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ORIGINAL ARTICLE

Case Control Study

Hepatitis E in hemodialysis and kidney transplant patients in south-east Italy

Gaetano Scotto, Filippo Aucella, Giuseppe Grandaliano, Domenico Martinelli, Mario Querques, Antonio Gesuete, Barbara Infante, Paolo Delli Carri, Salvatore Massa, Giovanna Salatino, Fabio Bulla, Vincenzina Fazio

Gaetano Scotto, Microbiology and Clinical Microbiology, Master's Degree in Dentistry, University of Foggia, 71100 Foggia, Italy

Filippo Aucella, Antonio Gesuete, Nephrology and Dialysis Unit IRCCS "Casa Sollievo della Sofferenza" San Giovanni Rotondo (FG), 71013 San Giovanni Rotondo, Italy

Giuseppe Grandaliano, Barbara Infante, Nephrology and Dialysis Unit, University of Foggia, 71100 Foggia, Italy

Domenico Martinelli, Institute of Hygiene, University of Foggia, 71100 Foggia, Italy

Mario Querques, Paolo Delli Carri, Giovanna Salatino, Division of Nephrology, Hospital of Foggia, 71100 Foggia, Italy

Fabio Bulla, Clinic of Infectious Diseases, University of Foggia, 71100 Foggia, Italy

Salvatore Massa, Department of Agricultural, Food and Environmental Sciences, University of Foggia, 71100 Foggia, Italy

Vincenzina Fazio, Clinical Chemistry Laboratory, Unit of Virology, Hospital of Foggia, 71100 Foggia, Italy

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Correspondence to: Gaetano Scotto, MD, Adjunct Professor, Chair of Microbiology and Clinical Microbiology, Master's Degree in Dentistry, University of Foggia, viale L. Pinto 1, 71100 Foggia, Italy. gaetano.scotto@unifg.it
Telephone: +39-33-37453981
Fax: +39-8-81732208
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Abstract

AIM: To investigate the serovirological prevalence and clinical features of hepatitis E virus (HEV) infection in end-stage renal failure patients and in the healthy population.

METHODS: HEV infection is a viral disease that can cause sporadic and epidemic hepatitis. Previous studies unexpectedly showed a high prevalence of HEV antibodies in immunosuppressed subjects, including hemodialysis (HD) patients and patients who had undergone kidney transplant. A cohort/case-control study was carried out from January 2012 to August 2013 in two hospitals in southern Italy (Foggia and S. Giovanni Rotondo, Apulia). The seroprevalence of HEV was determined in 801 subjects; 231 HD patients, 120 renal transplant recipients, and 450 health individuals. All HD patients and the recipients of renal transplants were attending the Departments of Nephrology and Dialysis at two hospitals located in Southern Italy, and were included progressively in this study. Serum samples were tested for HEV antibodies (IgG/IgM); in the case of positivity they were confirmed by a Western blot assay and were also tested for HEV-RNA, and the HEV genotypes were determined.

RESULTS: A total of 30/801 (3.7%) patients were positive for anti-HEV Ig (IgG and/or IgM) and by Western blot. The healthy population presented with a prevalence of 2.7%, HD patients had a prevalence of 6.0%, and transplant recipients had a prevalence of 3.3%. The overall combined HEV-positive prevalence in the two groups with chronic renal failure was 5.1%. The rates of exposure to HEV (positivity of HEV-IgG/M in the early samples) were lower in the healthy controls, but the difference among the three groups was not statistically significant ($P > 0.05$). Positivity for anti-HEV/IgM was detected in 4/30 (13.33%) anti-HEV Ig positive individuals, in 2/14 HD patients, in 1/4 transplant individuals, and in 1/12 of the healthy population. The relative risk of being HEV-IgM-positive was significantly higher among transplant recipients compared to the other two groups (OR = 65.4, 95%CI: 7.2-592.7, $P < 0.001$), but the subjects with HEV-IgM positivity were numerically too few to calculate a significant difference. No patient presented with chronic hepatitis from HEV infection alone.

