Hepatitis G Virus Infection among High Risk Population in Diyala Province

Hasan A. SH. **Ph.D.**
Noaman N.G. **Ph.D**
Manal E. Hasan **M Sc**

Abstract:

Background: Hepatitis G virus (HGV) is an enveloped RNA positive-stranded flavivirus. HGV is transmitted mainly by parenteral route; therefore patients on maintenance hemodialysis and multiple blood recipients are at risk for infection.

Objectives: The present study was designed to explore the HGV infection rate among certain high risk population including hemodialysis and thalassemia patients plus healthcare workers in Diyala province.

Materials and methods: This cross-sectional serological study was conducted in Diyala province for the period from August 2017 to May 2018. A general questionnaire form was pre-constructed for this purpose including information regarding socio-demographic and risk factors. A total of 203 subjects were enrolled. Blood samples were collected from 59 hemodialysis patients, 54 patients with thalassemia, 30 healthcare workers, and 60 apparently healthy blood donors. Seventy three (35.96%) were females with a mean age ± SD 27.17 ± 14.23 years and 130 (64.03%) were males with a mean age ± SD 32.72 ± 15.74 years. All serum samples were pretested for hepatitis B surface antigen (ADVANCED /China), anti-hepatitis B core total Abs (FORTREFF-UK), anti-hepatitis C Ab (ADVANCED /China) and anti- human immunodeficiency virus Abs (ADVANCED /China), beside the anti-hepatitis G virus IgG Ab (Sunlong-Biotech/China) using ELISA techniques. Statistical analysis was conducted using Chi-square test and the confidence interval of 95% (CI = 0.95) was considered to estimate significant results. Data were recorded and analyzed using SPSS software Version 16.

Results: The results revealed that none of the healthy controls was positive for anti-HGV IgG. Whereas, 12 hemodialysis patients were positive for anti-HGV IgG (20.3%, Odd ratio 31.84), with a statistically significant difference (P= 0.001), and the ratio of HCV/HGV co-infection among hemodialysis was 7.69%. Whereas in thalassemia patients, 8 (14.8%, Odd ratio 22.12) patients were positive for anti-HGV IgG, with a statistically significant difference (P= 0.004). All the healthy controls were negative for hepatitis B , hepatitis C, and human immunodeficiency viral markers, while 2 (3.70%) of the healthcare workers were positive for hepatitis B markers, but all negative for hepatitis C and human immunodeficiency markers. The rate of HCV/HGV co-infection was 14.28%. Only one healthcare worker was positive for anti-HGV IgG (3.3%, odd ratio 6.15) with a statistically insignificant difference (P= 0.33).

Conclusion: The hepatitis G virus infection among blood donors and healthy individuals in Diyala province was very low, but it was significantly higher among hemodialysis and thalassemia patients. Routine screening of hepatitis G virus infection of these risky groups is recommended.

Keywords: Hepatitis G virus, Hemodialysis, Thalassemia, Diyala.

Introduction:

GB virus C (GBV-C) or hepatitis G virus (HGV) is an enveloped RNA positive-stranded flavivirus that is transmitted by infected blood and blood products [1]. There is a geographic difference in distribution of hepatitis G virus (HGV) in the world [2]. Data from review study covering different countries reported that 3.3-15.9% of voluntary blood donors were positive for anti-HGV Abs, and 0.5-7.4% were positive for HGV-RNA [3]. Among healthy Saudi blood donors, the prevalence of HGV RNA was 1%-2%, while the rate of anti-HGV Abs was 4.3%, recommending HGV screening for blood donors [4]. In Iranian healthy blood donors, the rates of anti-HGV E2 Abs were variable among different studies [5,6]. The rate of HGV infection in healthy Kuwaiti and Jordanian blood donors was 24.6 and 9.8%, respectively [7]. Certainly, the rate of detection of HGV infection is largel affected by the laboratory techniques used. For instance among Tunisian blood donors, the HGV RNA was found in 5.3% while HGV antibodies were found in 4.9% [8]. Similar results were reported by other studies [9,10].

