GB Virus C Overview: Insights into Clinical Implication

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ABSTRACT

GB virus C (GBV-C) is a single stranded positive sense RNA virus, which is a member of the Flaviviridae, discovered in 1995 and it is the most closely related human virus to hepatitis C virus (HCV). Unlike HCV, GBV-C considered to be lymphotropic and related to the viral population infecting CD8 T cells and B cells. GBV-C infection has not been convincingly associated with any known human disease; however, several studies have found an association between persistent GBV-C infection and improved survival with slower disease progression among GBV-C/HIV co-infected patients. This virus is only may be important because of its inhibitory effect on human immunodeficiency virus (HIV) replication and its ability to inhibit HIV in vitro[14]. Some studies[15,16,17] showed that the virus is associated with improved survival, a lower mortality rate, slower disease progression among GBV-C/HIV co-infected patients and leading to a lower HIV viral load and higher counts of CD4+ cells in these patients, although some studies have failed to demonstrate these beneficial effects[18].

In this review we discuss the GB virus C natural history, epidemiology and its prevalence in different population, focusing on the disease associations and interaction with HIV infection.

INTRODUCTION

The GB virus C (GBV-C) is an enveloped, single-stranded positive RNA virus belonging to the family Flaviviridae[1], which contains a single open reading frame (ORF) encoding two structural (E1 and E2) and five non-structural proteins[2,3]. GBV-C has a close sequence homology and genomic organization to hepatitis C virus (HCV) with about 30% similarity[4], but its genome lacks the core region and hypervariable region of E2 gene[9].

Although this virus was initially identified as a possible etiological agent of viral hepatitis in humans, and despite its similarity with HCV[5], no convincing association between the virus and any disease entity has been identified and it appears to be a nonpathogenic human virus[6,7]. It does not seem that GBV-C be a hepatotrophic virus and replicates in hepatocytes[8,9]. In fact GBV-C is a lymphotropic virus and related to the viral population infecting CD8 T cells and B cells[10].

This virus is only may be important because of its inhibitory effect on human immunodeficiency virus (HIV) replication and its ability to inhibit HIV in vitro[11]. Some studies[12,13,15] showed that the virus is associated with improved survival, a lower mortality rate, slower disease progression among GBV-C/HIV co-infected patients and leading to a lower HIV viral load and higher counts of CD4+ cells in these patients, although some studies have failed to demonstrate these beneficial effects[18].

In this review we discuss the GB virus C natural history, epidemiology and its prevalence in different population, focusing on the disease associations and interaction with HIV infection.

THE GB VIRUS C TRANSMISSION

GBV-C can be transmitted parenterally through blood and its derivative[13,16,17] and blood transfusion considered as a main risk factor for GBV-C transmission[18]. Specific populations appeared to be particularly at risk for acquiring GBV-C infection, like those with exposure to blood and blood products, hemodialysis patients and injection drug users (IDUs)[19]. Several other non parenteral routes of infection have been considered for GBV-C transmission such as sexual contact[19], percutaneous contamination from saliva[20], nosocomial infection through patient to patient[21] and intrafamilial transmission[19,22].

Several studies have shown that the prevalence of GBV-C...
infections is correlated with sexual activity, independently of risks for parenteral exposures, in both heterosexual and homosexual populations and male to male sex has been described as an effective way of transmission.

Vertical route may also mediate GBV-C transmission and an observational study reported the possible transmission of maternal GBV-C during pregnancy and delivery.

NATURAL HISTORY OF GBV-C
GBV-C infection is found worldwide and can cause persistent human infection without clinical symptoms or disease in either immunocompromised or healthy individuals.

Similar to other lymphotropic viruses, GBV-C is transmitted by parenteral and non-parenteral routes such as sexually and vertically. Therefore, it is highly frequent in populations with other blood borne infections and sexually transmitted diseases.

