BRIEF REPORT

Hepatitis E Virus and Chronic Hepatitis in Organ-Transplant Recipients

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SUMMARY

Hepatitis E virus (HEV) is considered an agent responsible for acute hepatitis that does not progress to chronic hepatitis. We identified 14 cases of acute HEV infection in three patients receiving liver transplants, nine receiving kidney transplants, and two receiving kidney and pancreas transplants. All patients were positive for serum HEV RNA. Chronic hepatitis developed in eight patients, as confirmed by persistently elevated aminotransferase levels, serum HEV RNA, and histologic features of chronic hepatitis. The time from transplantation to diagnosis was significantly shorter and the total counts of lymphocytes and of CD2, CD3, and CD4 T cells were significantly lower in patients in whom chronic disease developed.

Acute hepatitis caused by the hepatitis E virus (HEV) is endemic in developing countries and appears to be an emerging disease in industrialized countries.[1,2] Seroprevalence studies have reported anti-HEV IgG antibodies in 6 to 16% of renal-transplant recipients.[3,4] This hepatotropic RNA virus is often not fully considered or routinely sought in cases of acute hepatitis in recipients of solid-organ transplants. Only three cases of acute HEV infection have been reported in organ-transplant recipients.[5-7] Even though two cases of persistent HEV infection have been reported,[8,9] HEV is considered an agent responsible for acute hepatitis that does not become chronic.[10]

We report here 14 cases of acute hepatitis E infection in organ-transplant recipients. We suggest that HEV infection may evolve to chronic hepatitis in immunocompromised patients.

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N Engl J Med 2008;358:811-7.

PATIENTS AND METHODS

Between January 1, 2004, and December 31, 2006, all recipients of liver, kidney, or kidney and pancreas transplants attending our outpatient and inpatient clinics who presented with unexplained short-term elevations of liver-enzyme levels were screened for HEV infection by serologic and molecular tools. Patients chronically infected with hepatitis B, C, or D viruses were excluded from the study. Biliary-tract complications were ruled out by abdominal ultrasonography. Toxin- and drug-related causes of abnormal liver-function test results were ruled out by patient history. Fourteen of 217 patients (6.5%) tested positive for serum HEV RNA.

Anti-HEV status was determined by an enzyme immunoassay (HEV EIA, Abbott). HEV RNA in serum and stool was detected by real-time polymerase-chain-reaction (PCR) amplification (TaqMan, Applied Biosystems) of a 189-bp product located in the ORF2 region.[11] Strains were sequenced and compared with reference HEV strains (GenBank). The grades and stages of chronic hepatitis were assessed according to the Metavir classification.[12]

Proportions were compared by the chi-square test or Fisher's exact test. Quantitative variables were compared by the nonparametric Mann–Whitney, Friedman, and Wilcoxon tests. A P value of less than 0.05 was considered to indicate statistical significance.

RESULTS

PREVALENCE OF ANTI-HEV IgG

All patients who received a kidney transplant (241 recipients) or a liver transplant (86 recipients) between January 1, 2004, and December 31, 2006, in the department of nephrology, dialysis, and multiorgan transplantation were screened for HEV infection at the time of transplantation. The prevalence of anti-HEV IgG was 13.5% for all recipients, 14.5% for kidney recipients, and 10.4% for liver recipients.

CLINICAL AND BIOLOGIC PRESENTATION

We identified 14 patients with a solid-organ transplant (3 liver recipients, 9 kidney recipients, and

Table 1. Demographic Features of Transplant Recipients at Diagnosis of Acute HEV Infection.*

