Hepatitis E virus IgG seroprevalence in liver transplant patients: A retrospective single-center experience

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Abstract

Background and Aim: Hepatitis E virus (HEV) may cause chronic liver disease in solid organ transplant recipients. We determined HEV seroprevalence and associated factors in liver transplant recipients.

Materials and Methods: Patients followed at the outpatient clinic of liver transplantation between January 2019 and January 2020 were screened retrospectively for HEV serology (HEV immunoglobulin M [IgM] and HEV immunoglobulin G [IgG]).

Results: Of the 150 patients (male/female, 104/46; age, 55.4±13.2 years), anti-HEV IgG was positive in 31 (20.7%), and anti-HEV IgM was negative in all. The mean time after liver transplantation (72 [48%] deceased and 78 [52%] living donors) was 81±78.5 months. Drinking water consisted of carboy and tap water in 88 (58.7%) and 62 patients (41.3%), respectively. Of the patients, 120 (80%) and 30 (20%) lived in urban and rural areas, respectively. On comparison, the difference between positive and negative anti-HEV IgG groups in terms of age, place of birth, water supply, and donor type was statistically significant (p=0.007, p=0.000, p=0.034, and p=0.049, respectively).

Conclusion: HEV seroprevalence was more frequent in liver transplant recipients compared with the normal population. Older age, water supply, and place of birth were risk factors for HEV seroprevalence.

Keywords: Anti-HEV IgG; liver transplantation; seroprevalence.

Introduction

Hepatitis E virus (HEV) is one of the major causes of acute viral hepatitis worldwide. Khuroo et al.[1] first identified HEV as an unknown non-A, non-B virus during an outbreak of jaundice in the winter of 1978–1979 in Kashmir. Later, a Russian army doctor provided the first evidence of feco-oral transmission of the virus. In 1980, the viral genome was cloned and named HEV.[2] HEV is a single-stranded, non-enveloped RNA virus of the Hepeviridae family.[3] According to the World Health Organization, approximately one-third of the world population has been exposed to HEV. Globally, HEV infection causes acute liver damage in approximately 3.5 million people and death in 56,000 people annually.[4] In Europe, the seroprevalence of HEV infection is approximately 25% among adults in the sixth and seventh decades of life.[5] In Turkey, the HEV seroprevalence is 6.3% (range, 0%–34%).[6,7] There are eight known HEV genotypes; however, only the first four of these genotypes are well-known and cause disease in humans. Genotypes 1 and 2 infect humans through the fecal–oral route and cause outbreaks, particularly in developing countries with poor hygiene conditions. Genotypes 3 and 4 are animal viruses that can cause zoonotic infections in humans.[10,11] Most HEV infections are asymptomatic. In symptomatic cases, acute icteric hepatitis may be seen in 5%–30% of the patients.[11,12]

Immunosuppressed individuals infected with genotypes 3 or 4 may develop chronic hepatitis E, which may lead to cirrhosis. They may be infected through the fecal–oral route, by administration of blood products, or through a transplanted organ.[13,14] In liver transplant recipients, anti-HEV immunoglobulin G (IgG) seroprevalence has been identified between 3% and 23%.[15] Therefore, the importance of recognizing HEV infection in organ transplant recipients has increased in recent years.

In Turkey, no studies are available on HEV seroprevalence in liver transplant recipients. This study aimed to determine the HEV IgG seroprevalence in liver transplant recipients in our transplant center and investigate sociodemographic characteristics and risk factors associated with HEV infection.

Materials and Methods

This was a cross-sectional retrospective study. The liver transplant recipients who tested positive for anti-HEV IgG antibodies during routine follow-up visits in the organ transplantation outpatient clinic of Ege University Liver Transplantation Department between January 2019 and January 2020 were included. Patient information was accessed through electronic records and HEV-related case report forms.

Data on patient age, sex, transplant age, time since transplantation, type of transplantation (living or deceased donor), pre-transplant liver disease etiology, presence of hepatocellular carcinoma (HCC), and levels of aspartate aminotransferase (AST), alanine amino-
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Results

This study included 150 liver transplant recipients (male/female: 104/46; mean age, 55.4±13.2 years). The liver transplants were from 72 (48%) deceased and 78 (52%) living donors. The mean time since transplantation was 81±78.5 months.

