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ORIGINAL ARTICLE

Hepatitis E virus infection in patients on dialysis and in solid organ transplant recipients in Argentina: exploring associated risk factors

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Abstract Infection with hepatitis E virus (HEV) leads to acute hepatitis infection in immunocompetent hosts. HEV genotype 3 can present with high frequency and lead to chronic infection in individuals with a compromised immune system. The risk factors related to increased seroprevalence or chronicity in this population are not entirely understood. Moreover, most studies addressing risk factors for HEV in non-endemic areas come from developed areas such as North America and Europe. In this study we evaluated seroprevalence, chronicity and risk factors for HEV in 120 transplant recipients and 88 patients on dialysis in Argentina. We found a significantly higher seroprevalence of HEV IgG in those undergoing dialysis compared with healthy controls (10.2% and 4.3% respectively, $p = 0.03$). No difference in HEV seroprevalence was observed between healthy controls and transplant recipients (5.8%). We found no association between previously identified risk factors for HEV, such as pork consumption or use of tacrolimus, and HEV seroprevalence. In univariate and multivariate analyses, consumption of fish was associated with higher seroprevalence of HEV (OR = 9.33; 95% CI: 2.07–42.2; $p = 0.04$). None of the samples showed HEV RNA amplification, indicating that chronicity does not seem to be an issue in these cohorts. Our results show increased seroprevalence of HEV in individuals undergoing dialysis but not in transplant recipients. We also found that fish consumption can be a potential risk factor for acquiring HEV.

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Introduction

Hepatitis E virus (HEV) infection has traditionally been considered an acute, self-limited disease, characterized by the development of hepatitis, when clinically evident. Recently, HEV, specifically genotype 3 (HEV-3), has been recognized as a cause of chronic hepatitis in immunosuppressed individuals, particularly in solid organ transplant recipients [1–3]. Also, some reports indicate a higher seroprevalence of HEV in patients undergoing hemodialysis, although there is no evidence of chronicity in these patients [4–6].

Most studies involving HEV infection in transplant recipients or patients on hemodialysis have been performed in high-income developed countries [4, 7, 8]. Little is known about HEV infection in medically immunosuppressed individuals in low- and medium-income countries. In Argentina, human cases of hepatitis E have been diagnosed sporadically in many parts of the country; all detected viruses belonged to genotype 3 [9, 10]. HEV-3 has also been detected in pigs of commercial farms in different areas [11] and our group has reported presence of HEV in watercourses in the central region of Argentina [12].

Seroprevalence data reported in the country varied according to the population studied: 4.4% in healthy adults [12], 0.15% in children [13] and 1.8% in blood donors [14]. Among HIV-infected individuals, HEV seropravelence values ranged between 6.6 and 35% [14–16].

Overall, the role of HEV in causing liver disease and the seroprevalence of HEV in immunocompromised patients in low- and medium-income countries is not well defined. Moreover, the risk factors associated with HEV infection or development of clinical significant disease are unknown in certain areas such as South America.

The aim of this study was to investigate the seroprevalence, presence of chronic infection and associated risk factors of HEV infection in solid organ recipients and in patients on dialysis in a prospective fashion.

Materials and methods

Study population

A total of 208 patients, who were on dialysis or who were solid organ transplant recipients (TR), were randomly and prospectively evaluated in a healthcare center in Córdoba, the second largest city in Argentina (1,329,604 inhabitants, located in the central area of the country). All subjects were analyzed according to their clinical conditions, social habits and the presence of the following potential risk factors for HEV infection: consumption of pork and/or fish, access to potable water, history of transfusion and travelling abroad. Each patient had a sample of blood taken during a clinical visit (for either hemodialysis or clinical follow up) after written informed consent was obtained by the primary physician. All samples were stored at −80°C before analysis. A group of 433 healthy adult subjects described elsewhere [12] was used as a control group.

Ethical approval

Ethics committee of the Health Ministry of the Province of Cordoba (CIEIS HP 4-231/14).

Enzyme Linked Immunosorbent Assay (ELISA)

Commercially available IgG and IgM antibodies against HEV were used (Dia.pro, Milan, Italy) and ELISA assays were performed following the manufacturer's instructions. ELISA microplates were coated with HEV-specific, synthetic, conserved and immunodominant antigens, derived from the open reading frames 2 and 3 (ORF-2 and ORF-3) of HEV genome of all genotypes. Test results were used to calculate the ratio of the sample (S) and the cut-off (CO) (S/CO). Samples with S/CO ratio bellow 0.9 were considered negative, between 0.9–1.1 as equivocal results, and above 1.1 as positive results.