Patient No.	Organ Transplanted	HEV Infection†	Donor‡	Years of Age	Sex	Mo since Transplantation	Initial Organ Disease	Induction Therapy	Immunosuppressive Therapy
1	Liver	Chronic	Cadaver	57	M	6	Alcoholic cirrhosis	None	Tacrolimus/mycophenolate mofetil/steroid
2	Liver	Chronic	Cadaver	67	M	53	Alcoholic cirrhosis	Basiliximab	Tacrolimus/mycophenolate mofetil/steroid
3	Liver	Chronic	Cadaver	28	F	10	Wilson's disease	None	Tacrolimus/mycophenolate mofetil/steroid
4	Kidney	Chronic	Cadaver	49	M	10	Thrombotic microangiopathy	Basiliximab	Mycophenolate mofetil/steroid
5	Kidney	Resolving	Cadaver	34	M	90	Malformative uropathy	Rabbit antithymocyte globulins	Everolimus/mycophenolate mofetil/steroid
6	Kidney	Resolving	Living	33	M	57	Interstitial nephropathy	Basiliximab	Sirolimus/mycophenolate sodium/steroid
7	Kidney	Chronic	Cadaver	52	M	63	IgA nephropathy	None	Sirolimus/steroid
8	Kidney	Resolving	Cadaver	42	M	168	Crescentic glomerulonephritis	Rabbit antithymocyte globulins	Cyclosporin A/mycophenolate mofetil
9	Kidney	Chronic	Cadaver	30	M	48	Alport's disease	Rabbit antithymocyte globulins	Sirolimus/steroid
10	Kidney	Resolving	Cadaver	51	M	67	Interstitial nephropathy	Rabbit antithymocyte globulins	Cyclosporin A/mycophenolate mofetil/steroid
11	Kidney	Resolving	Cadaver	62	F	108	Chronic glomerulonephritis	Rabbit antithymocyte globulins	Cyclosporin A/steroid
12	Kidney	Resolving	Cadaver	28	M	25	IgA nephropathy	Rabbit antithymocyte globulins	Tacrolimus/mycophenolate mofetil/steroid
13	Kidney and pancreas	Chronic	Cadaver	55	F	60	Diabetes mellitus	Rabbit antithymocyte globulins	Tacrolimus/azathioprine/steroid
14	Kidney and pancreas	Chronic	Cadaver	58	M	27	Diabetes mellitus	Rabbit antithymocyte globulins	Tacrolimus/mycophenolate mofetil

* All patients were born in France. HEV denotes hepatitis E virus.
† Resolving indicates clearance of HEV RNA from serum and stools, and chronic indicates persisting elevated liver-enzyme levels and detectable RNA in the serum or stools at least 6 months after the acute phase.
‡ Cadaveric donors had a heartbeat.

2 kidney and pancreas recipients) in whom acute HEV infection developed (Table 1). The acute hepatitis episode was asymptomatic in 7 of the 14 patients; these 7 patients were tested for HEV after liver-enzyme abnormalities were detected during routine biologic examinations that are performed every 3 to 4 months after organ transplantation. The seven other patients presented with fatigue, diffuse arthralgias, and myalgias that had evolved over a period of 1 to 2 weeks. One of the symptomatic patients also had marked weight loss (approximately 8 kg [18 lb] during the month before the presenting symptoms appeared) and was icteric. The symptoms disappeared within 2 weeks after diagnosis. No abnormalities were detected during physical examination of any other patient. No patients were febrile, and none had traveled outside France during the year before their hepatitis episode. Only two patients reported having been in contact with animals: one patient with chickens and rabbits and the other with birds. No patients had had an acute rejection episode after undergoing transplantation. Immunosuppressive therapy had remained unchanged in all patients for at least 6 months before their acute episode. Liver-enzyme levels were significantly higher than the levels 3 to 4 months before the diagnosis of HEV infection (Table 2).

DIAGNOSIS OF HEV INFECTION

At admission, classic causes of hepatitis were ruled out (Table 1 of the Supplementary Appendix, available with the full text of this article at www.nejm.org). The ferritin level was 567 ng per milliliter (range, 110 to 2007; normal range, 30 to 380), and the ceruloplasmin level was 0.35 ng per milliliter (range, 0.24 to 0.47; normal range, 0.20 to 0.45). At diagnosis, HEV RNA was detected in the serum of all patients and in the stool of the three patients whose stool was examined. PCR-amplification products of the serum HEV of 12 patients were sequenced and analyzed. Phylogenetic analysis revealed that all the strains belonged to genotype 3 (GenBank accession numbers, EU220992 to EU221003) (Fig. 1 of the Supplementary Appendix). We tried but failed to sequence the strains of the remaining two patients. No correlation was found between HEV RNA concentration and either liver-enzyme levels or liver-activity scores at diagnosis.

LIVER HISTOLOGIC FINDINGS DURING THE ACUTE PHASE

In the acute phase, 9 of the 14 patients underwent a liver biopsy to evaluate the severity of the acute episode of hepatitis; the remaining 5 patients declined biopsy. In liver-transplant recipients, liver biopsy also was performed to detect acute rejection. The mean (±SD) Metavir activity and fibrosis scores were 1.3±1.0 and 0.9±0.6, respectively (for assessment of disease activity, a Metavir score of 0 indicates no activity, 1 mild activity, 2 moderate activity, and 3 severe activity; for assessment of fibrosis, a Metavir score of 0 indicates no fibrosis, 1 portal fibrosis without septa, 2 a few septa, 3 numerous septa without cirrhosis, and 4 cirrhosis). The dominant lesions were lobular, with inflammation but no ballooning, and with spotty necrosis that included acidophilic bodies. The portal tract was mildly or moderately expanded and included an inflammatory infiltrate composed mainly of lymphocytes. Mild piecemeal necrosis was observed in six patients.

