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Prevalence and Clinical Correlates of Chronic Hepatitis E Infection in German Renal Transplant Recipients With Elevated Liver Enzymes

Mira Choi, MD,[1] Jörg Hofmann,[2,3] Anja Köhler,[3] Bo Wang,[4] Claus-Thomas Bock,[4] Eckart Schott,[5] Petra Reinke, MD, PhD,[1] and Peter Nickel[1]

Background. Elevated liver enzymes are frequently observed in renal transplant recipients and warrant further exploration. In immunosuppressed patients, hepatitis E virus (HEV) infection may cause chronic hepatitis, cirrhosis, and extrahepatic manifestations such as renal injury. **Methods.** We performed a retrospective cross-sectional study investigating the prevalence, clinical correlates, and outcome of chronic HEV infection in a cohort of renal transplant recipients with elevated liver enzymes. **Results.** Over a period of 30 months, 140 of 1469 renal transplant recipients had elevated liver enzymes, of which serum samples from 98 patients were available to determine HEV status. Seventeen patients were detected with HEV infection, of which 16 developed chronic HEV infection, while 1 patient controlled viremia (prevalence of chronic infection of 16.3%, with a minimum prevalence of 1.1% in the whole cohort). Increased liver stiffness was indicated by an average FibroScan result of 11.2 kPa in these patients. All 16 patients with chronic HEV infection were treated with ribavirin for a mean duration of 3 months. Five patients developed a viral rebound and received a second treatment course, of which 2 controlled HEV replication. Six months after the end of therapy, HEV clearance was achieved in 81.3% of the patients. One patient developed ribavirin resistance. Hemolytic anemia after ribavirin treatment was frequent, requiring blood transfusion in 3 patients. Four patients developed de novo glomerulonephritis, of which 2 were possibly associated with HEV infection. **Conclusions.** This retrospective study showed that prevalence of chronic HEV infection was high in our renal transplant patient cohort and was associated with significant liver impairment and the occurrence of renal injury. Ribavirin treatment was effective and should be initiated early to avoid complications, but the risk of severe hemolytic anemia makes strict monitoring essential.

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Liver enzyme alteration without any preexisting liver disease is a frequent finding in renal transplant recipients.[1] Thorough diagnostic evaluation is required to rule out multiple infectious and noninfectious causes. Among the most important being bacterial, fungal, and viral infections, but implicated are also drug toxicity and malignancies.[2] Hepatitis E virus (HEV) infection, particularly genotype 3, is well recognized in industrialized countries.[3-6] In Germany, a seroprevalence of 16.8% has been reported among healthy adults.[7] Usually, HEV infection is self-limiting, although an acute infection can lead to chronic HEV infection in immunocompromised patients with increased risk of developing significant chronic liver disease and cirrhosis.[5,8] Moreover,

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[1] Department of Nephrology and Intensive Care, Charité Universitätsmedizin Berlin, Germany.

[2] Institute of Medical Virology, Charité Universitätsmedizin Berlin, Germany.

[3] Labor Berlin, Charité-Vivantes GmbH, Berlin, Germany.

[4] Department of Infectious Diseases, Robert Koch-Institute, Berlin, Germany.

[5] Department of Hepatology and Gastroenterology, Charité Universitätsmedizin Berlin, Germany.

M.C. and J.H. are equal contributors to the article.

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M.C. initiated, designed the study, analyzed data and prepared the article. J.H. initiated, designed the study, analyzed data and prepared the article. A.K. analyzed data. B.W. analyzed data. C.-T.B. analyzed data and interpreted the data for analysis. E.S. performed liver elastography and interpreted the data for analysis. P.R. participated in conception and interpreted the data for analysis. P.N. initiated, designed the study, analyzed data and prepared the article.

All authors reviewed the article.

Correspondence: Mira Choi, MD, Department of Nephrology and Intensive Care Medicine, Charité, Germany. (mira.choi@charite.de).