CONCLUSION: This study indicated a higher, but not significant, circulation of HEV in hemodialysis patients *vs* the healthy population. Chronic hepatitis due to the HEV virus was not observed.

Key words: Hepatitis E virus infection; Prevalence; Immunosuppressed subjects; Hemodialysis patients; Transplant recipients

Core tip: Hepatitis E, a single-stranded RNA virus, is the main aetiological agent of enteric non-A hepatitis. Previous seroprevalence surveys in developed countries showed variable rates of anti-hepatitis E virus (HEV) positivity in healthy populations, and several studies reported an unexpectedly high prevalence of antibodies against HEV in hemodialysis patients. The purpose of this survey was: (1) to compare the rate of HEV infection in renal transplant recipients and patients undergoing chronic hemodialysis to a control population; (2) to determine if these patients have an increased risk for HEV exposure; and (3) to evaluate the stage of liver disease.

INTRODUCTION

Blood-borne viral hepatitis [hepatitis B virus (HBV) and hepatitis C virus (HCV)] infections represent relevant causes of liver disease in end stage renal failure patients on hemodialysis (HD)[1-5]. In recent years, preventive measures and extensive infection control guidelines guided a progressive decrease of HCV and HBV rates in these patients[2-9]. Nevertheless, a proportion of liver illnesses due to non A-B-C hepatitis occur in these individuals. Previous seroprevalence surveys in developed countries showed variable rates of anti-hepatitis E virus (HEV) positivity in healthy populations[10,11], and several studies reported an unexpectedly high prevalence of antibodies against HEV in hemodialysis patients[12-15]. The higher prevalence of HEV-IgG in chronic hemodialysis patients could be related to their impaired immunity, with an increased susceptibility to infections and decreased immune responses to antigenic stimuli (*e.g.*, HBV vaccination)[16-18]. Furthermore, they present a reduced response to HBV vaccination. In fact, these patients have an increased risk of contact with nosocomially-transmitted agents, and the role of enterically-transmitted hepatitis viruses in such cases needs to be defined.

Hepatitis E, a single-stranded RNA virus, is the main aetiological agent of enteric non-A hepatitis. In the recent past, it was believed to be present only in developing countries, where it was associated with epidemic outbreaks through the fecal-oral route from contaminated water supplies, but it is now recognized as a worldwide infection, sometimes related, in developed countries, to an asymptomatic zoonotic infection (as well as undercooked meat products)[19-21] or to parenteral/vertical transmission[22-24]. Furthermore, it has been recently noted that a variable rate of blood donors were positive for HEV-RNA[25-27]. There are scant reports on the prevalence and possible nosocomial transmission of HEV in HD patients. Some authors highlighted the high rates of anti-HEV antibodies in their HD patients and hypothesized other routes of transmission besides the fecal-oral route, although the real prevalence of HEV infection through the parenteral route, particularly via hemodialysis, is unknown[28]. Other investigators observed low rates of anti-HEV-positivity in their HD populations[15,29,30].

Previous seroprevalence studies showed anti-HEV/IgG positivity in 6%-16% of renal transplant recipients[31-33]; this variability is often because this virus is not routinely screened for in cases of acute hepatitis in recipients of solid-organ transplants. Recently, HEV infection has been presented as a chronic infection, sometimes with associated cirrhosis in immunosuppressed individuals. These cases included solid-organ (including kidney) transplant recipients receiving immunosuppressive therapy[33-36], patients with hematological malignancies[37-39], and subjects with HIV infection[40]. It is not known whether HEV can induce chronic hepatitis in subjects with defects of humoral and cellular immunity, such as in patients with end-stage renal failure requiring renal replacement therapy.

To our knowledge, few studies have examined the seroprevalence rate and clinical evolution of HEV infection among HD patients and in recipients of renal transplants in Italy. The purpose of this survey was (1) to compare the rate of HEV infection in renal transplant recipients and patients undergoing chronic hemodialysis to a control population; (2) to determine if these patients have an increased risk for HEV exposure; and (3) to evaluate the stage of liver disease.