In terms of the etiology of chronic liver diseases, chronic hepatitis B virus (HBV) infection was detected in 38 patients (25.3%), alcohol abuse in 27 patients (18%), chronic HBV + hepatitis D virus (HDV) infection in 18 patients (12%), and chronic hepatitis C virus (HCV) infection in 13 patients (8.7%). Cryptogenic cirrhosis was observed in 9 (6%) patients, primary sclerosing cholangitis in 9 (6%), non-alcoholic steatohepatitis in 7 (4.8%), autoimmune hepatitis in 6 (4%), toxic hepatitis in 5 (3.3%), Wilson disease in 5 (3.3%), Budd–Chiari syndrome in 3 (2%), primary biliary cholangitis in 3 (2%), hemangioendothelioma in 3 (2%), acute liver failure due to hepatitis A virus infection in 2 (1.3%), and cholangiocellular carcinoma in 2 (1.3) patients. Thirty-five (23.3%) patients had HCC. Table 1 shows the immunosuppressive therapy regimens administered to patients.

For the drinking water source, 88 (58.7%) and 62 (41.3%) patients used carboy and tap water, respectively. Table 1 also shows the sociodemographic and characteristics of the liver transplant recipients.

Anti-HEV IgG antibodies were detected in 31 (20.7%) patients, whereas anti-HEV IgM antibodies were not found. No relationship can be found between HEV seropositivity and ALT or AST values or any other biochemical test values.

A total of 134 transplanted patients lived in the Aegean region; 5 (3.3%) lived in the Marmara region, 4 (2.7%) in Eastern Anatolia, 3 (2%) in the Mediterranean region, 2 (1.3%) in Central Anatolia, 1 (0.7%) in Southeastern Anatolia, and 1 (0.7%) in the Black Sea region. In addition, 120 (80%) and 30 (20%) patients lived in urban and rural areas, respectively. In total, 22 (70.9%) and 9 (29.1%) patients with positive anti-HEV IgG were born in cities in the Eastern or Southeastern Anatolia and other geographical regions, respectively. Moreover, 27 (22.7%) and 92 (77.3%) of the patients with negative anti-HEV IgG were born in cities in Eastern or Southeastern Anatolia and other geographical regions, respectively (p<0.001) (Table 2).

The mean age of patients with positive anti-HEV IgG was 60.1±9.74 years, and these patients were older than those with negative anti-HEV IgG (p=0.007). Twenty-one (67.7%) and 10 (32.3%) HEV-seropositive patients had transplants from living and deceased donors, respectively; thus, patients who had living-donor liver transplants had a higher rate of HEV seropositivity (p=0.049). In the HEV-seropositive group, 14 (63.6%) of 21 living-donor liver recipients were born

Table 1. HEV seroprevalence and sociodemographic and clinical characteristics of the liver transplant recipients included in the study between January 2019 and January 2020 in the Ege University Liver Transplantation Department

| Characteristic | n | % |
|---------------|---|---|
| **Age in years (mean±SD)** | 55.4±13.2 |
| **Time after LT in months (mean±SD)** | 81±78.5 |
| **Sex** | | |
| Female | 46 | 30.7 |
| Male | 104 | 69.3 |
| **Type of donor** | | |
| Deceased donor | 72 | 48 |
| Living-donor | 78 | 52 |
| **Etiology of liver disease before LT** | | |
| HBV | 38 | 25.3 |
| Alcohol abuse | 27 | 18.0 |
| HBV+HDV | 18 | 12.0 |
| HCV | 13 | 8.7 |
| Cryptogenic cirrhosis | 9 | 6.0 |
| Others* | 45 | 30 |
| **Presence of HCC during LT** | | |
| Yes | 35 | 23.3 |
| No | 115 | 76.7 |
| **Immunosuppressive treatment** | | |
| Tacrolimus | 37 | 24.7 |
| Tacrolimus+MMF | 29 | 19.3 |
| Everolimus+MMF | 23 | 15.3 |
| Tacrolimus+everolimus+MMF | 22 | 14.6 |
| Everolimus | 16 | 10.7 |
| Others** | 23 | 15.0 |
| **Source of drinking water** | | |
| Carboy water | 88 | 58.7 |
| Tap water | 62 | 41.3 |
| **Type of living area** | | |
| Urban | 120 | 80.0 |
| Rural | 30 | 20.0 |
| **Anti-HEV-IgG** | | |
| Positive | 31 | 20.7 |
| Negative | 119 | 79.3 |