GBV-C viremia may persist for years but it is eventually cleared in 50-75% of cases and antibodies against the GBV-C E2 envelope usually appear. In most populations, the rate of anti-E2 is 2-6 times higher than the viremia prevalence, suggesting that the GBV-C clear spontaneously by the immune system in most times and the majority of infected cases with GBV-C clear viremia within 2 years of infection.

There is some evidences that HIV infected patients and children may clear GBV-C more slowly than those with intact immune systems and GBV-C viremia is much more common among immunosuppressed individuals than among healthy blood donors.

The presence of GBV-C RNA in serum is associated with active infection whereas detection of anti-E2 indicates prior infection. Therefore anti-E2 antibody is considered as a useful marker for diagnosing GBV-C infections recovery and can be detected after clearance of the virus.

The simultaneous detection of anti-E2 antibody and viral RNA seems to be rare and occurs only for a limited time. The coexistence of the GBV-C viremia and anti-E2 occurs just before clearance, probably in the form of an immunocomplex. In a multicenter study on HIV infected cases, 1.8% of patients with GBV-C viremia had detectable anti-E2 whereas 75% of patients who were negative for GBV-C RNA had E2 antibodies.

Anti-E2 is found more frequently than viremia among healthy blood donors suggesting prior exposure and viral clearance. Although anti-E2 is a marker of past infection, detection may be lost by time possibly more rapidly among HIV infected persons and thus it may be difficult to accurately estimate the true incidence of GBV-C infection.

EPIGENETIC AND DISEASE ASSOCIATION
GBV-C infection is relatively common and has a worldwide distribution. In the general population the GBV-C infection is more prevalent than other blood-borne viruses such as hepatitis C and HIV in Western industrialized countries. Between 1 and 5% of healthy blood donors in developed countries are viremic at the time of donation. The prevalence is higher in blood donors from developing countries which up to 20% of blood donors were viremic in some studies. Most people clear the virus and develop antibodies to the E2 envelope glycoprotein. Furthermore, infection is common in the normal population with up to 12.9% prevalence among paid blood donors in the United States of America, 11% to 14% in West Africa or South Africa, and as high as 37% among HIV-infected individuals.

Some specific populations considered to be particularly at risk to GBV-C infection. For example, some high risk groups such as IDUs have evidence of past or active infection in up to 90% in some populations. Amongst HCV infected patients, GBV-C incidence varies from 3.2 to 64.9% in HCV positive individuals it rates from 11.3% to 45% in HCV positive patients. Little work has been done on co-infection of GBV-C and HBV but no significant effect of this co-infection was reported.

Several surveys designed to determine if GBV-C represented an etiological agent for acute or chronic hepatitis or not? Prospective and retrospective studies provided no evidence of epidemiological association between viremia and acute or chronic hepatitis and further studies failed to demonstrate GBV-C replication in the livers of patients infected with hepatitis viruses.

Numerous efforts were also made to link GBV-C with other disease such as hepatocellular carcinoma, lichen planus, cryoglobulinemia, Sjogrens syndrome, malignant or non-malignant hematological illnesses, but all have failed to identify a specific association with these diseases and GBV-C infection.

However, an association between this virus and improved clinical course in HIV infected patients has been suggested and inverse relationship between GBV-C and HIV plasma viral load was demonstrated in some studies. GBV-C infection modulates T cell homeostasis in vivo through different mechanisms, such as alteration of cytokine and chemokine release and receptor expression; reduce T cell activation, proliferation and apoptosis, all of them have a role in improving HIV clinical outcomes. In vitro studies confirm these clinical data and show a beneficial effect of GBV-C on HIV infection.

Some recent studies were carried out to identify the association between HCV and GBV-C infection. Barbosa et al showed the lower degree of hepatic lesions in HCV/GBV-C co-infected patients, in comparison to HCV/HIV co-infected cases. Boodram et al reported an increased rate of GBV-C clearance in HIV negative IDUs with HCV infection. Another survey demonstrated that co-infection with GBV-C in patients with chronic HIV does not worsen the clinical course of chronic hepatitis C or diminish response of HCV to viral therapy.