MATERIALS AND METHODS

This observational study was carried out from January 2012 to August 2013. The seroprevalence of HEV was determined in 801 subjects (231 HD patients, 120 renal transplant recipients, and 450 individuals coming from the general population as controls). All of the HD patients and the recipients of renal transplants were attending the Departments of Nephrology and Dialysis at two hospitals located in southern Italy (Foggia and S. Giovanni Rotondo, Apulia), and were included progressively in this study. The controls were aged > 18 years and were identified from out-patient populations attending these hospitals for blood tests. Among the control patients, most were healthy, others had a range of acute/chronic general medical conditions, and some (approximately 6%) had a history of liver disease. All of the subjects included in the study were orally informed about the purpose of the study and invited to participate. Each patient gave informed consent. The research was conducted in accordance with the Declaration of Helsinki (as revised in 2008) and according to local guidelines and laws. Because this was a case-control study, the assent of the local Ethics Committee was not mandatory. At baseline, all study participants were requested to complete a questionnaire to obtain demographic, lifestyle, socio-economic, and clinical data in order to assess their previous exposure to viral hepatitis. These data included sexual orientation, ethnicity, and liver function tests; underlying nephrological diagnosis, previous transplantation (if on chronic hemodialysis), hemodialysis, and transplant vintage and previous/current immunosuppressive treatment data were obtained for HD and transplant patients. Routine HD techniques were performed with 0.75 h treatments three times a week. The history of blood transfusion requirements for each patient was evaluated. No patient admitted had a history of intravenous drug abuse. All enrolled subjects also received a full clinical examination and were treated according to their clinical situation. The demographic, clinical, and laboratory data of all patients are presented in Table 1.

The samples were investigated for the presence of anti-HEV immunoglobulin (IgG/IgM) using a commercial enzyme immunoassay (EIA) based on recombinant proteins (HEV IgG/IgM; DIA.PRO, Diagnostic BioProbes, Milan, Italy). If repeatedly positive (when sera gave an absorbance greater than the cut-off value), the results were confirmed by a Western blot assay (HEV-recomBlot, Nuclear Laser Medicine, Milan, Italy).

To determine HEV-RNA, a commercially-available assay was used (Qiamp viral RNA mini-kit, Qiagen, Chatsworth, CA). After RT-nested PCR, genotyping was performed using restriction endonuclease analysis; a technique in which DNA fragments obtained from digestion with restriction enzymes are compared to construct a restriction map showing the position of specific sites along a sequence of DNA[41]. Anti-HEV antibodies, Western blots, determination of HEV-RNA, and genotype assessments were performed using the same assays in a single laboratory (Foggia).

HBV markers were assayed by commercial immunoassay (Abbott-Auszyme Mc, Abbott Laboratories, North Chicago, IL, United States). The presence of antibodies to HCV was determined by the use of a third-generation enzyme-linked-immunoabsorbent assay (HCV-ELISA, Ortho Diagnostic System, Raritan, NJ, United States) and confirmed by a third-generation-recombinant-immunoblot assay (RIBA, Ortho Diagnostic Systems, Raritan, NJ, United States). To determine HBV-DNA and HCV-RNA, a commercially-available assay was used (Qiamp viral RNA, Qiagen, Chatsworth, CA). The presence of antibodies to HIV 1 and 2 was determined by a commercial immunoassay (Ortho Diagnostic Systems, Raritan, NJ, United States). To determine HIV-RNA, a commercially-available assay was used (Artus HIV virus 1, Rg RT-PCR kit, Qiagen, Chatsworth, CA, United States).

Serum alanine-amino-transferase (ALT) was quantified by ultraviolet-enzymatic-assay (normal range, 0-40 IU/L). Each patient's hepatic biochemical, epidemiological, and virological parameters were recorded, and a serum sample was taken and frozen at -70 ℃ prior to being tested for HEV by reverse transcriptase-polymerase chain reaction (RT-PCR), anti-HEV immunoglobulin G (IgG, IgM) immunoassays, and western blotting.