COURSE OF HEV INFECTION

Immunosuppressive therapy and target immunosuppressive trough levels were not modified after the diagnosis of HEV infection (data not shown). HEV infection resolved in six patients (43%); serum and stool HEV RNA in these patients became undetectable within 6 months after diagnosis and remained undetectable until the last follow-up at a mean of 12 months (range, 5 to 36) (Table 2). However, in the eight other patients (57%), HEV infection evolved to chronic hepatitis, as indicated by persistently elevated liver-enzyme levels and detectable HEV RNA in the serum or stool for a mean of 15 months (range, 10 to 24) after the acute phase.

Among the patients with resolving HEV infection, the levels of aspartate aminotransferase and alanine aminotransferase returned to preinfection values within 1 month (five patients) or 3 months (one patient) after diagnosis. The levels of γ-glutamyltransferase and alkaline phosphate returned to baseline levels within 3 months after diagnosis. Among those with chronic HEV infection, liver-enzyme levels remained above the upper limit of normal at the last follow-up. In both groups, the total bilirubin levels rapidly returned to preinfection levels. In both groups, hematologic and re-

Table 2. Liver Function in Patients with HEV Infection.

Patient No.	Time of Measurement	Alanine Aminotransferase*	Aspartate Aminotransferase†	γ-Glutamyl-transferase‡	Bilirubin§	Liver Biopsy	
			units/liter		*mg/dl*	*Metavir activity score*¶	*Metavir fibrosis score*‖
1	Baseline	10	16	18	584		
	Diagnosis	69	37	40	584	0	1
	15-Mo follow-up	59	41	30	409	3	2
2**	Baseline	102	95	1164	584		
	Diagnosis	248	229	3482	2339		
	16-Mo follow-up	59	54	173	701	1	3
3	Baseline	49	23	35	584		
	Diagnosis	169	76	76	994	1	1
	17-Mo follow-up	85	47	35	701	1	1
4	Baseline	26	12	19	701		
	Diagnosis	166	47	167	760	1	1
	15-Mo follow-up	135	57	146	760	3	1
5	Baseline	41	26	73	584		
	Diagnosis	66	47	118	526	0	1
	5-Mo follow-up	52	35	148	584		
6	Baseline	26	25	26	608		
	Diagnosis	245	104	118	468		
	12-Mo follow-up	30	32	18	584		
7	Baseline	26	18	55	397		
	Diagnosis	874	436	669	701	1	0
	10-Mo follow-up	158	89	156	584		
8	Baseline	32	24	32	1286		
	Diagnosis	770	340	373	2514		
	36-Mo follow-up	22	22	19	1169		
9	Baseline	42	39	26	584		
	Diagnosis	310	160	92	643	2	2
	24-Mo follow-up	90	39	42	760	2	2
10	Baseline	37	30	26	584		
	Diagnosis	518	235	459	1286		
	36-Mo follow-up	28	27	109	1286		
11	Baseline	23	18	42	351		
	Diagnosis	255	154	1055	3041	3	1
	12-Mo follow-up	13	7	80	351		
12	Baseline	12	14	19	368		
	Diagnosis	298	71	216	818	2	1
	5-Mo follow-up	15	24	51	877		
13	Baseline	13	22	8	643		
	Diagnosis	156	115	47	935	2	0
	15-Mo follow-up	298	238	79	760		

Table 2. (Continued.)

