; Alter et al, 1997), the virus has also been shown to be transmitted vertically (Feucht et al, 1996), as well as sexually (Persico et al, 1996).

Clinical course of HGV infection

Regarding the epidemiology of HGV infection, its prevalence is higher than that observed for HCV infection. However, when it comes to clinical manifestations the opposite seems to be the case in that HGV infections are almost invariably asymptomatic, whereas HCV infections more frequently cause chronic hepatitis and are also associated with hepatocellular carcinoma.

Moreover, there has been a body of indirect evidence demonstrating that HGV can be eliminated by the patient's immune response. This hypothesis is supported by data reporting a low prevalence of HGV infection, compared to that of HCV, among IVDUs. Likewise in these patients, HGV RNA seroprevalence significantly decreased with increasing time since first drug injection

(Stark et al, 1996), whereas the seroprevalence of both HCV RNA and anti-HCV antibody increased. Our observations of thalassemic children who have undergone multiple blood transfusions lead to very similar conclusions in that the prevalence of detectable HGV RNA increases in proportion to the number of blood transfusions until a certain level reminiscent of saturation has been attained. From then on, the amount of HGV RNA steadily decreases so that in most cases the virus has been cleared by the time the children have reached adolescence (Poovorawan et al, 1997b). This can easily be proven once serological screening of patients for anti-HGV antibodies becomes possible. Direct evidence of the immune system's capability to eliminate HGV has been provided by a research group in the United States reporting cases in which viral RNA became undetectable 12 to 18 months after onset of infection (Linnen et al, 1996; Alter et al, 1997).

Is it necessary to screen blood donors for HGV?

All the data reported thus far, conflicting though they sometimes may be, suggest an as yet rather benign, yet possibly opportunistic virus that hasn't quite discovered its ecological niche yet. Or, in other words, though quite "innocent" on its own, HGV appears to "look for a free ride" in either HBV or HCV infected patients in whom it may actually contribute, however slowly and in whichever way, to resulting hepatic damage. Moreover, considering the well-known tendency of viruses to evade the respective host's immune response by rapid and frequent mutations especially in those genes coding for the antigenic determinants among the envelope proteins, and further considering the generally vulnerable condition of patients in need of blood or blood products, routine screening of blood donors for the presence of HGV RNA would appear advisable, at least at first glance. However, at present the only reliable method to detect HGV in serum consists of RT-PCR which undoubtedly is too costly and too time-consuming to be introduced as a routine procedure. Hence, the decision as to whether to routinely screen blood donors for the presence of HGV will depend on the one hand on the availability of a reliable serological test, and on the other on the outcome of further studies regarding the short-, as well as long-term clinical significance of HGV infection which, at least at present, is still poorly understood.

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