Prevalence of and risk factors for hepatitis G (HGV) infection in haemodialysis patients: a multicentre study

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Abstract

Background. Hepatitis G virus (HGV) or GB-virus type C (GBV-C) is, like hepatitis C, a blood-borne virus and a member of the family of flaviviridae. HGV is distributed globally and is present in the volunteer blood donor population. Thus, for epidemiological reasons, HGV is of interest in haemodialysis patients, who are at risk of parenterally transmitted infections. The aim of the present investigation was to assess the prevalence of HGV by antibody testing and HGV-RNA determination by PCR.

Methods. The study was performed in haemodialysis units of the Patienten-Heim-Versorgung, an organization of haemodialysis units throughout Germany. A total of 2796 out of 3042 patients (92%) from 43 haemodialysis units were enrolled prospectively in the trial. Liver function tests were performed and epidemiologic data were obtained to evaluate risk factors for HGV in haemodialysis patients.

Results. Antibodies against HGV were detected in 485 patients (17.5%). Viraemia was seen in 380 out of 1935 patients tested (19.6%). Fifty-eight patients (3.0%) were positive for both antibodies and HGV-RNA. Using a standard questionnaire in 1717 out of the 2786 patients, it was found that more than five blood transfusions increased the risk of HGV infection significantly (P < 0.05). There was no association found between HGV infection and the length of time on haemodialysis.

Conclusion. HGV is common in German haemodialysis patients but, in contrast to other parenterally transmitted viruses, there is no further risk for new infections during haemodialysis, except for patients who have received several blood transfusions.

Keywords: GBV-C; haemodialysis; hepatitis G; prevalence; risk factors; viraemia

Introduction

Hepatitis G virus (HGV) or GB-virus type C (GBV-C) is a blood-borne virus and, like hepatitis C, a member of the flaviviridae [1,2]. Infection with HGV is common [3] and the virus is present in the volunteer blood donor population [3,4]. There are weak associations of transmission of HGV and the onset of acute hepatitis; however, there is no convincing evidence in favour of fulminant hepatic failure due to acute HGV infection. Although HGV is able to persist in humans, so far a chronic hepatitis due to HGV infection has not been reported [2,4].

A high prevalence of HGV infection in small cohorts of haemodialysis patients has been reported [5–14]. Due to the parenteral transmission of HGV-contaminated blood, blood transfusions are suggested to be the main risk factor for viral infections [1,4]. For epidemiological reasons, the common HGV infection in humans, and particularly in haemodialysis patients, is of interest for the control of parenterally transmitted viral infections in patients at high risk. Determination of viraemia (HGV-RNA) can be obtained exclusively by polymerase chain reaction (PCR) [3,14], whereas HGV antibody testing by using an antibody against an envelope protein (anti-E2 antibody) is able to distinguish between active and cured infections [3,14,15]. Only a few prevalence studies of hepatitis G have been undertaken in haemodialysis patients with both determination by PCR and antibody testing [7,11,14].

The aim of the present study was to assess prospectively the prevalence of cured HGV infection measured serologically by HGV anti-E2 antibody testing and detection of HGV viraemia by PCR in a large...
cohort of German chronic haemodialysis patients. Furthermore, risk factors for viral transmission were investigated.

Patients and methods

Study design and patient selection

The study was performed in haemodialysis units of the Patienten-Heim-Versorgung (PHV), an organization of haemodialysis units throughout Germany. A total of 2796 out of 3042 patients (92%) from 43 haemodialysis units were enrolled prospectively in this trial between October 1996 and March 1997, and gave their informed consent. The remaining 246 patients could not be tested due to the following reasons: vacation, hospital stay, death before investigation and informed consent withdrawn (<1%). The study protocol was approved in 1996 by the ethics committee of the Medical Faculty of the Christian-Albrechts-University, Kiel. All patients underwent chronic haemodialysis treatment for end-stage renal disease during the study period. The number of patients in the haemodialysis units varied from 17 to 177. The following epidemiological data could be obtained in 1717 patients (61.4%): (i) gender and age; (ii) length of time on haemodialysis in months; (iii) number of blood transfusions (none, 1–5, 6–15, >15); (iv) known risk factors such as i.v. drug abuse, immunosuppression and haemophilia; and (v) known chronic liver disease.