In a worldwide review study revealed that the rate of HGV-RNA detection among DH patients was in a range of 3.5-54.4 %, and the rate of anti-HGV Abs was 25.4% [3]. These variations depend on location, genotype distribution, and laboratory technique for detection as well as socio-demographic factors [11-13]. Since high prevalence of HGV infection was reported in patients under chronic hemodialysis worldwide [6,11]. So it is one of main risk factors of HGV transmission [14]. The rate of HCV/HGV or HIV/HGV co-infections may also increase the rate of HGV infection among HD patients [15,16]. It has been suggested that HGV may be transmitted nosocomially from patient-to-patient within the hemodialysis unit [17].

Thalassemias are inherited blood disorders characterized by abnormal hemoglobin production. Therefore, as multitransfused patients, it is not unusual to found high infection rate by HGV that is efficiently transmitted parenterally. In a review study worldwide reports found that the rate of HGV-RNA and the anti-HGV Abs were detected in a range of 5.6%- 40.9% and 37.3% respectively among HCV positive patients [3]. Among thalassemia patients in Lebanon, 14% were found positive for anti-HCV, and among anti-HCV-negative patients 8% were anti-HGV positive, while only 0.28% of all patients investigated was found to be HBsAg-positive [18]. HGV infection is also prevalent in thalassemia as high risk group of multiple transfused patients in Pakistan [19]. Undoubtedly, the HGV infection was differed in HCV positive versus HCV negative thalassemia patients [20]. Several studies had documented that HGV infection can be transmitted in health care settings, so it is regarded as a potential occupational

hazard for medical staff [21,22]. Age and duration of employment may significantly influence the HGV prevalence in medical staff [23].

Material and methods:

This cross-sectional serological study was conducted in Diyala province for the period from first of August 2017 to the end of May 2018. Generally, it was designed to explore the infection rate of HGV infection among acute and chronic icteric patients as well as other risky groups and to figure out the effect of socio-demographic and risk factors. This is a part of that large study, devoted to the exploration of anti-HGV IgG among certain high risk groups including hemodialysis patients, thalassemia patients and healthcare workers. A general questionnaire form was pre-constructed for this purpose including information regarding socio-demographic and risk factors. The human privacy was respected by taken participant's consent. Furthermore, this study was submitted for the Ethical Committee in the Diyala College of Medicine and it was ethically approved under issue No. (MD 9 December 2017 ASH).

A total of 203 subjects were enrolled; 73 (35.96%) were females with a mean age ± SD 27.17 ± 14.23 years and 130 (64.03%) were males with a mean age ± SD 32.72 ± 15.74 years. 59 blood samples were collected from HD patients in dialysis center at Baquba Teaching Hospital. 37 (62.71%) were males and 22 (37.28%) were females. The ages range was 10 to 65 years. 54 blood samples were collected from patients with thalassemia who were attending the Center of Blood Diseases in the Central Blood Bank in Baquba. 32 (59.25%) were males and 22 (40.74%) were females. The age range was 5 to 45 years. 30 blood samples were collected from healthcare workers including 2 doctors, 6 dentists, 15 medical stuffs, 2 laboratory stuffs and 5 hemodialysis unit stuffs. 22 (73.3%) were males and 8 (26.67%) were females. The ages range was18 to 60 years. Additionally, 60 blood samples were collected randomly from apparently healthy blood donors who attended the Central Blood Bank in Baquba and healthy individuals who were attending the Public Health Laboratory for premarriage medical checkup. 39 (65%) were males and 21 (35%) were females**.** The ages ranged between15 and 55 years. All serum samples were pretested for HBsAg (ADVANCED /China), anti-HBc total Abs (FORTREFF-UK), anti-HCV Ab (ADVANCED /China) and anti-HIV Abs (ADVANCED /China), beside the anti-HGV IgG Ab (Sunlong-Biotech/China) using ELISA techniques. Statistical analysis was conducted using Chi-square test and the confidence interval of 95% (CI = 0.95) was considered to estimate significant results. Data were recorded and analyzed using SPSS software Version 16.