HEV: Hepatitis E virus; HBV: Hepatitis B virus; HDV: Hepatitis D virus; HCV: Hepatitis C virus; LT: Liver transplantation; SD: Standard deviation; HCC: Hepatocellular carcinoma; n: number of patients. *Primary sclerosing cholangitis (n=9), non-alcoholic steatohepatitis (n=7), autoimmune hepatitis (n=6), toxic hepatitis (n=5), Wilson disease (n=5), Budd–Chiari syndrome (n=3), primary biliary cholangitis (n=3), hemangioendothelioma (n=3), acute hepatitis A virus infection (n=2), cholangiocellular carcinoma (n=2). **Tacrolimus+everolimus (n=14), mycophenolate mofetil (MMF) (n=4), cyclosporine (n=3), steroid+tacrolimus+MMF (n=1), steroid+tacrolimus (n=1). IgG (54.12±13.7) (p=0.007). Twenty-one (67.7%) and 10 (32.3%) HEV-seropositive patients had transplants from living and deceased donors, respectively; thus, patients who had living-donor liver transplants had a higher rate of HEV seropositivity (p=0.049). In the HEV-seropositive group, 14 (63.6%) of 21 living-donor liver recipients were born

The local ethics committee approved the study (no:20–4.2T/16).

The IBM SPSS v.20.0 software was used for statistical analyses. The chi-squared test or Fisher exact test as appropriate was used to test the association between categorical variables. The Mann–Whitney U test was used to compare continuous variables. In addition, Spearman test was used for correlation tests. Probability (p) values <0.05 were considered to indicate statistically significant difference.

For the drinking water source, 88 (58.7%) and 62 (41.3%) patients used carboy and tap water respectively. Table 1 also shows the sociodemographic and characteristics of the liver transplant recipients.

Anti-HEV IgG antibodies were detected in 31 (20.7%) patients, whereas anti-HEV IgM antibodies were not found. No relationship can be found between HEV seropositivity and ALT or AST values or any other biochemical test values.

A total of 134 transplanted patients lived in the Aegean region; 5 (3.3%) lived in the Marmara region, 4 (2.7%) in Eastern Anatolia, 3 (2%) in the Mediterranean region, 2 (1.3%) in Central Anatolia, 1 (0.7%) in Southeastern Anatolia, and 1 (0.7%) in the Black Sea region. In addition, 120 (80%) and 30 (20%) patients lived in urban and rural areas, respectively. In total, 22 (70.9%) and 9 (29.1%) patients with positive anti-HEV IgG were born in cities in the Eastern or Southeastern Anatolia and other geographical regions, respectively. Moreover, 27 (22.7%) and 92 (77.3%) of the patients with negative anti-HEV IgG were born in cities in Eastern or Southeastern Anatolia and other geographical regions, respectively (p<0.001) (Table 2).

The mean age of patients with positive anti-HEV IgG was 60.1±9.74 years, and these patients were older than those with negative anti-HEV IgG (p=0.007). Twenty-one (67.7%) and 10 (32.3%) HEV-seropositive patients had transplants from living and deceased donors, respectively; thus, patients who had living-donor liver transplants had a higher rate of HEV seropositivity (p=0.049). In the HEV-seropositive group, 14 (63.6%) of 21 living-donor liver recipients were born
in Eastern and Southeastern Anatolia regions where HEV is relatively common. Meanwhile, in the HEV-seronegative group, only 16 (28.1%) of 57 living-donor liver recipients were born in Eastern and Southeastern Anatolia regions. For the drinking water source, 13 (42%) and 18 (58%) patients with positive HEV IgG used carboy and tap water, respectively. Moreover, 75 (63%) and 44 (37%) seronegative patients used carboy and tap water, respectively (p=0.034) (Table 2).

No statistically significant differences were noted between patients with positive and negative anti-HEV IgG in terms of sex, time elapsed after transplantation, HCC presence, biochemical tests, immunosuppressive therapy uses, pre-transplant liver disease etiology, geographical region of residence, including rural/urban areas, and the number of household members.