In the present study, men (n=917; 53%) were on haemodialysis more often than women (n=800; 47%). The mean age was 61 years, ranging from 19 to 92 (men 59 years, women 63 years). The mean duration of haemodialysis treatment was 54 months (52 in men and 57 in women). Haemodialysis was performed routinely 2–3 times weekly in the patient population. An aliquot of 16 ml of blood (serum and plasma) was drawn in each patient before haemodialysis started. The blood was centrifuged immediately at the unit, and plasma and sera were separated and stored in aliquots at −80°C. All samples subsequently were subjected to liver function tests [alanine aminotransferase (ALAT; U/l), aspartate aminotransferase (ASAT; U/l), γ-glutamyl transpeptidase (GGT; U/l) and the bilirubin concentration (mg/dl)] in the central laboratory of the First Department of Medicine in Kiel. Anti-HGV antibodies were measured by an investigational antibody kit kindly provided by Boehringer Mannheim, Germany. The enzyme-linked immunosorbent assay (ELISA) detects antibodies against the envelope E2 protein of HGV and is able to detect cured infections, as described previously [16]. HGV-RNA testing was performed using RT–PCR (Boehringer Mannheim, Germany). This PCR contains two different primers of the 5'-non-coding region and the NS5a region which are amplified simultaneously to detect an HGV infection confidentially. All positive samples for HGV-RNA were tested twice with different aliquots and declared to be negative for further detailed presentation of the data if the results were negative or borderline in both measurements. The prevalence data are given in Figure 1. There was a wide range of HGV antibody and RNA prevalence in the haemodialysis units investigated. HGV antibodies were found in all 43 centres, ranging from 5.8% in 69 patients up to 26.2% in 65 patients tested. In all 30 centres testing for HGV-RNA, viraemia could be seen with a range of from 6.1% in 99 patients up to 37.5% in 40 patients investigated.

In 1717 out of the 2796 patients (61.4%), including all patients with HGV viraemia, epidemiological data could be obtained. Thus possible risk factors could be investigated. Figure 2 demonstrates that there is no increase over time in the number of haemodialysis patients carrying hepatitis G E2 antibodies and

pre- and post-PCR laboratory buildings was maintained to avoid the possibility of post-PCR contamination.

Epidemiological data are presented by the mean and percentage of the mean. Further statistical analysis of risk factors for HGV infection (age, length of time on haemodialysis and number of blood transfusions) was performed by multivariate analysis and Fisher’s exact test (P<0.05).

Results

Of the 2796 patients tested for HGV E2 antibodies by ELISA, 485 were positive (17.5%). HGV-RNA measured by RT–PCR with a detection limit of 100 genomes/ml could be detected in 380 out of 1935 patients tested (19.6%). As HGV E2 antibodies detect HGV infection, the prevalence data for HGV E2 antibodies and viraemia (HGV-RNA) suggest that spontaneous remission of hepatitis G occurred in nearly 50% of infected haemodialysis patients. In 58 patients (3.0%), positive results for HGV antibodies and HGV-RNA could be observed. Borderline results for antibody testing were obtained in 117 patients (4.2%). For HGV-RNA, borderline results were seen in 27 patients (1.4%). Borderline results for HGV antibodies and HGV-RNA were tested twice in different aliquots and declared to be negative for further detailed presentation of the data if the results were negative or borderline in both measurements. The prevalence data are given in Figure 1.

Fig. 1. Prevalence of hepatitis G antibodies in 2786 patients and hepatitis G viraemia in 1935 haemodialysis patients studied.
HGV-RNA. Furthermore, a high prevalence of hepatitis G E2 antibodies (12.5%) and HGV-RNA (24.6%) could be seen in the first year of haemodialysis treatment. Thus the pre-haemodialysis status is more important for acquisition of hepatitis G than is the length of time on haemodialysis. As HGV is transmitted parenterally, patients receiving blood transfusions are at a high risk for HGV infection. The prevalence data for HGV E2 antibodies and HGV-RNA in relation to the number of blood transfusions are given in Figure 3. There is a consistent increase in HGV antibody positivity and HGV viraemia with the number of blood transfusions administered. HGV E2 antibodies were found in 23% and hepatitis G viraemia in 35% of patients with >15 transfusions. More than five blood transfusions were found to produce a high risk for HGV infection for both HGV E2 antibodies and HGV-RNA ($P<0.05$). As only the number of blood transfusions was found to be a risk factor for HGV infection in haemodialysis patients, further epidemiological data have been determined. Figure 4 presents the influence of age on hepatitis G viraemia or antibody positivity. There is a high prevalence of HGV-RNA in the third decade of life, with no further increase over time, whereas HGV E2 antibodies rise until the fourth decade of life, followed by a plateau. Thus, in the present investigation, there is a tendency for age to be inversely correlated with hepatitis G, but this was not statistically significant. Liver function tests were normal in the whole patient population as well in the subgroups of patients with positive HGV-RNA and those with positive HGV E2 antibodies; thus the results are not presented in detail.