Statistical analysis

The χ^2 test was used to compare categorical variables (sex, positivity for anti-HEV IgG/M, Western blot test results for HEV antibodies, HCV antibodies, and HBV markers). When possible, odds ratio and 95%CIs were calculated. Continuous variables (age and ALT levels) were compared by Student's *t*-test for independent samples and ANOVA. Logistic-regression models were used to account for the confounding effects of patient demographics. *P* values < 0.05 were considered significant. The data were analyzed by STATA 10 MP software (Stata Corp., United States) for Mac OS X.

Table 1 Clinical characteristics, *n*			
	Transplant patients	**HD patients**	**General population**
Total	120	231	450
Sex (male:female)	82:38	126:105	178:272
Median age (yr)	48	63	40
Causes of renal failure	Chronic glomerulonephritis: 43	Chronic glomerulonephritis: 73	
	Nephroangiosclerosis: 21	Nephroangiosclerosis: 27	
	Polycystic kidney disease: 16	Polycystic kidney disease: 32	
	Diabetic nephropathy: 14	Diabetic nephropathy: 44	
	Chronic interstitial nephritis: 11	Chronic interstitial nephritis: 26	
	Other aetiologies: 15	Other aetiologies: 29	
Median HD treatment	18 mo (range: 1-54 mo)	79 mo (range: 3-154 mo)	
	17 mo (range: 1-48 mo) HEV-negative	78.9 mo (range: 3-149 mo) HEV-negative	
	21 mo (range: 3-54 mo) HEV-positive	81 mo (range: 7-154 mo) HEV-positive	
Immunosuppressive treatment	All of the patients (120)	Yes: 2 (males)	

HEV: Hepatitis E virus; HD: Hemodialysis.

Table 2 Hepatitis E virus antibodies *n* (%)			
	Transplant patients	**HD patients**	**General population**
Total	120	231	450
Anti-HEV Ig pos.	4 (3.3)	14 (6)	12 (2.7)
HEV IgM pos.	1	2	1
HEV RNA pos.	2	3	1

HEV: Hepatitis E virus; HD: Hemodialysis.

RESULTS

A total of 30/801 (3.7%) patients were anti-HEV Ig (IgG and/or IgM) and Western blot positive; almost none of the patients showed any clinical symptom that could be related to acute or chronic hepatitis. The prevalence in dialysis patients was 6.0% (14 patients); in transplant recipients the prevalence was 3.3% (4 individuals) and in the general population the prevalence was 2.7% (12 subjects). The combined overall HEV-positive prevalence in the two groups with chronic renal failure was 5.1%. The rates of exposure to HEV (positivity of HEV-IgG/M in the early samples) were lower in the healthy controls, but the difference among the three groups was not statistically significant ($P > 0.05$).

Positivity for anti-HEV/IgM was detected in 4/30 (13.33%) anti-HEV Ig positive individuals, in 2/14 HD patients, in 1/4 transplant individuals, and in 1/12 individuals from the healthy population (Table 2).

There was not a statistically significant difference between the rates in HD patients and healthy controls (0.98% *vs* 0.22%, $P > 0.05$). The relative risk of being HEV-IgM-positive was significantly higher in transplant recipients compared to the other two groups (OR = 65.4, 95%CI: 7.2-592.7, $P < 0.001$), but the subjects with HEV-IgM positivity were numerically too few to determine a significant difference. The origin of acute HEV infection (IgM positive and HEV-RNA detectable) in HD patients, transplant recipients, and the healthy population was uncertain.

HEV-RNA determination was positive in all IgM-positive patients and in two of the IgG positive patients (1 dialysis and 1 transplant, both HEV/HCV co-infected), who presented with hepatic fibrosis. Among dialysis and transplant patients with acute hepatitis (anti-HEV IgM), one carried genotype 1 (an immigrant) and two presented with genotype 3; among the general population the only anti-HEV IgM patient presented with genotype 3.