### Discussion

HEV is one of the major causes of acute viral hepatitis worldwide. In immunosuppressed individuals, typically in solid organ transplant recipients, chronic HEV infection may cause progressive hepatic fibrosis and liver cirrhosis. The prevalence of the disease varies according to socioeconomic status and geographical region. HEV seroprevalence rates are higher in the developing countries compared with developed countries. Anti-HEV IgG positivity was detected between 10% and 70% in populations in developing countries compared with 1%–21% in developed countries. The highest prevalence is observed in Asian and African countries. High prevalence rates may reflect HEV outbreaks related to drinking contaminated water.\(^{[16,17]}\)

Olcay et al.\(^{[6]}\) found an anti-HEV antibody seroprevalence rate of 6.3% (57/910) in Turkey. It was 2.7% in Elmada\(^{[18]}\)/Ankara, 3.8% in Manisa and 11.7% in Diyarbakir. They observed a significant difference between Diyarbakir (South East Anatolia) and the other two regions in their study.\(^{[6]}\) The anti-HEV IgG seroprevalence in children aged between 0 and 6 years was 0% in Konya,\(^{[18]}\) 4.2% in Van,\(^{[19]}\) and 0% in Antalya.\(^{[20]}\) Therefore, the prevalence of HEV is possibly higher in Southeastern and Eastern Anatolia in Turkey.\(^{[18–20]}\)

In our study, anti-HEV IgG antibodies were detected in 20.7% of the patients, which was higher than expected in the background popula-

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**Table 2. Seroprevalence of hepatitis E virus in liver transplant recipients according to sociodemographic characteristics, liver function tests, and risk factors**

|                         | Anti-HEV IgG-positive n (%) | Anti-HEV IgG-negative n (%) | p   |
|-------------------------|-----------------------------|----------------------------|-----|
| Sex                     |                             |                            | ns  |
| Female                  | 11 (35.5)                   | 35 (29.4)                  |     |
| Male                    | 20 (64.5)                   | 84 (70.6)                  |     |
| Age (mean±SD)           | 60.10±9.74                  | 54.12±13.7                 | 0.007|
| Time after transplantation in months (mean±SD) | 93.77±90.19 | 77.72±75.18 | ns  |
| Type of donor           |                             |                            | 0.049|
| Deceased donor          | 10 (32.3)                   | 62 (52.1)                  |     |
| Living-donor            | 21 (67.7)                   | 57 (47.9)                  |     |
| Presence of HCC during LT |                             |                            | ns  |
| Yes                     | 9 (29.0)                    | 26 (21.8)                  |     |
| No                      | 22 (71.0)                   | 93 (78.2)                  |     |
| Source of drinking water|                             |                            | 0.034|
| Carboy water            | 13 (42)                     | 75 (63)                    |     |
| Tap water               | 18 (58)                     | 44 (37)                    |     |
| Place of birth          |                             |                            | <0.001|
| East and Southeast Anatolia | 22 (70.9) | 27 (22.7) |     |
| Others*                 | 9 (29.1)                    | 92 (77.3)                  |     |
| Type of living area     |                             |                            | ns  |
| Urban area              | 25 (80.6)                   | 95 (79.8)                  |     |
| Rural area              | 6 (19.4)                    | 24 (20.2)                  |     |
| Number of household members | 3.26±1.59     | 2.98±1.54                  | ns  |
| Liver function tests (median, range) | | | 
| AST (U/L)               | 19 (10–47)                  | 18 (8–328)                 |     |
| ALT (U/L)               | 19 (5–109)                  | 19 (6–388)                 |     |
| ALP (U/L)               | 97 (39–415)                 | 113 (42–889)               |     |
| GGT (U/L)               | 37 (5–387)                  | 32 (7–878)                 |     |
| T. Bilirubin (mg/dL)    | 0.47 (0.14–1.66)            | 0.47 (0.14–13)             |     |

HEV: Hepatitis E virus; LT: Liver transplantation; ns: Not significant; HCC: Hepatocellular carcinoma; n: Number of patients; SD: Standard deviation; AST: Aspartate aminotransferase; ALT: Alanine aminotransaminase; ALP: Alkaline phosphatase; GGT: Gamma-glutamyl transferase; T. Bilirubin: Total bilirubin. *Black Sea region, Mediterranean region, Central Anatolia, Aegean Region, Marmara Region.
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In conclusion, HEV infection may be a cause of hepatitis in organ transplant recipients, which may progress to chronic liver disease. In the liver transplant recipient patients in our center, the HEV seroprevalence was higher (20.7%) compared with the background population. Old age, water supply, and place of birth were risk factors associated with HEV seropositivity. Therefore, the risk of HEV infection in liver transplant patients should be borne in mind, particularly in those born in East or Southeast Anatolia. Further studies are needed to investigate whether HEV seropositivity contributes to the progression of liver disease after transplantation.

Ethics Committee Approval: The Ege University Local Ethics Committee granted approval for this study (Approval date: 15.05.2020, approval number: 20-5T/39).

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