Results:

The preliminary results revealed that within the 59 HD patients, 46 (78.0%) were negative for HBV markers (HBsAg plus anti-HBc total Abs) and anti-HCV antibody, while 13(22.0 %) were positive for anti-HCV antibody. The difference was statistically significant (P= 0.001). Whereas, within 54 thalassemia patients, 47 (87.0%) were negative for HBV markers (HBsAg plus anti-HBc total Abs) and anti-HCV antibody, while 7 (12.96%) were positive for anti-HCV antibody. Again the difference was statistically significant (P= 0.01). On the other hand, all the 60 healthy individuals, were negative for HBV markers (HBsAg plus anti-HBc total Abs), anti-HCV Ab and anti-HIV Abs, while 2 (3.70%) of the 30 HcWs were positive for HBV markers, but all negative for anti-HCV and anti-HIV antibodies, table (1).

Concerning the HGV infection, the results showed that none of the healthy control individuals was positive for anti-HGV IgG. Whereas, 12 hemodialysis patients were positive for anti-HGV IgG (20.3%), the 95% confidence interval was (10 – 30.6) and the Odd ratio was 31.84. Therefore, there was a statistically significant difference compared to the healthy controls (P= 0.001). Besides that, one of the 13 anti-HCV Ab positive HD patients was also positive for anti-HGV IgG giving a ratio of HCV/HGV co-infection among HD of 7.69%.

Among the thalassemia patients, there were 8 patients positive for anti-HGV IgG (14.8%) with 95% confidence interval (5.3 – 14.3) and the Odd ratio was 22.12. Consequently, there was a statistically significant difference compared to reference health controls (P= 0.004). Again among the 7 patients who were anti-HCV Ab positive, there was one patient also positive for anti-HGV IgG giving a ratio of HCV/HGV co-infection among thalassemia patients of 14.28%, while none of thalassemia patients were HBV/HGV co-infected. The results also showed that only one healthcare worker was positive for anti-HGV IgG (3.3%) with 95% confidence interval (0 – 9.7) and the odd ratio was 6.15,so the difference compared to reference value was statistically insignificant (P= 0.33), table (2).

Table (1) Anti-HCV antibody and HBs Ag positivity rates among study groups.

Anti-HCV Ab positivity rate						
Category	Total No.	HCV + No.(%)	95% CI	OR	95% CI-OR	P value
Healthy control	60	0 (00)	Ref			
Hemodialysis	59	13 (22)	(11.4 - 32.6)	35.13	(4.4 - 276.7)	0.001
Thalassemia	54	7(12.96)	(2.7 - 19.5)	16.22	(1.9 - 136.3)	0.01
Healthcare workers	30	0 (00)	**	**	**	**
HBsAg positivity rate						
Category	Total N0.	HBsAg + N0.(%)	95% CI	OR	95% CI-OR	P value
Healthy control	60	0 (00)	Ref			
Hemodialysis	59	0 (00)	**	**	**	**
Thalassemia	54	2 (3.70)	(0 to 8.7)	5.76	(0.58 - 57.07)	0.134 [NS]
Healthcare workers	30	0 (00)	**	**	**	**

Table (2) Anti-HGV IgG positivity rate among high risky groups.

Category	Total No.	HGV IgG No.(%)	95% CI	OR	95% CI-OR	P value
Healthy control	60	0		Ref.		
Hemodialysis	59	12 (20.3)	(10 - 30.6)	31.84	(4.02 - 252.34)	0.001 [S]
Thalassemia	54	8 (14.8)	(5.3 - 24.3)	22.12	(2.71 - 180.8)	0.004 [S]
Healthcare workers	30	1 (3.3)	(0 - 9.7)	6.15	(0.54 - 70.59)	0.33[NS]

Discussion:

Before this time, so many serological surveys were conducted in Diyala province on different types of viral hepatitis, and in each time there still a proportion of acute or chronic hepatitis patients gave non-A-E hepatitis negative results. Of course, HGV was one of the mysterious speculations. Therefore, designation and accomplishment of this study was very important to complete the epidemiological view of viral hepatitis in Diyala province. Probably the prime limitation of the current study is the limited sample size and this is merely due to expensiveness of the imported diagnostic kits.