GBV-C GENOTYPES
Currently, GBV-C has been classified into six genotypes and many subtypes based on their sequence diversity of either full genome length or a particular genomic range. Geographically, these genotypes and subtypes showed distinct distribution patterns. Genotype 1 is found mainly in Ghana, Zaire and West Africa and is divided into five subtypes; genotype 2 (sub-classified as both 2a and 2b) in the United States and Europe, Egypt, Nepal, Thailand, India, Turkey, Saudi Arabia, Pakistan, UAE and Myanmar; genotype 3 in Asia, Japan, Philippines, China and Bolivia; genotype 4 in Southeast Asia like Myanmar, Cambodia, and Vietnam; genotype 5 in South Africa and genotype 6 which first detected from blood donors and hepatitis patients living in Indonesia.

In South America, the genotypes 2a and 2b have been reported. In Colombia, a high prevalence of GBV-C RNA and presence of genotype 3 were found among Colombian native Indians.

In the Middle East like Iran, Turkey, Saudi Arabia and UAE, the prominent GBV-C was genotype 2, subtype 2a.
GBV-C RNA prevalence rates in HD patients ranged from 11.5 to 29% in the USA[75-77,81], increased number of sexual partners[78,79], having had sex with other men[82-84], history of sexually transmitted infections (STIs)[79,80], healthcare work[85], incarceration[86], hospitalization for performing medical procedures[87], endoscopy[88], snorting cocaine[89] and history of travel to Africa[90].

GBV-C viremia is found in about 20% of high risk patients for parenteral exposure to blood borne pathogens, and past exposure was found in some HCV infected individuals without evidence of active GBV-C infection. For example, in some populations, the evidence of past or active infection was found in up to 90%[91]. Other high risk groups for GBV-C infection include hemophiliaics, hemodialysis patients, transfusion recipients and commercial sex workers, as well as HCV and HIV infected subjects[7].

Due to shared transmission routes, co-infection with GBV-C is common among HIV infected patient with or without HCV. 10%-25% of chronic HCV infected patients and 14%-36% of HIV positive IDUs show the evidence of GBV-C co-infection[92,93]. Some recent studies have shown much higher GBV-C triple infection rate of 30%-36% among HIV/HCV co-infected individuals[94,95].

GBV-C PREVALENCE IN SPECIFIC GROUPS

Blood donors
In European countries, the prevalence of anti-E2 which indicate resolved infection ranges from 10.5% to 24.2%[37,44,45,46], in South Africa (20.3%) and Brazil (19.5%), even higher anti-E2 prevalence rates have been recorded[94]. Anti-E2 has been found in 7.3% of Canadian[97], 10.5% of Norwegian[98] and 11.3% of Russian blood donors[99].

In United States, GBV-C prevalence in blood donors was reported ranging from 0.8% to 12.9%[40,41]. In Egypt, El-Zayadi et al[42] found the prevalence rate 12.2% for GBV-C infection among blood donors and they also showed that GBV-C co-infection rate in HBV and HCV infected patients were 9.7% and 64.9%, respectively[100].

In Asian countries[101-103], anti-E2 seropositivity has been found to be significantly lower (2.5-6.3%). In Iranian volunteer blood donors the prevalence of GBV-C was around 1%[104,105]. In Turkey the prevalence of GBV-C was 5% in blood donors[106] and in Thailand the GBV-C RNA positivity among blood donors was 4.8%[107]. Although in blood donors in Taiwan, a higher prevalence (10.2%) has been reported[108]. Besides, another study among northeastern Thai blood donors carrying HBsAg and anti-HCV revealed a higher frequency of GBV-C RNA (10% and 11%, respectively) in the coinfected cases when compared with the controls[109].

Hemodialysis patients
Patients with chronic renal failure are at high risk of acquiring the GBV-C because they require frequent blood transfusions and undergo medical procedures that accompany bleeding[75,76].