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HEV-infected patients may develop various extrahepatic complications including glomerular injury.[9] In fact, histopathologic findings, such as membranoproliferative, membranous, or mesangioproliferative glomerulonephritis, in transplant patients have been described.[10] Because glomerulonephritis is a major cause of long-term renal graft failure, HEV infection is a potential risk factor for renal graft survival.[11]

In renal transplant patients with persisting HEV infection resistant to reduction of immunosuppression, treatment with ribavirin for a period of 3 to 6 months has been reported to be effective.[12,13] Ribavirin therapy usually leads to rapid normalization of liver enzyme levels, HEV clearance, and a sustained virologic response (SVR) in up to 78% of patients.[13] Nevertheless, side effects are a limiting factor.

Diagnosing HEV infection in immunosuppressed patients is not trivial. As serology is of limited value due to compromised humoral immune responses, a quantitative HEV reverse transcription polymerase chain reaction (RT-PCR) is required to exclude active infection.[14,15] The HEV ribonucleinic acid (RNA) prevalence in patients with elevated liver enzymes has not been systematically addressed in kidney transplant recipients. Furthermore, additional data regarding clinical relevance and outcome of chronic HEV infection in renal transplant patients are warranted.

This study is the first systematic cross-sectional screening for HEV infection in a large cohort of renal transplant recipients with elevated liver enzymes. Over a period of 30 months, all renal and combined renal and other organ transplant recipients were screened for abnormal liver enzymes, HEV RNA, and IgG/IgM antibodies. The clinical correlates of renal transplant recipients with chronic HEV infection were also established in detail.

MATERIALS AND METHODS

The local ethics committee (approval number EA1/249/16) approved the study and written informed consent was obtained.

In June 2015, all single or combined renal transplant patients that were seen in our center between January 2013 and June 2015 were screened retrospectively for elevated liver enzymes using our transplant database (tbase). Inclusion criteria were elevated liver enzymes (alanine transaminase, aspartate transaminase, and gamma glutamyltransferase) greater than 2 times the upper limit of normal range, and availability of stored samples. Exclusion criteria were death or graft loss before study end. HEV antibody status and HEV RNA were tested with the use of frozen or fresh samples. In patients with positive HEV RNA, the viral genotype was determined, and earlier frozen samples were tested to define the time point of infection. Chronic infection was defined as HEV viremia for more than 3 months.[16] In patients with chronic HEV infection, hepatic elasticity was assessed by FibroScan® (Echosense, Paris, France). Ribavirin monotherapy was initiated in patients with chronic HEV. The term SVR was defined as absence of viremia for at least 6 months after end of treatment.[13] Renal transplant biopsies were performed if proteinuria was above 1 g/g creatinine.

Serologic and Molecular Diagnostics of Hepatitis E Infection

Anti-HEV IgM and anti-HEV IgG antibodies were detected with the recomWell HEV IgM and recomWell HEV IgG, and positive results were confirmed with the recomBlot HEV IgG/IgM (all Mikrogen GmbH, Neuried, Germany). Real-time RT-PCR for the detection of HEV RNA targeting the viral capsid gene (open reading frame [ORF]2) was used. Primers and probes have been described elsewhere.[17] The nucleic acid was extracted from ethylenediaminetetraacetic acid plasma or serum using the QIAamp Viral RNA Mini Kit (Qiagen, Hilden, Germany) according to the manufacturer's instructions. The viral RNA was reversely transcribed with random hexamer primer p(dN)6 (Roche, Basel, Switzerland) and SuperScript III Reverse Transcriptase (Invitrogen, Carlsbad, CA). The real time RT-PCRs were performed with LightCycler FastStart DNA Masterplus kits (Roche Diagnostics, Mannheim, Germany) using LightCycler 2.0 instruments. All samples were controlled for presence of inhibiting factors by the use of an internal coamplified nucleic acid.

Genotyping

For genotyping of the HEV strains targets in the ORF1 and ORF2 were used. A detailed protocol and used primers are given in **Table S1 in the supplemental digital content,** http://links.lww.com/TXD/A61.