The HGV infection rate among the healthy individuals included in this study was 0%. It is worth to mention that similar studies conducted elsewhere had yielded variable results depending on geographical location, target population, sample size and laboratory technique used. In this regard, data from review study covering different countries reported that 3.3-15.9% of voluntary blood donors were positive for anti-HGV Abs, and 0.5-7.4% were positive for HGV-RNA [3]. Regarding the neighbor countries, among healthy Saudi blood donors, the prevalence of HGV- RNA was found to be 1-2%, recommending HGV screening for whole blood donors [4]. Whereas in a similar study in Turkey, the prevalence and genotypic distribution of HGV-RNA in sera of blood donors was 4.1%, suggesting low endemicity of HGV infection in Eastern Turkey [24]. In an Iranian study, a similar low HGV exposure was found (1%) among healthy blood donors [5]. Furthermore, in a Kuwaiti - Jordanian collaborative study a relatively high prevalence of HGV among healthy blood donors 24.6% and 9.8% respectively were documented [7]. Similar high prevalence was reported from Tunisian blood donors, in whom the positivity rate was 4.9%, using ELISA technique [8].

The current results is consistent with that conducted on Polish donors who were tested by RT-PCR to detect HGV-RNA and anti-E2 HGV Abs by EIA method, found that HGV-RNA was identified in 0% of blood donors, while anti-E2 HGV Abs were found in 25% [10]. It is also in agreement with Thai healthy blood donors who reported 0% detection rate by HGV- RNA [25]. However, the present result are much lower that documented a high prevalence of HGV viremia (1-4%) within healthy populations in Europe and North America, and an even higher prevalence (10-33%) among residents in South America and Africa [26]. As well as those reported in German healthy individuals as determined by immune blot assay, 17.9% had positive antibodies to HGV [9].

Thus, it is obvious that the rate of HGV infection among healthy individuals was varied worldwide. The result of this study seems to be acceptable in a semi-conservative Iraqi community. A step behind, and since the mid of eightieths of last century, the Iraqi blood units were actively screened for HIV and HCV infection, and of course

all positive units were compulsorily excluded. These health policies may indirectly reduce the rate of HGV infection among Iraqi general population, as high rate of HGV infection was reported among HIV and HCV positive individuals [27-29]. Moreover, it is worth to emphasize that ELISA technique was employed in this study which is undoubtedly less sensitive and less specific than PCR technique and this may further explain the low infection rate of HGV among healthy population. Therefore a future studies using molecular techniques are recommended**.**

Results revealed that12/59 (20.33%) of HD patients were anti-HGV IgG positive, so this positivity rate was significantly higher compared to healthy control (P = 0.001). Furthermore, the HCV/HGV co-infection rate among this group was 7.69%. In a worldwide review study revealed that the rate of HGV-RNA detection among DH patients was in a range of 3.5-54.4 %, and the rate of anti-HGV Abs was 25.4% [3]. The current results are slightly lower that that reported by an Iranian study conducted on HD patients who were tested for anti-E2 HGV Abs, anti HCV Abs and HBs-Ag by ELISA techniques, 25.0% were anti-E2-HGV positive; However, the rate of HBV/HGV and HCV/HGV co-infections were insignificant [6]. Meanwhile it is higher than the results presented by another Iranian study using the nested reverse transcription RT-PCR method, were only 4.3% had positive results for HGV and all patients had negative results for HIV Ab, HCV Ab and HBs Ag [13].

Additionally, HCV and HGV were recognized as highly prevalent in maintenance dialysis population in Poland. The anti-HGV (+) Abs, HGV-RNA (+) were detected in 63.6%, and anti-HCV (+) and anti-HGV (+) patients were dialyzed longer as compared with negative counterpart patients [16]. Our results seems very close to that reported by an Italian study, in which 20% of patients on HD had HGV- RNA as detected by PCR technique which was much higher than that in blood donors [30]. It is clear from worldwide studies that although the rate of HGV infection among HD patients was variable; however, it was generally high, and this make the current study with agreement with other studies involved for instance; renal failure HD patients in Brazil [31] , HD patients from KSA [32], and HD and kidney transplant patients from Iran [6]. Actually the high HGV infection rate among end stage renal diseases undergoing dialysis was in common with HCV, which are both *flaviviridae* viruses. This feature probably can be explained by the ability of these viruses for extrahepatic replication since it has a wide cell tropism including the kidney epithelial cells [33]. Moreover, as a muttiple blood recipients, HD patients were prone to the risk of HGV infection, and other blood transmitted pathogen, through blood and other blood products; in this context, the median levels of serum HGV viremia was found to be 10 times higher than that of HCV in chronically infected subjects; therefore, the risk of transmission through blood, sexual contact, and vertically may be higher for HGV than HCV [34]. Furthermore, the positivity of HGV-RNA is about twice as frequent in patients with non-A-E hepatitis following blood transfusion than in sporadic A-E hepatitis cases [35].