There was no significant correlation for either group between sex (males 7/14 in HD patients, 2/4 in renal transplants recipients, and 8/12 in the healthy population) and HEV-IgG/IgM and Western blot positivity ($P > 0.05$). The mean age in the transplant individuals and in the dialysis patients was not significantly different between subjects who were HEV-positive (age of transplant subjects: 48.5 ± 12.1 years; age of HD patients: 59.0 ± 6.7) *vs* HEV-negative (age of transplant subjects: 48.5 ± 18.9 years; age of HD patients: 62.9 ± 6.3; $P > 0.05$). Instead, the mean age of the healthy population was significantly higher in HEV-positive subjects (49.8 ± 12.1 years) *vs* HEV-negative (39.7 ± 18.9 years, $P < 0.05$). However, in logistic-regression models adjusted for age, sex, and group, the risk of anti-HEV positivity was not significantly higher in HD patients compared with the other two groups. The only statistically significant association in HD patients was with age (OR = 11.7, 95%CI: 5.9-23.2, $P < 0.001$). The cohort of patients > 45 years presented with HEV positivity more frequently than the groups aged 21-45 years. The risk of Western blot positivity was related to age and was higher in HD patients (OR = 12.3, 95%CI: 5.9-25.5, $P < 0.001$).

The hemodialysis vintage in HD patients ranged between 4-121 mo (median 79.2 mo) for anti-HEV positive patients and between 1-184 mo (median 79.4 mo) for the anti-HEV negative patients ($P > 0.05$). Among the patients with a functioning transplant, only 2/4 patients who were HEV positive had a prior history of HD treatment (median 21 mo *vs* 17 mo for HEV-negative patients). The length of hemodialysis treatment in these subjects also did not seem to be a significant risk factor for HEV IgG positivity; however,

the duration of HD treatment before renal transplant in HEV-positive individuals was lower compared to that of hemodialysis patients.

Five out of one hundred and thirty one (2.2%) HD patients and 1/120 (0.83%) transplant recipient presented with HBV infection (hepatitis B surface antigen positive), while 67/231 (29.0%) HD patients and 29/120 (24.2%) transplant recipients had serological parameters of previous HBV infection (anti-HBc and/or anti-HBs positivity). The individuals who had been immunized with hepatitis B vaccine were not included in this calculation of HBV infection. Co-infection with HBV/HEV was not present in any of the HD or transplant subjects.

Moreover, we observed 18/231 (7.8%) patients with an anti-HCV antibody among HD patients and 19/120 (15.8%) patients with an anti-HCV antibody among the transplant recipients. Co-infection with HEV/HCV was present in 1/14 (7.1%) of the HD patients and 1/4 (25%) of the transplant subjects. No co-infection with other hepatitis viruses was present in the HEV positive subjects from the general population.

Patients with chronic renal failure and HEV-IgG positivity were for the most part asymptomatic; only 7/18 (38.9%) reported moderate asthenia, whereas jaundice was present in 1/3 (33.3%) IgM-positive patients and hepato-splenomegaly and distended abdomen were observed in 2/3 (66.76%).

Among the HD patients and transplant recipients who were anti-HEV positive, approximately 67% of individuals had normal ALT values. Higher serum levels of ALT were observed in HEV-IgM positive *vs* HEV-IgM negative subjects (178.8 ± 131.1 *vs* 33.7 ± 14.5, $P < 0.001$). Among the HEV-IgG positive subjects, ALT levels were not significantly different among HD patients (31.59 ± 18.05 UI/mL) *vs* transplant individuals (28.8 ± 13.1) and the general population (54 ± 30 UI/mL), $P > 0.05$.

There is no connection between any stage of chronic hepatitis and HEV infection alone in any of the patients groups who presented with chronic renal failure. In fact, the two IgG positive patients (1 dialysis and 1 transplant patient) who presented with chronic active hepatitis with advanced fibrosis were HCV-HEV co-infected, and both patients presented with genotype HEV 3.

DISCUSSION

In the past few years, there has been increasing evidence that HEV, with the development of acute/chronic clinical disease (mainly in immune-compromised patients, HD patients, and transplant recipients), may occur in non-endemic areas, with the zoonotic pathway (porcine zoonosis) having been found to be the major reason for this infection[20,21,42,43]. There are few data on the prevalence of HEV infection and/or the prevalence of circulating HEV antibodies in end-stage renal failure patients for Italy as a whole or in just in southern Italy[11,44,45].