Preliminary sequence management and analyses were carried out using Geneious software package (Version 9.1.3; Biomatters Limited, Aukland, New Zealand) and sequence alignment and editing were performed using ClustalW.[18] The phylogenetic analyses inferred from the neighbor-joining (NJ) algorithm with a bootstrap values determined by 1000 replicates in MEGA version 7 software.[19]

Statistical Analyses

Predictive analytics software (PASW, applied statistical software) statistics 18.0 was used for statistical analysis. For continuous variables, differences between groups were assessed using Mann-Whitney *U* test. For categorical variables, χ^2, Fisher exact or Kruskal Wallis tests were used. Wilcoxon signed-rank test was used to evaluate changes in hemoglobin concentration before and during ribavirin treatment.

RESULTS

One thousand four hundred sixty-nine single or combined renal transplant recipients were treated between January 2013 and June 2015 in our center, of which 140 patients were retrospectively identified with elevated liver enzyme levels. Ninety-eight of these 140 patients had preserved graft function and serum samples available and were tested further.

Of these 98 patients, 17 patients were detected with HEV infection, 16 with chronic infection and 1 patient with cleared infection after reduction of immunosuppression due to unrelated reasons. At the time of screening 6 of 16 patients with chronic infection were already diagnosed and treated with ribavirin, while 10 patients received treatment thereafter. Thus, the prevalence of chronic HEV infection in the 98 patients with elevated liver enzymes was 16.3%, and the minimum prevalence of chronic HEV infection in the whole cohort was 1.1% (16 of 1469).

Patient characteristics are shown in Table 1, subdivided according to HEV status. Chronic HEV patients were predominantly male compared with the 81 HEV negative patients with increased liver enzymes (75% vs 59%, not significant). HEV-positive patients were significantly more likely to have a history of prior rejection therapy, which, in most cases, was indicated within the first year after transplantation ($P < 0.05$).

TABLE 1.

Baseline characteristics at the time of HEV PCR determination in patients with elevated liver enzymes and diagnosis of chronic HEV infection versus without hepatitis E infection by HEV PCR determination (controls)

	Chronic HEV infection (n = 17)	Controls (n = 81)	*P*
Male sex, no. (%)	13 (76.5)	48 (59.3)	n.s.
Age, y	52 ± 11	54 ± 13	n.s.
Serum creatinine, mg/dL	1.56 ± 0.6	1.84 ± 1.2	n.s.
Platelet count	179 ± 41	226 ± 93	0.065
WBC count	6.3 ± 2.5	8.6 ± 4.0	0.011
Prior rejection treatment (yes/no)	12/5	31/50	0.015
Immunosuppressive regimen			
Triple with Tac	17[a]	59	n.s.
Triple with CsA	0	7	
Dual with Tac	0	8	
Dual with CsA	0	4	
mTOR MPA steroid	0	3	
Calcineurin inhibitor (Tac/CsA)	17/0	67/11	n.s.
Liver enzymes at the time of HEV RT-PCR determination			
ALT (ref.: male, <41; female, <31), U/L	171 ± 272	110 ± 112	n.s.
AST (ref.: male, <50; female, <35), U/L	87 ± 97	74 ± 80	
γGT (ref.: male, 8-61; female, <5-36), U/L	142 ± 135	204 ± 238	
Time between transplantation and first HEV RNA measurement, mo	64 ± 51	78 ± 85	n.s.

[a] Quadruple therapy with mTOR on top (n = 1).

WBC, white blood cell; γGT, gamma-glutamyl transferase; ref, reference; n.s., not significant.

Notably, all patients with chronic HEV infection had intense immunosuppression with triple therapy of a corticosteroid, mycophenolic acid (MPA), and tacrolimus as calcineurin inhibition. In contrast, although not statistically significant, 22 of 81 from the control patients were on cyclosporine A (CsA) or mammalian target of rapamycin (mTOR) inhibitor instead of tacrolimus or on dual therapy with tacrolimus and MPA only. Elevation of liver enzymes in patients with chronic HEV infection occurred within 1 week to 97 months after renal transplantation (mean, 34 ± 32 months), and HEV replication was observed 3.5 to 155.1 months after renal transplantation (mean, 59.9 months).

