
Hepatitis G virus (HGV): where we stand and what to do?

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Abstract: Hepatitis G virus was identified in 1995. Some work was done on HGV until 1997 and the FDA declared it as a non-harmful virus. This resulted in no screening of virus for blood donors and bags from 1997 until today. A review of scientific literature of the last 16 years, majority identify with polymerase chain reaction (PCR) has shown that HGV is quite prevalent around the globe with low to high prevalence in different countries among blood donors and other groups. It was found to be associated in hepatitis, cirrhosis of the liver and possibly present in hepatocellular carcinoma. It was also seen in hematological disorders and hematological malignancies. It is advisable that screening of blood is better than transferring HGV ignorantly to blood recipients as it was done before, where we did transfer HCV to many individuals which resulted in a lot of morbidities and mortalities.

Keywords: hepatitis G virus; HGV; hepatitis; polymerase chain reaction; PCR.

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1 Introduction

Hepatotropic viral infections include hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis C virus (HCV), hepatitis D virus (HDV) and hepatitis E virus (HEV), all of

which are quite prevalent in our population. Viral hepatitis has been known to us for more than 40 years. For example, HAV was discovered in 1973 and belongs to the Picornaviridae family. HBV was discovered earlier in 1970 and belongs to the Hepdnaviridae family. HCV was recognised in 1988 and belongs to the novel Flaviviridae family. HDV was identified in 1977 and belongs to the Deltaviridae family and HEV was discovered in 1985 belongs to the Calciviridae family. Hepatitis G virus (HGV) was identified in 1995 and belongs to the Flaviviridae family same as HCV, however, it is not a pure hepatotropic virus (Table 1) (Mujeeb, 1998; Chopra, 2010; Zuberi, 1996; Khokhar, 2002; Hamid et al., 2004; Taylor et al., 2000; Reshetiyak, 2008; Chang and Chen, 1999; Quer et al., 2003; Lai et al., 2004; Magder et al., 2005; Terrault, 2002; Marx et al., 2003; Rehman and Hafiz, 2000; Rafiq et al., 1999).

Table 1 Different types of hepatitis viruses

Name	Genome	Genus	Mode of trans.	Ag. in blood	Antibody in blood	Chronic carrier	Chronic hepatitis/cirrhosis	Liver cancer	Envelope
HAV	ssRNA	Picorna-virus	Orofecal	HA ag	Anti HA	No	No	No	No
HBV	dsDNA	Hepdna-virus	Blood, sex, placental	HBs Core E-antigen	Anti HBs Anti-core Anti-e	5%–10%	1%–5%	Yes	Yes
HCV	ssRNA	Flavi-virus	Blood, sex, placental	HC ag	Anti-HC	50%	20%	Yes	Yes
HDV	ssRNA	Delta-virus	Blood	HD ag	Anti-HD	>50%	>50%	?	Yes
HEV	ssRNA	Calci-virus	Orofecal	HE ag	Anti-HE	No	No	No	No
HGV	ssRNA	Flavi-virus	Blood, sex, placental	HG ag	Anti-HG	?	?	?	Yes

HAV is a single stranded RNA (ssRNA) virus without an envelope. The size of this virus is 27 nm and it belongs to Picornaviridae family. There are no chronic carrier states or chronic hepatitis/cirrhosis or cancer with HAV. In addition a vaccine is available for HAV (Mujeeb, 1998; Chopra, 2010; Zuberi, 1996; Khokhar, 2002; Hamid et al., 2004). The other virus transmitted by orofaecal route is HEV. HEV is also an ssRNA virus and is without an envelope. The size of the HEV virus is 30–37 nm and it belong to Calciviridae family. HEV infection is self-limiting and without any complications. However, deaths from this virus in pregnant women have been recorded (Mujeeb, 1998). HBV is transmitted by parenteral, perinatal and through sexual practices. HBV is the only DNA virus in hepatotropic viruses. HBV is a double stranded DNA (dsDNA) with a small portion of ssDNA. The size of virus is variable (42 nm) with an envelope and belongs to Hepdnaviridae family. HBV virus leads to chronic carrier state in 5%–10% of those infected and chronic hepatitis and cirrhosis in 1%–5%. There is a definite association of HBV with liver cancer (Hepatocellular carcinoma) (Mujeeb, 1998; Chang and Chen, 1999; Quer et al., 2003; Lai et al., 2004; Magder et al., 2005; Terrault, 2002; Marx et al., 2003). HBV vaccine and immunoglobulins prevention and treatment modalities are available. HCV has both parenteral and sexual routes of transmission. This virus is ssRNA, 30–60 nm in size with an envelope and belongs to the Flaviviridae family. This virus can lead to chronic carrier states in 50% and chronic hepatitis and