Polymerase Chain Reaction (PCR)

Nested-PCR assay, targeting ORF-2, was performed following previously described protocols [17]. PCR products were analyzed by gel electrophoresis using TBE buffer and a 2% agarose gel containing GelRed (Biotium, Inc), following the manufacturer's instructions, and visualized under UV light. The lower limit of detection for this PCR was 31.6 PID (pig infectious dose) [17].

Statistical analysis

Continuous variables are expressed as means and standard deviations (SD) or as medians and ranges, on the basis of their homogeneity. Categorical variables are expressed as numbers and percentages. To assess the association between individual risk factors and IgG anti-HEV, we used independent t or chi-square tests. All variables that were significant in the univariate analysis with a P value <0.20 were considered for a multivariate logistic regression analysis, to determine the independent risk factors for anti-HEV IgG. The associations are presented as odds ratios (ORs) and 95% confidence intervals (CIs). A two-sided probability value <0.05 was considered to be significant. Statistical analysis was performed with the SPSS 17.0 statistical package (SPSS, Inc., Chicago, IL).

Results

We evaluated a total of 208 patients: of these, 88 were undergoing dialysis and 120 were solid organ transplant recipients. The male-to-female ratio for patients on dialysis was 2.4/1 with a mean age of 60 years (SD = 15.57; range = 23–88 yrs). The male-to-female ratio in transplant recipients was 1.5/1, with a mean age of 50 years (SD = 15.62; range = 18-77 yrs). There were 106 kidney transplant recipients, 14 liver transplant recipients, 82 patients on hemodialysis and 6 on peritoneal dialysis. Seropositivity for anti-HEV IgG was observed in 9 out of 88 patients on dialysis (10.22%). The mean age for those who tested positive for HEV, was 59 years (SD = 14.6; range = 36–75 yrs) and the male-to-female ratio was 2.3/1. Prevalence of HEV infection among patients on hemodialysis was 9.7% (8/82), and this was 16.7% (1/6) among patients on peritoneal dialysis. Among solid organ transplant recipients, 7 out of 120 tested positive for anti-HEV IgG (5.83%) (Table 1). The mean age among HEV-positive transplant recipients was 61 years (SD = 17.0; range = 42–77 yrs) and the male-to-female ratio was 1.5/1.

Table 1 Comparison of anti-HEV IgG seroprevalence in transplant recipients, patients on dialysis and healthy controls

	N	anti-HEV IgG		95% CI	p-value
		Positive samples (%)	OR		
Control group	433	4.4	Reference		
Transplant recipients	120	5.8	1.35	0.55–3.29	0.66
Kidney - TR	106	5.7	1.31	0.51–3.36	0.56
Liver - TR	14	7.1	1.68	0.21–13.49	0.62
Dialysis	88	10.2	2.48	1.08–5.67	0.031
HD patients	82	9.7	2.36	0.99–5.58	0.052
Peritoneal dialysis	6	16.7	4.36	0.48–39.16	0.19

None of the patients showed any clinical symptom that could be attributed to acute or chronic hepatitis.

Seropositivity for anti-HEV IgM was detected in 5 of the 8 anti-HEV IgG-positive patients on hemodialysis. None of the transplant patients had anti-HEV IgM. All patients were negative for HEV RNA.

In our previous study there was a statistically significant difference between the rates of HEV IgG seroprevalence in patients on dialysis and healthy controls (10.22 % vs. 4.4%) with an OR of 2.48 of being HEV IgG-positive for dialysis patients vs. healthy controls (95% CI: 1.08–5.67, $p = 0.03$). Interestingly, we found no statistically significant difference in HEV seroprevalence between transplant recipients and healthy controls (5.8% vs. 4.4%, $p = 0.51$), or between transplant recipients and patients on dialysis (5.8% vs. 10.2%, $p > 0.05$). There were also no differences in HEV seroprevalence between kidney or liver transplant recipients (5.7% vs. 7.1%, $p > 0.05$). There was no significant correlation between HEV seroprevalence and gender or age, in any of the patient groups studied.

Among all the variables evaluated by univariate analysis, only fish consumption and lack of traveling abroad were significantly associated with HEV seropositivity ($p < 0.05$ for each variable) (Table 2). Interestingly, consumption of pork or charcuterie did not correlate with HEV seropositivity. Due to the dependence structure between covariates, we fitted multiple logistic regression models in order to obtain the adjusted risk estimates. This multivariate analysis found that fish consumption (more than once a week) was the only statistically significant variable associated with HEV infection (OR = 9.33, 95% CI: 2.07–42.2) (Table 3).