The prevalence of anti-E2 in HD patients has been established in several studies, this rate is variable from 3.8% in Iran[71], 7% in Japan[101], 12.9-29% in Germany[77,78], 14.2% in Belgium[100], 15.6% in Taiwan[110] to 22% in Austria[11].

In a study in Egyptian children, anti-E2 was positive in 41.2% of HD and 28.8% of predialysis children[81].

GBV-C RNA prevalence rates in HD patients ranged from 11.5 to 27% in the USA[76,77], 6-57.5% in Europe[102,103] and in Asia, from less than 2.2% in India[104] to 55% in Indonesia[93].

In a study of hemodialysis patients in Germany, antibodies against GBV-C were detected in 17.5% of patients and viremia in 19.6%. In addition, 3% of the patients were positive for both antibodies and GBV-C RNA[83]. In another study in Iran, 13.6% of HD patients had GBV-C RNA[91]. In a Chinese study, 16.42% of dialysis patients were GBV-C RNA positive and the positive rate of GBV-C RNA increased with the number of times of dialysis[92]. Ramos et al[93] reported that 14.6% of dialysis patients were GBV-C RNA positive in Brazil.

In a study conducted by Hanci et al[71] in Turkey the prevalence of GBV-C RNA in hemodialysis patients was 14% but in another study by Ozdareneldi et al[91], GBV-C RNA was detected in 10.2% of HD patients.

In a study in Egyptian children, GBV-C RNA was positive in 26.5% of HD and 13.6% of predialysis children[81].

Few reports are available in patients on peritoneal dialysis treatment, but these report rates ranging from 0% by Campo et al to 10.5% by Hyunjin and 20% by Fabrizi et al[71].

HIV INFECTED INDIVIDUALS
Over the past several years there has been substantial controversy regarding the interactions between GBV-C and HIV. A number of studies have revealed improved survival among HIV coinfected patients, as compared with those only infected with HIV[11,13,27,62]. Other studies, however, have not shown such a survival advantage[93,94].

GBV-C viremia is associated with improved initial response to antiretroviral regimens and sustained suppression of HIV viral loads for prolonged periods[62]. It is also associated with increased CD4+ cell count, and delayed progression to AIDS in many studies[93].

Two GBV-C proteins that specifically inhibit HIV replication are E2 and NS5A. The GBV-C NS5A mediates HIV inhibition by decreasing the surface expression of CXCR4, a major HIV co-receptor. The E2 protein inhibits HIV gp 41 which is necessary for membrane fusion and viral entry. GBV-C and HIV co-infection leads to reduced expression of the two major HIV co-receptors, CCR5 and CXCR4, on CD4+ cells in terminal HIV infection, which cause delayed progression of HIV in GBV-C/HIV co-infected patients[3,52]. Besides GBV-C can elevate the levels of T helper 1 (Th1) cytokines, especially interleukine-2 which effectively control HIV viral load[18,62].

GBV-C has worldwide distribution with a varying prevalence in subjects infected with HIV. The GBV-C RNA prevalence in patients with HIV range from 11.3%-15.5% in Iran, 13.5% in Argentina, 14%-22% in Spain, 16.7% in Ghana, 21% in Brazil, 26.2% in the Russian Federation, 16.8% -27% in Germany, 41% in Italy, and 24.2-45% in France[16,14,44,41,90,91].

The study included 41 Japanese HIV-infected hemophilia patients, GBV-C viremia was detected in 26.8% of patients[97] and in an investigation in Danish cohort of HIV-infected men 24% of patients were positive for GBV-C[83]. In another study in three cohorts of pregnant women in Thailand, the prevalence of GBV-C infection was 33% among HIV infected women[93].

HCV INFECTED PATIENTS
GBV-C and HCV co-infection is common and GBV-C infection is related to HCV endemcity. GBV-C does not seem to have any negative impact on the course of HCV-related chronic liver disease. GBV-C also does not have any affect on the liver histology, transaminase levels or response to antiviral therapy; it was shown that GBV-C is sensitive to interferon-alpha with a relapse rate up to 53% comparable to HCV[90].