cirrhosis in 20% of those infected. It has been associated with liver cancer (hepatocellular carcinoma). HBV and HCV are the most likely causes of viral hepatitis in Pakistan (Mujeeb, 1998; Chopra, 2010; Khokhar, 2002; Taylor et al., 2000). There is no vaccine available in the market against HCV (Rehman and Hafiz, 2000; Rafiq et al., 1999; Mibagheri, 1999; Ahmed et al., 2006, 2008; Oliveira et al., 2002; Kumar et al., 2007; Alter et al., 1997a, 1997b; Martinol et al., 1997a; Alter, 1996; Odeh et al., 2005; Ling et al., 1997; Simon et al., 1995; Moaven et al., 1998; Ather, 1997; Ramla and Al-Falehh, 1999; Praharaj et al., 2005; Xu et al., 2001; Forns et al., 1997; Noh et al., 1998; Hammad and Zaghloul, 2009; Nogueira et al., 2001; Tanka et al., 1998; Linnen et al., 1996; Tanaka et al., 1996a). HDV is a defective virus which needs the envelope of HBV to overcome its defect. HDV is ssRNA virus, 25 nm in size with an envelope and belongs to Deltaviridae family. This virus can lead to chronic carrier states in 50% and chronic hepatitis and cirrhosis in 50% (Rehman and Hafiz, 2000). Two newly identified viruses in Japan are TT Virus circular ssDNA, naked with 40 Genotypes belongs to Circoviridae identified 1997, second is the SEN virus observed in Italy for the first time in 2000 and belongs to genus similar to TT virus with eight genotypes (Ahmed et al., 2006, 2008).

2 Different results and discussion on global studies

HGV was first identified about 15 years ago. A lot of work has been done throughout the world on this virus. However, very little work is being done in Pakistan. The clinical course of acute and chronic viral hepatitis has not been studied at length. HGV is transmitted as conventional blood borne pathogens. This virus is composed of ssRNA, size 30–60 nm with an envelope and belongs to novel family of Flaviviridae same as HCV with 29% amino acids less in HGV. Other names of this virus are accidental tourist virus/human orphan flavivirus/innocent bystander virus. Interestingly HGV was isolated from blood of blood donors. It is quite prevalent amongst intravenous drug users. There are several modes of transmission for HGV by blood and blood products. It has sexual mode of transmission. It is transmitted from infected mothers to their fetuses. It can also be transmitted to hemophilia patients using factor VIII, parenteral drug users, peritoneal dialysis, hemodialysis and organ transplantation. This virus can lead to acute or chronic liver disease alone or it may co-exist as dual or triple infection (HGV and HCV or HGV, HCV and HBV) (Rafiq et al., 1999; Mibagheri, 1999; Ahmed et al., 2006, 2008; Oliveira et al., 2002; Kumar et al., 2007; Alter et al., 1997a, 1997c). HGV has five genotypes. Genotype 1 is present in West Africa. Genotype 2 is present in North and South America, Europe, East Africa and Subcontinents (Pakistan and India). Genotype 3 is present in China and other Asian Countries. Genotype 4 is present in Myanmar and Vietnam and Genotype 5 is present in South Africa (Reshetiyak, 2008; Ahmed et al., 2006, 2008; Oliveira et al., 2002; Kumar et al., 2007; Alter et al., 1997a). HGV status from different studies ranged from a low prevalence of 0.9%–5.7%, to a medium prevalence of 5.8%–9.9%. For high prevalence the range is 10%–20% and for very high prevalence it is above 20%. Possible mode of transmission is blood and blood products transfusion (s) 0.5–20.0 haemophiliacs 48.0%, sexual transmission (11.0%–21%), intravenous drugs users (13.5%), haemodialysis (26.5%), peritoneal dialysis (13.6%), organ transplants (25.0% in liver transplant) and vertical transmission (12.5% to 33.3%). Clinical signs and symptoms although asymptomatic in the majority of cases, may include fatigue, jaundice, abdominal pain, nausea, diarrhea and loss of appetite. The incubation period of HGV has