At the time of transplantation, all but 1 of the 17 patients who developed chronic HEV infection were seronegative. During follow-up, 16 of 17 patients became seropositive for HEV IgG and IgM, whereas only 1 patient remained seronegative (patient 15 in Figure 1). All seropositive patients displayed IgM persistence until the end of this study. The mean duration of positive IgM status was 16 months (range, 6.3-43.1) independent of viremia (detectable RNA). Immunoblot analyses revealed a strong humoral immune response to the c-terminal part of the HEV O2 antigen in all seropositive patients. The early humoral response included reactivity to HEV O3, although this seemed to be transient (data not shown).

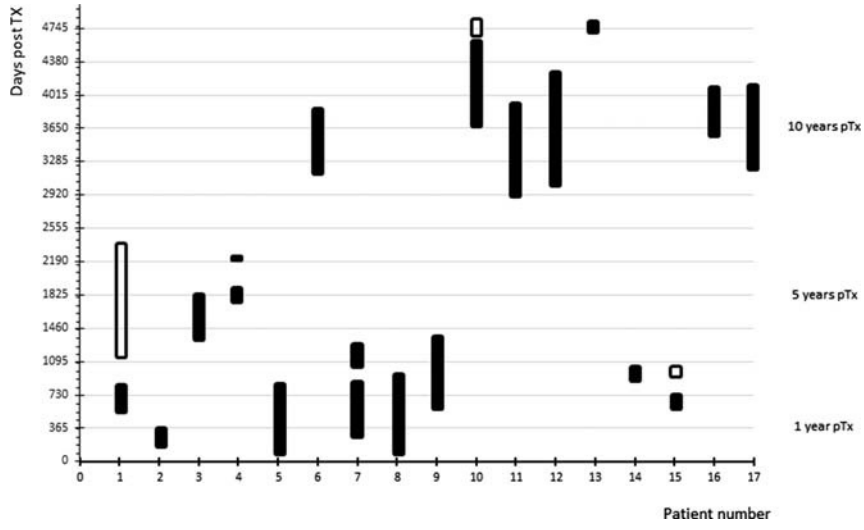

FIGURE 1. Start and duration of HEV viremia of 17 kidney transplant recipients. Filled columns indicate duration of viremia, open columns indicate persistent viral rebound after stop of ribavirin therapy (patients 1, 10, and 15). Note: y-axes is scaled in years (multiples of 365 days) starting from the time point of transplantation, the scale spacing is 90 days (90 days of continuous virus shedding is considered chronic HEV infection).