Discussion

In non-endemic countries, such as Argentina, HEV genotype 3 has been proposed to be transmitted to humans in a zoonotic fashion, from animal reservoirs or from water sources. However, the specific routes of transmission and risk factors for the development of infection are not entirely understood. It is therefore important to investigate the epidemiological pattern of circulation of HEV, especially in susceptible populations from areas where HEV has been reported [12].

This is the first assessment of HEV seroprevalence and risk factors in hemodialysis patients and transplant recipients in Argentina. In transplant recipients, the HEV IgG seroprevalence was 5.83%. This prevalence was higher than that reported in Italy (3.3%) using the same ELISA kit (Dia.pro, Milan, Italy) and lower than that found among Iranian kidney transplant recipients (30.8%) [6, 18]. Globally, there is controversy on whether transplant recipients of specific organs have variable prevalence of HEV. Some studies suggest that patients who have undergone a kidney transplant could be more susceptible to infection by HEV, due to exposure to higher doses of immunosuppressive drugs. Other studies indicate that patients who receive a liver transplant could be more likely to develop HEV infection and progress to a chronic infection as a result of local inflammation, which can generate a favorable environment in the target organ [19–21]. Our study found no significant differences between HEV prevalence among recipients of different organs (kidney or liver).

Numerous studies have reported the development of chronic infections with HEV in transplant recipients [7, 22–28]. However, in line with other studies, such as Harrison et al. (2013), Naik et al. (2013) and Scotto et al. (2015), which did not describe such viral persistence, we did not find HEV RNA amplification in any sample, suggesting that progression of HEV infection to chronicity does not seem to represent a problem in our community [4, 6, 29].

The use of the immunosuppressive drug tacrolimus has been found to be a factor independently associated with chronic HEV infection, when compared with the use of cyclosporine A [20]. In our study we could not evaluate this association because all the patients were treated with tacrolimus. Nonetheless it is important to note that, although all transplant recipients in our study were treated with a drug associated to HEV infection, none had HEV RNA in their blood.

Table 2 Univariate analysis of factors associated with anti-HEV seroprevalence

Variable	IgG positive, n (%) (N = 16)	IgG negative, n (%) (N = 192)	p-value
Age (years)	57.3 (SD = 15,5)	52.9 (SD = 15.9)	0.31
Gender, male*	9 (56.3%)	103 (52.0%)	0.75
Comorbidities*			
Hemodialysis	8 (9.7%)	74 (90.2%)	0.32
Peritoneal dialysis	1 (16.7%)	5 (83.3%)	0.94
Liver - transplant	1 (7.1%)	13 (92.9%)	0.64
Kidney - transplant	6 (5.7%)	100 (94.3%)	0.46
Grouped comorbidities			
Dialysis	9 (10.2%)	79 (89.8%)	0.20
Transplant	7 (5.83%)	113 (94.2%)	0.24
Blood transfusion*	10/16 (62.5%)	109/156 (69.9%)	0.54
Food habits*			
Pork meat consumption	12/16 (75%)	106/159 (66.7%)	0.59
≤1/week	7/7 (100%)	110/115 (95.7%)	0.67
>1/week	0/7 (0%)	5/115 (4.3%)	0.67
Charcuterie consumption	10/16 (62.5%)	104/159 (65.4%)	0.81
≤1/week	6/7 (85.7%)	99/115 (86.1%)	0.98
>1/week	1/7 (14.3%)	16/115 (13.9%)	0.98
Fish consumption	13/16 (81.3%)	121/159 (76.1%)	0.77
≤1/week	4/8 (50%)	113/125 (90.4%)	0.004
>1 week	4/8 (50%)	12/125 (9.6%)	0.004
Drinks tap water	10/15 (66.7%)	94/156 (60.3%)	0.63
Drinks bottled water	8/16 (50%)	79/156 (50.6%)	0.96
Alcohol consumption	3/16 (18.8%)	55/159 (34.6%)	0.27
≤1/week	2/2 (100%)	58/71 (81.7%)	0.79
>1/week	0/2 (0%)	13/71 (18.3%)	0.79
Coffee consumption	13/16 (81.3%)	106/158 (67.1%)	0.39
≤1/week	4/8 (50%)	45/115 (39.1%)	0.81
>1/week	4/8 (50%)	70/115 (60.1%)	0.81
Residence*			
Cordoba city (urban)	12/16 (75%)	90/159 (56.6%)	0.19
Periphery of Cordoba city (non-urban)	4/16 (25%)	41/159 (25.8%)	0.94
Others provinces	0/16 (0%)	28/159 (17.6%)	0.08
Travel abroad*			
Yes	4/14 (28,6%)	52/84 (61.9)	0.04
Never	10/14 (71.4%)	32/84 (38.1%)	0.04