Co-infection with hepatitis C was uncommon in the present cohort. In 1922 out of the 1935 patients, HCV-RNA testing was performed simultaneously. Seventy-nine patients (4.1%) were identified to be chronically infected with hepatitis C by positive HCV RNA. Only 11 patients (0.6%) infected with HGV measured by HGV-RNA were positive for HCV-RNA. Thus, combined viral replication of HCV and HGV is rare in the patients investigated.

Discussion

It is well known that haemodialysis patients are at high risk for parenterally transmitted viral infections [16–19]. This has been shown for HCV in several trials [16,18,19]. However, in general, hepatitis C is rare in haemodialysis patients in North America and Northwestern Europe [19,20]. As nosocomial transmission is unlikely to be a frequent cause of parenterally transmitted viral infections in haemodialysis patients [19], hepatitis G is a good predictor for nosocomial transmission, as the virus is common in our population [3]. Nearly 2–3% of volunteer blood donors are infected with HGV [3]. There is a wide range of prevalence in different regions of the world, from 2–6% in Asia to >20% in South Africa [3].

In the present prospective study in a large cohort of haemodialysis patients, a high prevalence of 17.5% antibody positivity and 19.6% viraemia could be confirmed. In this study, HGV E2 antibody testing and HGV-RNA determination in haemodialysis patients were compared, as has been reported in a recent study [14], since antibody testing is available only for a short period [15]. Prevalence data for hepatitis G in the
general population of Germany suggest that there is a prevalence of 2% for viraemic patients [3]. Thus haemodialysis patients in Germany have a 10-fold increase in risk. This is comparable with the increased risk of developing HCV infection. In Germany, HCV is found in ~0.5% of the general population and in >4% of German haemodialysis patients. Thus there is a >8-fold increased risk. Many problems exist in designing hepatitis G prevalence studies: a representative cohort of haemodialysis patients is necessary. In general, the published studies enrolled <200 patients [7,11,14]. No studies performed in >1000 patients have been published. Our data demonstrate that results obtained in <200 patients might under- or overestimate the prevalence of HGV antibodies (5.8–26.2%) and HGV-RNA (6.1–37.5%). The wide range could be explained by the varying number of patients in the centres tested. Furthermore, geographical reasons and the fact that in some cases patients with known hepatitis are referred to central dialysis centres also led to the wide range of HGV-infected patients in this study. Since in the present study 2796 patients were enrolled, the calculated prevalence data for hepatitis G in haemodialysis patients are reliable. Furthermore, the methods used for detection of hepatitis G led to differences in prevalence data previously reported. However, in general, all results published showed that hepatitis G infection measured by HGV E2 antibodies and/or HGV-RNA is common in haemodialysis patients, which is confirmed by our study. We found hepatitis G viraemia in 19.6% of the haemodialysis patients tested. HGV E2 antibodies were seen in 17.5%. Thus spontaneous recovery is common and only 50% of the patients are viraemic. Anti-E2 antibody and HGV-RNA were found to be mutually exclusive, since only 58 patients (3.0%) displayed positive results for both HGV antibodies and HGV-RNA, confirming the notion that anti-E2 antibodies have to be considered as a marker of past infection [3]. We were able to show, that administration of blood products is a main risk factor for developing hepatitis G, but not length of time on haemodialysis. Only an inverse correlation for age could be assumed to be a risk factor, but this was not statistically significant. Thus, patient to patient transmission during haemodialysis is not common as suggested for HCV in several trials [16,18,19].

The pre-haemodialysis status is also of interest. This has not been studied up to now. As patients with end-stage renal disease who received a renal transplant earlier were included in this study, this might be one reason for the high prevalence in the first year of haemodialysis, as those patients could have been infected during their first period on haemodialysis before transplantation. Furthermore, blood products may have been administered before starting haemodialysis, and data therefore are not available. However, this is unproven and does not by itself explain the 10-fold increase of hepatitis G viraemia compared with the general population. Liver function test measurements remained normal in the majority of hepatitis G patients, confirming that only a small number of patients suffer from acute hepatitis. An elevation is still non-specific and does not correlate with viral status as chronic hepatitis G viraemia does not correlate with chronic liver disease [4]. Co-infection with HCV virus is uncommon, which confirms data of previous trials [7], but is still discussed controversially [5]. This is of interest, as both viruses are parenterally transmitted and have a high homogeneity of their genome, as both are members of the family flaviviridae [1].

In conclusion, patients on maintenance haemodialysis treatment are still at high risk for acquisition of parenterally transmitted viral infections. However, for the common HGV infection, no increased risk during haemodialysis was observed, except after administration of blood products. Thus prevention of nosocomial transmission of hepatitis viruses is effective in the investigated German haemodialysis patients.


References