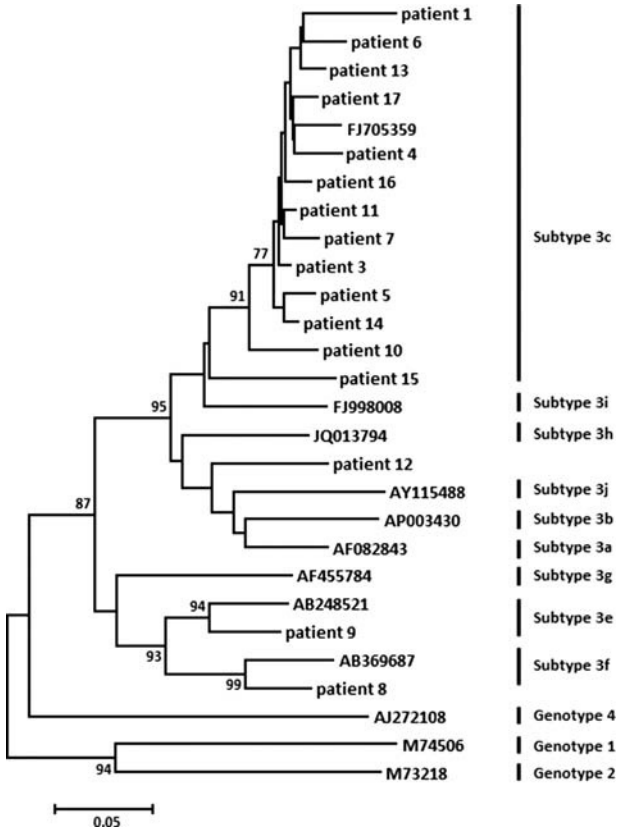

FIGURE 2. Phylogenetic analysis of positive HEV samples. The phylogenetic tree was generated with neighbor-joining method by MEGA7 software. Genetic distances were calculated with maximum composite likelihood model; values at deep node points indicate support from 1000 bootstrap reiterations. Values below 75% are hidden for clarity of presentation. Each branch was labeled according the GenBank accession number of the reference sequences for HEV genotype 3 subtypes. The analyzed partial RNA-dependent RNA polymerase (RdRp) gene comprised 302 nucleotides corresponding to positions 4280 to 4582 within species Orthohepevirus A reference strains Burma and Mexico (GenBank accession numbers M73218 and M74506).

In the 17 patients with chronic HEV infection, HEV RNA was determined at an average of 12 (range, 4-28) different time points during an average follow-up period of 37 months (range, 8-62). Figure 1 depicts duration of viremia of all patients, time of diagnosis after transplantation, and viral rebounds or ongoing viremia during the observation period. The duration of viremia ranged from 125 to 1072 days. Less than one fourth of the patients developed HEV infection within the first year after transplantation, and 7 of the 17 patients became persistently infected later than 8 years after renal transplantation. Sixteen patients were treated with ribavirin doses of between 85.7 mg (200 mg, thrice a week) and 1000 mg per day for a mean duration of 3.8 ± 2.9 months. Hemolytic anemia was present in all ribavirin-treated patients (hemoglobin before ribavirin therapy 13.1 +/– 1.3 g/dL vs 9.2 +/– 1.9 g/dL during ribavirin therapy, $P < 0.05$), which in 10 patients lead to a relevant decrease of greater than 3 g/dL, requiring its discontinuation in 3 patients who received red blood cell transfusions. HEV clearance was initially achieved in all 16 patients. However, 5 patients developed viral rebounds, patients 1, 4, and 15 after the end of treatment, whereas patient 7 and 10 relapsed after ribavirin discontinuation due to severe side effects. All 5 patients were re-treated with ribavirin, and finally patients 4 and 7 controlled HEV, whereas patients 10 and 15 remained positive until the most recent follow-up. Patient 1 developed ribavirin resistance, defined by persistently elevated viral load despite continued high dose ribavirin treatment. Hence, at the most recent follow-up, 13 of 16 ribavirin-treated patients had reached a SVR, whereas 3 of 16 did not control chronic HEV infection (SVR rate 81.3%).

Peak viral loads ranged from 4.45×10^5 to 2.02×10^7 RNA copies/mL. As depicted in the phylogenetic tree based on ORF1 sequences (Figure 2), all patients were infected with HEV genotype 3 (majority subgenotype 3c), which is predominant in central Europe.[20] Subsequent analyses of ORF2 sequences (positions nts from 6358 to 6737) confirmed the ORF1 based subgenotyping (data not shown).

All patients showed elevated liver stiffness as measured by FibroScan corresponding to grades of fibrosis between 1 and 4 (from mild liver fibrosis to cirrhosis, average ≥ 3, Table 2), when reference values for patients with chronic hepatitis B or C were used.

Interestingly, new-onset or unexplained proteinuria developed in 5 patients (patients 2, 7, 8, 10, 13), of which 4 had biopsy-proven de novo glomerulonephritis. Patients 2 and 7 with previously unknown renal disease were diagnosed with IgA nephropathy within their renal transplant and patient 8 with formerly known lupus nephritis was diagnosed with membranous nephropathy. Patient 10 with new-onset proteinuria did not undergo renal biopsy. Patient 13 was diagnosed with phospholipase 2 receptor antibody-negative membranous nephropathy. In contrast, only 4 of the 81 HEV-negative patients had new-onset proteinuria, which was significantly less (29.4% of patients with chronic HEV infection vs 4.9% of patients in the HEV negative control group, $P < 0.01$). Renal biopsy findings were humoral rejection and chronic transplant glomerulopathy in 2 cases and unexplained causes in the other 2 patients who did not underwent biopsy yet due to proteinuria

TABLE 2.