In this survey, we studied three cohorts of individuals (hemodialysis patients, kidney transplant recipients, and the general population as a control); the overall prevalence of circulating HEV-Ab was 3.7% with appreciable, but not significant, deviations between the general population (2.7%) and HD patients (6.0%), but not kidney transplant recipients (3.3%), compared to the general population.

There are few studies with conflicting results about HEV epidemiology among HD patients[10,11,14,15]. The different prevalence of HEV infection in the general population[42,43,46], the parameters for the inclusion of patients, the routes of HEV transmission[22,24], and the serological assays used[47,48] could partially explain the different findings. In our research in patients with defects in cellular and humoral immunity, we confirmed HEV-Ig positivity with western immunoblotting techniques, which validated both the acute-phase and chronic-phase with better sensitivity and specificity[49]. The seroprevalence of anti-HEV/IgG observed in our HD patients is lower than that reported in other recent studies in the United Kingdom[10], France[46], and Japan[15], and is consistent with HEV seroprevalence data in Greece[13,30], another study in Japan[29], Spain[31], and Saudi Arabia[50]. In all of these studies, there was a higher anti-HEV seroprevalence in HD patients *vs* controls.

A logistic regression analysis showed that neither length of HD, nor other variables related to HD, such as blood transfusion, were associated with HEV, while a significant link was reported between the presence of antibodies type IgG and older age (> 70 years).

The correlation of HEV/older age could reflect a cohort phenomenon due to infections acquired some decades ago. Antibodies for HEV/IgG can persist over the long-term, and it may be that water-borne hepatitis outbreaks of unknown aetiology occurred in Apulia earlier in the 20th century and became present as sporadic cases owing to the fecal pollution of drinking water with hepatitis E and not A (previously related to the high circulation of HAV in our region, which is approximately 60% of subjects older than 50 years).

HEV is usually associated with an enterically-transmitted infection, but the high prevalence of anti-HEV reported in some studies in HD patients indicated that the fecal-oral route may not be the only route of transmission of HEV and these individuals with a high risk for HBV and HCV could also have been infected by unknown HEV. In fact, experimental transmission of HEV in humans showed a transient phase of viremia preceding the onset of clinical symptoms, and prolonged viremia has been observed in some patients[50]. Therefore, a theoretical possibility of HEV parenteral transmission has been suggested, mainly in endemic areas[50,51]. In our study, only two patients presented with an association between HEV and HCV. Our data are probably different than that of regions

with high rates of HEV infection for two reasons: first, in Italy, there is a modest rate of anti-HEV and a low flow of HEV in our community, resulting in a reduced risk of chronic HCV co-infection; second, a relatively small number of patients were tested.

Another interesting and stimulating hypothesis was suggested by Harrison *et al*[52], claiming that the use of heparin, derived from porcine small intestine, in HD patients might be one possible cause of HEV infection[53]; HEV has been found in the porcine small intestine after experimental HEV infection in pigs[54]. It is not known whether heparin regularly used in humans is infected with HEV, but this might be a possible route of infection and merits further studies[52].

Acute HEV in HD and transplant patients is infrequent and possibly under-diagnosed. Only 0.9% (2/31) of HD patients and 1/120 (0.8%) of transplant recipients in the present survey were anti-HEV/IgM positive, and only one of the patients had any symptoms/signs suspected or diagnosed as acute hepatitis. The clinical events usually associated with acute hepatitis are often less evident in these patients (low grade or subclinical hepatitis); this factor might have contributed to the failure to recognize and document any clinical episodes of hepatitis in our patients. Serum levels of ALT are low in HD patients, and its elevation is usually less pronounced in these individuals, even in the presence of acute hepatitis. In fact, chronic uremic patients present with a reduced immune competence, and this situation can be responsible for the attenuated inflammatory reactions in the liver and consequently reduced hepatocyte destruction, and, therefore, the AST/ALT levels in HD patients are usually suppressed[50,55]. The ALT levels in the three patients found to be IgM anti-HEV positive in our study showed only mild abnormalities; the highest ALT levels, with a peak elevation within 1 ± 3 d of the onset of the illness followed by a decline, were less than twice the upper limit of normal levels.