Another questionable feature arise in this study is the high affinity of HGV to infect patients who are already infected by HCV and less frequently with HBV. However, this puzzling subject was extensively investigated; in a review study worldwide reports found that the rate of HGV-RNA and the anti-HGV Abs were detected in a range of 5.6%- 40.9% and 37.3% respectively among HCV positive patients [3]. Furthermore, it seems that the aggregation of HGV infection with HCV is genotype-dependent, as Ghanbari *et al.*, (2010) [28] reported that 43.6% of HCV-infected patients were positive for HGV- RNA and phylogenic analysis showed that the predominant was genotype 2 of HGV. Additionally, this partnership may be related to the unique routes of transmission of HBV, HCV, and HGV [36].

The current results also found a high prevalence of HGV infection among Iraqi thalassemia patients (14.8%) and the HGV/HCV coinfection in this group (14.28%). Upon reviewing the literature, studies in this context had yielded variable results. For instance, our results are much lowers that of Turkish study, in which the HGV-RNA was detected in 63% of thalassemia patients, with no significant association with clinical features, and annual transfusion numbers**,** but it is higher than that documented in Lebanon, where 8% of HCV negative thalassemia were anti-HGV positive [18]. Among polytransfused β- thalassemia major Pakistani children, the HGV-RNA was detected in 21% of patients and 4% of these were positive for both HCV-RNA and HGV-RNA [19]. Furthermore, HGV-RNA was investigated in 28 HCV positive multitransfused Italian thalassemia patients, and the positivity rate of HGV-RNA was 12.5% [20]. In Brazil, the HGV-RNA was detected in 14.2% of thalassemia patients with the absence of HBV and HCV co-infections suggesting that HGV is capable of independent transmission and does not contribute to liver disease [31].

Thalassemias are inherited blood disorders characterized by abnormal hemoglobin production. Therefore, as multitransfused patients, it is not unusual to found high infection rate by HGV, a virus that is efficiently transmitted parenterally, thus high frequency of infection was expected in all groups of patients repeatedly exposed to infected blood or blood products [1,35]. These results are concordant with those reported by Salama and SelimOel (2009) [36] who reported that the HGV-

RNA was detected in 61% and the anti-HGV Abs in 12% of multitransfused Egyptian children. However, the current results are slightly lower than those documented by Asim *et al*., (2008) [37] who reported that the HGV-RNA was detected in 17.7% of Indian multitransfused and 93.5% of HGV-positive patients were co-infected with either HBV 38.7% or HCV 74.1%. Again the present results are less than those reported that HGV- RNA was detected in 39.7% multitransfused thalassaemic Pakistani children [19].

The HGV positivity rate among healthcare workers in current study was 3.3%. It is important to know that all of them were negative for HBV, HCV and HIV Abs using ELISA techniques. Studies on the prevalence of HGV infection in healthcare workers are limited; however, the documented ones had yield variable results. For instance, in an Iranian study on dialysis unit staff found that none (0%) of these were positive for anti- HGV E2 Abs [22]. Nevertheless, the current results are slightly lower than that reported by Egyptian study which found that HGV-RNA was detected in 6.6% by RT-PCR [38]. On the other hand, high infection rate was reported in German study which reported that 24% of medical staff had HGV-RNA positive, affirming the occupational risk for HGV in medical staff of dialysis unite and transmission routes other than parenteral may play a role in this setting [23]. In this context, it has been reported that in patients on maintenance HD, new HGV infection occur without blood transfusion, suggesting that HGV may be a marker of nosocomial viral transmission . Consequently, it can be assumed that healthcare workers in HD units are under the risk of infection. Supporting that it has been reported that HGV-RNA was detected in saliva of 33% of infected subjects, thus it is possible that HGV like other flaviviruses, can be spread horizontally or be transmitted by mosquitos [1,39].

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