Among newly diagnosed cases of blood-borne viral hepatitis in the
United States, GBV-C reported in 18% of cases, and 80% of them were also HCV co-infected[21].

In a study in Germany on HCV infected patients, 17.5% showed GBV-C co-infection. The rate of co-infection varied significantly according to geographical area; 20.5% in European vs. 10.9% in Japan (except some at risk groups such as IDUs, hemodialysis patients, patients after liver transplantation). Additionally, co-infection occurred in 38% of IDUs[20].

Other studies have reported the incidence of GBV-C co-infection with HCV, varying from 3.2% in Colombian blood donors to 64.9% in Egyptian HCV infected patients[14,15].

In Europe the prevalence of GBV-C infection in HCV infected patients, ranges from 16-21% in France[28,29], 16% in UK[30], 19-21% in Spain[31,32] and 24.4% in Germany[17]. In United States, GBV-C prevalence in patients with chronic HCV was reported about 20%[33]. GBV-C/HCV co-infection was seen more prevalent in Asian countries such as Saudi Arabia (31.5%)[34], China (31.5%)[35] and Iran (43.6%)[36].

Only in Japan this co-infection is low as 11% in HCV infected cases.

Little work has been done on HBV and GBV-C co-infection but it has been shown that GBV-C has no effect on HBV-DNA levels or disease progression[37].

SUMMARY

The GBV-C is an enveloped, single-stranded positive RNA virus belonging to the family Flaviviridae and has a close sequence homology to HCV.

Overall findings indicate that GBV-C infections generally are asymptomatic, transient and self-limiting and have not been associated with any known human disease; however, several studies found an association between GBV-C infection and improved survival in GBV-C/HIV co-infected patients.

GBV-C can be transmitted parenterally through blood and blood products, hemodialysis, intravenous drug use, sexual and vertical routes.

GBV-C viremia may persist for years but it is cleared eventually in 50-75% of cases and antibodies against GBV-C E2 envelope usually appear. GBV-C infection is relatively common and has a worldwide distribution. 1-5% of healthy blood donors in developed countries have GBV-C RNA in their sera. The prevalence is higher in blood donors from developing countries, which up to 20% of blood donors were viremic in some studies. Currently, GBV-C has been classified into six genotypes and many subtypes based on their sequence diversity.

The advances studies on GBV-C, especially in the context of HIV co-infection, should be carried out to identify the essential mechanisms of HIV clearance for future anti-HIV research. Better understanding of this influence of GBV-C on HIV infection is important to identify novel approaches to HIV therapy to slow the progression of HIV infection, without treatment problems such as drug resistance and toxicity.

REFERENCES


26 Posada D, Crandall KA. MODELTEST: testing the model of DNA substitution. *Bioinformatics* 1998; 14: 817-818


33 George SL, Wünschmann S, McCoy J, Xiang J, Stapleton JT. Interactions Between GB Virus Type C and HIV. *Curr Infect Dis Rep* 2002; 4: 590-598


42 Tillmann HL, Marus MP. GB virus C infection in patients infected with the human immunodeficiency virus. *Antiviral Res* 2001; 52: 83-90


55 Muerhoff AS, Dawson GJ, Desai SM. A previously unrecog-


70 Hanci SY, Cevahir N, Kaleli I, Hanci V. [Investigation of hepatitis G virus prevalence in hemodialysis patients and blood donors in Denizli, Turkey]. Mikrobiyol Bul 2008; 42: 617-625


72 Barusruk S, Urwijitroon Y. High prevalence of HCV coinfection with HBV or HCV among northeastern Thai blood donors. Southeast Asian J Trop Med Public Health 2006; 37: 289-293


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Yan J, Dennin RH. A high frequency of GBV-C/HGV coinfection in hepatitis C patients in Germany. World J Gastroenterol 2000; 6: 833-841


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