*Only data from individuals having this factor were included

Table 3 Multivariate analysis of factors independently associated with anti-HEV seroprevalence

Variable	OR (95% CI)	Adjusted OR (95% CI)	p-value
Fish consumption >1/week	9.42 (2.08–42.6)	9.33 (2.07–42.2)	0.04
Never travel abroad	4.06 (1.18–14.04)	-	NS

Regarding hemodialysis patients and HEV seropositivity, it is known that chronic renal disease induces defects in cellular and humoral immunity characterized by increased susceptibility to viral and bacterial infections [4]. In this context, our study found a higher HEV seroprevalence in patients undergoing hemodialysis, compared with a control

group. These results are similar to those observed in Italy (6.0%), Iran (7.4–10.6%) and Turkey (20.6%), which were obtained using the same commercial ELISA test to detect anti-HEV antibodies, but our seroprevalence data is much lower than that detected in England (36%) using a different ELISA test [4–6, 30–32].

Scotto et al. (2015) reported a low frequency of acute HEV infection (IgM positive) in hemodialysis patients and transplant recipients, 0.9% and 0.8%, respectively [6]. Our study found a high percentage of HEV IgM positivity among patients on HD: 6.09% of the entire cohort and 62.5% of those who were positive for HEV IgG. None of these patients exhibited symptoms consistent with acute viral hepatitis and liver transaminases level in blood were similar to those from patients that were HEV IgM-negative. It should be noted though that there was a more pronounced change in ALT (6.75 U/l) than in AST (0.86 U/l), three months after diagnosis in those patients with HEV IgM. Whether these changes were related or not to acute infection with HEV is difficult to assess, due to the low number of patients.

Continuous exposure of HD patients to heparin could be related to higher HEV seroprevalence rates when compared to healthy controls [4]. Heparin is derived from porcine small intestine and HEV has been found in the digestive organs of these animals after experimental infection [33]. We performed PCR for HEV in a small batch of heparin samples used in these patients, but found no amplification of HEV RNA. Parenteral transmission has also been proposed as a potential explanation for higher HEV seroprevalence in this group [6]. Patients with chronic kidney disease have impaired erythropoiesis and therefore are prone to receive more blood transfusion than the general population. However, in our study, blood transfusion was not a risk factor independently associated with HEV infection. We found no significant differences in prevalence or risk factors between those on hemodialysis or peritoneal dialysis. However, the number of patients on peritoneal dialysis was quite low.

Interestingly, we did not find risk factors commonly reported to be associated with HEV infection, such as consumption of pork or sausages, drinking of tap water and traveling abroad, to correlate with HEV seropositivity. Unexpectedly, fish consumption, with a frequency of more than once per week, was the only variable independently associated with increased IgG HEV detection. A limitation of this study is that the survey did not inquire about the kind of fish consumed (sea fish, freshwater or shellfish), sources of fish or type of consumption (raw or cooked), which would have provided more information about fish consumption and routes of transmission. Although there are no studies that report an association between HEV and consumption of fish, Yugo and Meng (2013) reported that coastal waters could be contaminated by HEV, leading to accumulation of the virus in the digestive tissues of shellfish, which could be a risk for human infection through ingestion [34]. Most often, mussels, cockles, and oysters are eaten raw or slightly cooked, and HEV is stable in both alkaline and acidic environments, as well as in frozen food for more than 10 years, and remains infectious at temperatures of up to 60 °C, suggesting that raw, poorly-cooked, or slightly steamed contaminated seafood may transmit HEV to consumers [35]. Also, high seroprevalence of HEV infection in seafood processing workers from China has been reported [36]. In that study, Cui et al. (2016) showed that direct contact with raw seafood was a significant risk factor for HEV infection [36]. Our findings, albeit interesting, are also limited by the low number of patients who reported consuming fish, and therefore larger studies addressing this risk factor will be needed.

In conclusion, our study found a higher seroprevalence of HEV IgG among patients on dialysis, but not in solid organ transplant recipients, compared with healthy controls. Chronic hepatitis due to HEV was not observed. The long-term effects of HEV exposure in liver function are still unknown and further long-term studies are needed to evaluate HEV seroprevalence and HEV RNA prevalence in the blood of immunocompromised patients as well as HEV's effect on liver physiology.

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Compliance with ethical standards

This study was approved by the ethics committee of the Health Ministry of the Province of Cordoba (CIEIS HP 4-231/14).

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Conflict of interest The authors declare that they have no conflict of interest.

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