yet to be determined. Prevalence of HGV infection ranges from 0.5%–20.0% for example, It is 4.0% in Australia (1996), Brazil 4.4% (2001) and 7.1% (2002) now 4.4%–10.0%, Colombia 6.1% (1998), India 2.3% (2005) and 6.0% (2007), Iran 5.5% (2003) and 4.8% (2009), Hungary 5.5% (1999), Japan 5.0% (2005), Pakistan 0.5%–2.3% (1999), Africa 10.0%–20.0% (1996, 1997 and 1998) and USA 1.6% (1996), although it is now 1.2%–2.0%. Further it has been observed that HGV infection was 11.3% in patients with HIV infection. HGV infection with HIV was 11.0% in other study. In another study, in Tanzania HGV with HIV infection was 23.0% (Rafiq et al., 1999; Mibagheri, 1999; Ahmed et al., 2006, 2008; Oliveira et al., 2002; Kumar et al., 2007; Alter et al., 1997a, 1997b; Martinol et al., 1997a; Alter, 1996; Odeh et al., 2005; Ling et al., 1997; Simon et al., 1995; Moaven et al., 1998; Ather, 1997; Ramla and Al-Falehh, 1999; Praharaj et al., 2005; Xu et al., 2001; Forns et al., 1997; Noh et al., 1998; Hammad and Zaghoul, 2009; Nogueira et al., 2001; Tanka et al., 1998; Linnen et al., 1996; Tanaka et al., 1996a; Stapleton et al., 2004; Xu et al., 2001; Ren et al., 2005; Singh, 2002; Anthony, 2000; Lampe et al., 1998; Yang et al., 2006). In our study HGV was 1.3% amongst total blood donors. In professional donors it was high 2.3% and in volunteer donors it was much less 0.5%. The highest number of positive for HGV in the total group was 3.3% in 50–59 years age. The group of professional donors aged 50–59 years age group, it was 6.7%. In volunteer donors aged 40–49 years of age it was 2.2%. HGV infection is an emerging infection that needs more research and liver function monitoring for longer periods before predicting its outcome (Ahmed et al., 2006, 2008). HGV in Intra venous drugs users (IDUS) is 13.5%. HGV infection was detected in alcoholics at 56.0%. Parenteral drug users also acquired HGV infection. The methods of transmission mentioned earlier are all possible modes with HGV. Although, there is no vaccine currently available, response to alpha interferon therapy was seen in some studies. Further viremia persists for years and it is five times more than HCV. The standard method of diagnosis is use of polymerase chain reaction (PCR). Although, HGV appears to benefit HIV positive patients, it can not be declared as innocent virus (Rafiq et al., 1999; Mibagheri, 1999; Ahmed et al., 2006, 2008; Stark et al., 1996).