Characteristics of all 17 patients with chronic HEV infection

Time between transplantation and elevation of liver enzymes, mo	34.0 ± 32.0
Serostatus at study end	
IgG and IgM positive	16
IgG and IgM negative	1
Maximum of liver enzyme elevation (mean/range)	
ALT (ref.: male, <41; female, <31), U/L	268/80-1200
AST (ref.: male, <50; female, <35), U/L	139/49-438
γGT (ref.: male, 8-61; female, <5-36), U/L	271/84-826
Bilirubin (ref., 0.1-1.2), mg/dL	0.9/0.3-2.2
Maximum of viral load (range), $\times 10^5$ copies/mL	4.45-202
Duration of viremia (range), d	125-1072
Spontaneous clearance of HEV (n)	1
Average liver elastography (grade)	11.2 kPa (>3)
Ribavirin treatment (yes/no)	16/1
Ribavirin dose, mg/d	85.7-1000
Relevant anemia related to ribavirin (yes/no) (>3 g/dL decrease of hemoglobin)	10/6
Viral rebound (n)	5
New-onset proteinuria (n)	5

of less than 1 g/g creatinine. To illustrate therapy and clinical course of chronic HEV, 2 patient vignettes from our cohort were described in detail.

Case Description 1

A 52-year-old man (patient 1) received a first cadaveric renal transplant in 2009. His primary renal disease was IgA nephropathy. After 3 months, he developed renal cell carcinoma in one of his kidneys. After surgical resection, tacrolimus was replaced by an mTOR inhibitor. One month later, renal function deteriorated due to severe cellular rejection. Subsequent treatment included steroid bolus and thymoglobulin. Thereafter, his continued immunosuppressive regimen included tacrolimus, MPA, and corticosteroids. His renal function stabilized with a baseline serum creatinine of 1.1 mg/dL. Twelve months after transplant, liver enzyme elevation occurred caused by HEV infection. The time course of elevated liver enzymes, viremia, and ribavirin treatment are depicted in Figure 3. Therapy with ribavirin was initiated with a rapid control of viremia and continued for 12 months due to a single positive HEV RNA measurement during follow-up. For a short period of 4 months, the patient was aviremic. Afterward, a viral rebound accompanied by increased liver enzymes was observed. Despite a reduced dose of MPA and a second treatment period with ribavirin (800 mg per day), viremia continued. Finally, ribavirin administration was discontinued because of treatment failure and unexplained toe necrosis.

Case Description 2

A 57-year-old man was diagnosed with HEV infection 9.5 months after renal transplant (patient 7). His immunosuppressive regimen included corticosteroids, MPA, and tacrolimus with stable graft function and a baseline creatinine of 1.3 mg/dL. However, after initiation of ribavirin therapy (600 mg daily), severe hemolytic anemia (hemoglobin declined from 13.2 to 6.5 g/dL) developed, requiring red blood cell transfusion. Other severe side effects included diarrhea with declining renal function, nausea, and vomiting. Ribavirin was stopped after 5 weeks. At that time point, liver enzymes had normalized, and HEV RNA was no longer detectable. Five months after ribavirin discontinuation, liver enzymes were elevated again, followed by a subsequent viral rebound. At the same time, the patient developed new-onset proteinuria up to nearly 2 g/g creatinine. Renal transplant biopsy revealed IgA nephropathy. His primary renal disease was unknown. The daily dose of MPA was reduced and ribavirin was restarted with 200 mg 3 times a week only with concomitant high dose erythropoietin supplementation (darbopoietin, 40 μg once a week). Low-dose ribavirin was well tolerated with stable hemoglobin. The patient responded with normalization of liver enzyme levels with control of HEV after 9 weeks and subsequent resolution of proteinuria. Notably, patient 10 also developed de novo proteinuria, which was resolved as liver enzymes normalized with ribavirin therapy. Nevertheless, HEV was not completely cleared at the time of this report.