We observed that the HD patients had a higher HEV seroprevalence than transplant recipients (6% *vs* 3.3%), suggesting that hemodialysis could represent a risk factor for HEV infection. However, in our study, renal transplant recipients with a prior history of HD had the same rate of HEV infection than that seen in transplants recipients without prior HD treatment. The different seroprevalence between the HD patients and transplant recipients is unexplained, although it is possible that anti-HEV serological assays perform poorly in transplant recipients receiving immunosuppressive treatment are the cause, thereby determining a percentage error with false negative results[56]. In the transplant recipients in our survey, the numbers and the doses of immunosuppressive drugs were decreased when they were diagnosed anti-HEV IgM and HEV-RNA positive. In fact, this is the first approach to control HEV infection in these patients[33], because these drugs decrease the synthesis of antibodies and inhibit the cell-cycle progression and

differentiation of human B lymphocytes. The humoral immune response is necessary to clear HEV and prevent hepatitis[57,58].

However, in the past few years, many studies have reported a surprisingly high prevalence of chronic HEV hepatitis in immunosuppressed patients, including kidney transplant recipients[34-36]. In our survey, at 6 mo of follow-up, no patient remained chronically viremic and there was not a correlation between any stage of chronic hepatitis and HEV infection alone in any patient of the two groups with chronic renal failure. The only patients who presented with chronic active hepatitis were HCV-HEV co-infected.

Finally, this study showed a higher circulation of HEV in end-stage renal failure in the district of Foggia *vs* the healthy population, but this high prevalence is mainly related to hemodialysis patients.

There was no relationship between the duration of HD treatment and the risk of acquiring a HEV infection. None of the kidney transplant recipients or HD patients had any evidence of chronic HEV. Although no specific therapy is currently available, unexplained hepatitis in the dialysis setting and in kidney transplant recipients undergoing chronic immunosuppression calls for an evaluation of HEV infection, especially in kidney transplant candidates.

COMMENTS

Background
Hepatitis E is the main aetiological agent of enteric non-A hepatitis. In the recent past, it was believed to be present only in developing countries, where it was associated with epidemic outbreaks through the fecal-oral route from contaminated water supplies, but it is now recognized as a worldwide infection, sometimes related, in developed countries, to an asymptomatic zoonotic infection (as well as undercooked meat products).

Research frontiers
Recently, previous seroprevalence surveys in developed countries showed variable rates of anti-hepatitis E virus (HEV) positivity in healthy populations, and several studies reported an unexpectedly high prevalence of antibodies against HEV in hemodialysis patients.

Innovations and breakthroughs
There are scant reports on the prevalence and possible nosocomial transmission of HEV in hemodialysis (HD) patients. Some authors highlighted the high rates of anti-HEV antibodies in their HD patients and hypothesized other routes of transmission besides the fecal-oral route, although the real prevalence of HEV infection through the parenteral route, particularly via hemodialysis, is unknown. Other investigators observed low rates of anti-HEV-positivity in their HD populations.

Applications
This study showed a higher circulation of HEV in end-stage renal failure in the district of Foggia *vs* the healthy population, but this high prevalence is mainly related to hemodialysis patients. There was no relationship between the duration of HD treatment and the risk of acquiring a HEV infection. None of the kidney transplant recipients or HD patients had any evidence of chronic HEV. Although no specific therapy is currently available, unexplained hepatitis in the dialysis setting and in kidney transplant recipients undergoing chronic immunosuppression calls for an evaluation of HEV infection, especially in kidney transplant candidates.

Terminology
Hepatitis E, a single-stranded RNA virus, is the main aetiological agent of enteric non-A hepatitis. The prevalence of HEV-IgG in chronic hemodialysis patients and transplant recipients could be related to their impaired immunity, with an increased susceptibility to infections and decreased immune responses

to antigenic stimuli.

Peer-review

Scotto *et al* report the results from screening a large number of HD and control patients for prior and current HEV infection. This is of interest because chronic HEV has been shown to infect immunosuppressed populations, and hemodialysis patients are in some respects immunocompromised. There has also been a relatively high prevalence found in renal transplant patients that come from this population.

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