In a study fulminant hepatitis with HGV was seen in 16.7% and acute viral hepatitis in 10.0% of cases. HGV alone was present in hepatitis cases at a rate of 33.8% (52/154) with other viruses 66.2% (102/154) in a study. Chronic Hepatitis was up to 9.8% as compared to 21% HBV in another study. In a study done at other centre it was observed that HGV infection in 75% of cases has presented with normal LFT. HGV in chronic liver diseases was from 3.5% to 8.3% in a study done at Singapore. In another study it was found that HGV infection biopsies showed similar changes seen in HCV. Further in Japan 50% of HGV infections were acute fulminant hepatitis. While in the USA. Acute viral hepatitis with HGV was 0.3% and it was positive in 20.0% of cryptogenic cirrhosis. On the contrary HGV infection was detected 89.0% in cirrhotic patients. HGV was detected in 10.0% cases of autoimmune hepatitis or alcoholic hepatitis. In another study it has been reported that HGV-RNA in patients with hepatocellular carcinoma was around 6.0%. Recent studies suggest that 88% hepatocellular carcinoma cases had cirrhosis which was related to presence of HBV (62.0%), HCV (38.0%) and HGV (28.0%). However, isolated HGV infection was detected in only 3.0% cases. HGV infection among Brazilian patients with chronic liver disease and blood donors were also seen. Prospective evaluation of infection with HGV in relation to hepatocellular carcinoma is under study in Shanghai, China (Reshetiyak, 2008; Chang and Chen, 1999; Stark et al.,

1996; Yuan et al., 2000; Tagger et al., 1997; Kanda et al., 1997; Xuezhong et al., 2000; Leao-Filho et al., 2007). Hepatitis GB virus-C RNA has been detected from Japanese patients with hepatocellular carcinoma and cirrhosis. In chronic hepatitis prevalence and clinical significance is very important in assessing future outcome of such infections. HGV viremia persist for years in such patients as compared with HCV and it is five times more in quantity. HGV has also been present in patients with autoimmune hepatitis and alcoholic hepatitis besides already mentioned clinical identities/diseases. *Macaca mulatta* monkey type now can be used as animal model for future research and studies on the HGV (Ren et al., 2005; Martinol et al., 1997b; Adrian and Bisceglie, 1996; Tanaka et al., 1996b; Stark et al., 1996; Yuan et al., 2000; Tagger et al., 1997; Kanda et al., 1997; Xuezhong et al., 2000; Leao-Filho et al., 2007). HGV has been incriminated also in different hematological disorders. Further HGV in Haemophilia patients is 48%. Additionally HGV in haematological diseases of different Malignant potential, such as Hodgkin's lymphoma, non-Hodgkin's lymphoma, acute leukaemia, myeloid-dysplasia, myelo-proliferative disease, multiple myeloma, thrombocytopenia, aplastic anaemia and leucopenia. HGV infection in Hodgkin's disease was 8.0% (HCV 9.0%). Hepatitis G virus (GBV-C) is primarily a lymphotropic virus. Myeloiddysplasia, myeloproliferative disease, multiple myeloma, thrombocytopenia, aplastic anaemia, haemophilia and leukopenia also positive for HGV. HGV is also seen in malignant potential Hodgkin's lymphoma, non-Hodgkin's lymphoma, acute leukaemia. It was also seen in malignant potential Hodgkin's lymphoma, non-Hodgkin's lymphoma, acute leukaemia (Anthony, 2000; Tucker et al., 2000; Reshetiyak et al., 2008; Pavlova et al., 1999; Idilman et al., 2000; Keresztes et al., 2003).

3 Conclusions

The findings from the subject of studies done on HGV infection in different parts of the world can be found in patients with hepatocellular carcinoma, other malignancies such as acute, chronic fulminant hepatitis, cirrhosis of the liver and in other morbidities can contribute to this. It is advisable to recommend HGV testing become mandatory for each blood bag prior to transfusion. In the interest of safety, it is better that each blood bag be screened for HGV rather than risk transferring HGV to blood recipients. Although it will increase cost incurred on each blood bag, patient safety standards and safeguards must be the priority. The lesson learned from our past experiences must be heeded. In right condition of the latest evidence-based research outcomes, we follow old recommendations from FDA or reexamine our practices in light of recent studies.

4 Recommendation

Multi-centre studies for HGV in patients with acute and chronic hepatitis, fulminant hepatitis, cirrhosis and hepatocellular carcinoma and other malignancies should be done at different centres around the globe. It should be done with the support of national and international donor agencies to ascertain our position on the efficiency of HGV blood bags screening.

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