DISCUSSION

This study describes the first cross-sectional study assessing the prevalence of HEV infection by HEV RNA screening along with clinical correlates and outcome of chronic HEV infection in a large cohort of renal transplant patients with elevated liver enzymes. The minimum prevalence of chronic hepatitis E patients in the whole cohort of 1469 renal and combined renal and other organ transplant recipients was comparable to the prevalence of chronic HEV infection to that of other chronic hepatitis virus infections (1.7% for chronic hepatitis B and 2.0% for chronic hepatitis C infection in our cohort, own observations). Furthermore, the prevalence of chronic HEV infection was similar to that reported

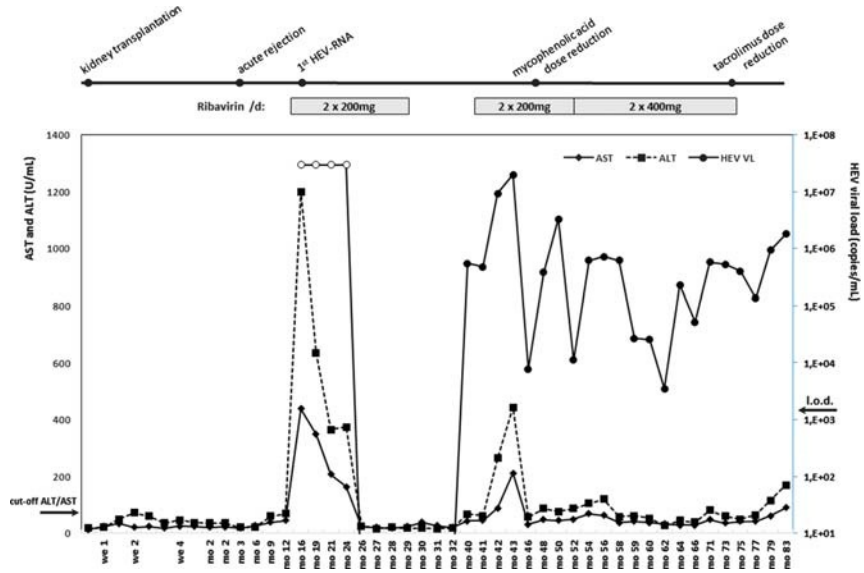

FIGURE 3. Clinical pattern, ribavirin treatment intervals, liver enzyme levels and hepatitis E viral load in patient 1. The liver enzyme levels ALT and AST are depicted on the primary y-axis with reference ranges of < 41 and < 50 U/L, respectively, and HEV RNA viral loads are shown on the secondary y-axis. Note: the open circles (mo 12-26) indicate qualitative RNA detection and are empirically defined to be 3 E + 07 (quantitative RT-PCR at that time or retain samples for retesting were not available). The filled circles represent true quantitative copy numbers. For detailed information regarding doses and duration of immunosuppressive therapy see case description 1. AST, aspartate transaminase; ALT; alanine transaminase; l.o.d., limit of detection.

by other authors who observed a HEV RNA prevalence of 0% to 3.2% among renal or solid organ transplants.[15,21,22] Differences in prevalence might be due to different HEV infection rates between different populations; however, many studies have relied primarily on HEV serology to diagnose HEV infection.[9]

Despite the recently published seroprevalence of 16.8% in Germany,[7] only 1 of the 17 patients with chronic HEV infection had a weak preexisting humoral immune response at the time of transplantation. This observation would fit with the following 2 hypotheses: first, seropositive renal recipients may not have a significant risk for chronic HEV infection, and second, a preexisting low IgG titer may not protect against a HEV reinfection.

Almost all persistently infected patients seroconverted after HEV infection, albeit within variable time frames up till 18 months after infection. Once patients had seroconverted, a long lasting IgM response was observed in most cases. Thus, serologic methods are not helpful and molecular approaches are necessary to rule out active HEV infection in renal transplant patients. In areas of high seroprevalence testing for anti-HEV IgG could be beneficial for risk stratification of renal transplant recipients.

In line with previous observations monitoring of HEV, RNA in our persistently infected patients revealed peak values similar to those of patients experiencing an acute infection.[7,23] All HEV strains that were identified belonged to genotype 3. Ingestion of poorly inactivated infected pork is believed to be the main risk factor to acquire a HEV genotype 3 infection in Germany.[23] Subgenotyping on 2 different target sequences revealed, not surprisingly, a dominance of 3c genotype.

In the univariate analysis of risk factors, more intense global immunosuppression was associated with chronic HEV infection. Previous courses of steroids or T- or B-cell targeting therapies to treat episodes of cellular or humoral rejection after transplantation were more frequent in patients with chronic HEV infection ($P < 0.015$). This might also explain the significantly lower white blood cell count found in the 17 patients with chronic HEV infection compared to controls. Notably, although not statistically significant, all patients with chronic HEV infection in our study received triple immunosuppression with tacrolimus as calcineurin inhibition. In contrast, 14 of 81 patients received CsA as calcineurin inhibition or mTOR inhibitor in the HEV negative group. This is in accordance with previous observations by Kamar et al[24] were more intense immunosuppressive with tacrolimus, rather than with CsA was associated with chronic HEV infection.

In our cohort, HEV infection did not typically occur within the first months after transplantation (23.5%), suggesting that infection might not be an instantaneous consequence of the organ transplantation itself. While about one third of the patients were diagnosed within 2 to 5 years after transplantation (35.3%), almost half appeared between 8 and 13 years (41.2%). These results are consistent with earlier reports.[3,15,22,25] Changes in food habits with less attention paid to uncooked meat, especially regarding consumption of pork products, is considered as the main transmission route of HEV infection[4,26] and may explain late infection times. Other routes of transmission include administration of blood products or plasma exchange.[27,28] Hewitt et al[27] reported 1 viremic among 2848 blood donors and an associated transmission rate of 42% to the recipients. Transmission via the transplanted organ might be rare, but did occur as described for a liver transplanted patient.[29] Acute HEV infections from donor derived kidneys within the first year after transplant could be excluded by negative HEV RT-PCR results in donor-derived blood samples from our cohort (own observations). However, absence of HEV antibodies and HEV RNA might still lead to HEV transmission by infected donor tissue.[29] Very recently, Pourbaix et al[30] described 2 cases of HEV infection transmitted via a renal graft that led to chronic hepatitis E.

Notably, patients with chronic hepatitis E infection had significantly altered liver stiffness using liver elastography, which has been shown to predict clinical liver-related events in liver disease other than hepatitis E infection, such as chronic hepatitis B and C.[31] Extrahepatic manifestations from our cohort were malaise, pruritus, and renal injury. New-onset proteinuria was considered suspicious for renal involvement due to HEV infection. Even with renal transplant biopsy, renal involvement due to HEV infection is difficult to prove due to a lack of HEV-specific renal findings. Two patients had mesangioproliferative glomerulonephritis with deposition of IgA in their biopsies. It remains unclear whether the renal pathology is recurrent disease or HEV-related. Interestingly, proteinuria resolved in one of our patients with ribavirin treatment and control of HEV viremia, and it increased again when ribavirin therapy was discontinued. Along the same line, proteinuria of a second patient also improved during ribavirin therapy. In contrast, 2 patients had proteinuria with membranous nephropathy, which did not improve with ribavirin therapy.

Ribavirin is known to cause severe side effects like hemolytic anemia, which warrants close monitoring with substitution of erythropoietin.[32] From our observations, ribavirin doses much lower than recommended in relation to renal function[33] were effective to clear HEV in individual patients. Three of 17 patients experienced a viral rebound after end of treatment and 2 due to interruption of ribavirin treatment. To assess the true risk of HEV reinfection or reactivation in the settings of ribavirin therapy, more comprehensive studies are needed. In summary, in patients with elevated liver enzyme levels after organ transplantation testing for HEV RNA should routinely performed, particularly in regions with high seroprevalence. Regarding the high prevalence and clinical relevance, the benefit of screening for HEV infection in organ and blood donors as well as an assessment of HEV IgG in recipients at the time of transplantation should be further evaluated. Treatment should be initiated early, as spontaneous clearance of HEV is very unlikely in these patients. Treatment of HEV infection should include reduction of immunosuppression whenever possible, keeping in mind the higher risk of rejection. Awareness of renal injury is needed because this reflects a possible threat for decline of renal function and decreased organ survival.

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