Patient No.	Time of Measurement	Alanine Aminotransferase*	Aspartate Aminotransferase†	γ-Glutamyl-transferase‡	Bilirubin§	Liver Biopsy	
			units/liter		*mg/dl*	*Metavir activity score*¶	*Metavir fibrosis score*‖
14	Baseline	14	23	30	1169		
	Diagnosis	143	106	132	877		
	13-Mo follow-up	126	118	585	994	1	3
Median							
	Baseline	26	23	32	584		
	Diagnosis††	248	115	167	818		
	Follow-up‡‡	59	40	79.5	731		

* Normal values for alanine aminotransferase range from 5 to 34 units per liter.
† Normal values for aspartate aminotransferase range from 3 to 30 units per liter.
‡ Normal values for γ-glutamyltransferase range from 7 to 38 units per liter.
§ To convert values for bilirubin to micromoles per liter, multiply by 17.1. Normal values range from 2 to 21 mg per deciliter.
¶ For assessment of disease activity, a Metavir score of 0 indicates no activity, 1 mild activity, 2 moderate activity, and 3 severe activity.
‖ For assessment of fibrosis, a Metavir score of 0 indicates no fibrosis, 1 portal fibrosis without septa, 2 a few septa, 3 numerous septa without cirrhosis, and 4 cirrhosis.
** Patient 2 had substantial alcohol consumption before the acute phase.
†† The differences between values at baseline and at diagnosis are significant for alanine aminotransferase, aspartate aminotransferase, and γ-glutamyltransferase (P=0.001) and for bilirubin (P=0.02).
‡‡ The differences between values at diagnosis and at last follow-up (median, 15 months) are significant for alanine aminotransferase (P=0.003), aspartate aminotransferase (P=0.02), and γ-glutamyltransferase (P=0.03).

nal measurements remained unchanged during the follow-up as compared with preinfection levels (data not shown). HEV seroconversion was observed in four patients with resolving HEV infection (two at 1 month and one each at 3 and 6 months after diagnosis) and seven patients with chronic infection (one at 3 months, two at 6 months, two at 12 months, and one each at 13 and 15 months after diagnosis).

Only six of the eight patients with chronic infection underwent a second liver biopsy (one at 10 months, two at 12 months, and one each at 13, 15, and 18 months after the diagnosis of acute HEV infection). The two remaining patients declined liver biopsy. The mean Metavir activity and fibrosis scores of the six patients who underwent biopsy were 2.0±1.0 and 1.8±0.8, respectively. All biopsy specimens showed features of chronic viral hepatitis, characterized by fibrosis and portal hepatitis, with dense lymphocytic infiltrate and variable degrees of piecemeal necrosis. Lobular hepatitis was mild to moderate in all cases. In the four patients who underwent a liver biopsy during both the acute phase and the chronic phase, the Metavir activity scores progressed from 1.0±0.8 to 2.2±0.9 and the fibrosis scores from 1.2±0.5 to 1.5±0.5.

RESOLVING VERSUS CHRONIC HEV INFECTION

During the acute phase, there were no significant differences between the patients with resolving HEV infection and those with chronic infection in median serum HEV RNA concentrations (5.97 $\log_{10}$ copies of RNA per milliliter [range, 5.79 to 6.44] and 6.18 $\log_{10}$ copies per milliliter [range, 4.92 to 7.28], respectively). There also were no significant differences between the groups in peak liver-enzyme levels. Hepatitis developed later after transplantation in patients with resolving HEV infection than in those in whom the infection progressed. Patients in whom chronic hepatitis developed had significantly lower serum creatinine levels at baseline and significantly lower counts of leukocytes, total lymphocytes, platelets, and CD2, CD3, and CD4 lymphocytes (Table 3). The percentages of patients who received induction therapy at transplantation or who received calcineurin inhibitors, mycophenolate mofetil or sodium, or inhibitors of the mammalian target of rapamycin (mTOR) were similar in the two groups. The dosage and trough levels of immunosuppressive drugs, as well as the proportions of patients with anti–hepatitis A virus, anticytomegalovirus, or IgG antibodies to Epstein–Barr virus, were similar in the two groups (data not shown).

Table 3. Patients with Resolving HEV Infection and Those in Whom the Infection Evolved to Chronic Hepatitis.

Variable	Patients with Resolving Infection (N=6)	Patients with Chronic Infection (N=8)	P Value
	median (range)		
At diagnosis			
Time since transplantation — mo	78.5 (25–168)	37.5 (6.0–63.0)	0.03
Leukocyte count — $\times 10^{-3}/mm^3$	8.85 (6–9.66)	4.31 (2.19–7.20)	0.004
Lymphocyte count — $\times 10^{-3}/mm^3$			
Total	1.73 (1.12–2.33)	0.75 (0.63–1.04)	0.004
CD2+	1.59 (0.84–2.25)	0.66 (0.58–0.92)	<0.001
CD3+	1.54 (0.70–1.88)	0.61 (0.49–0.79)	0.01
CD4+	0.93 (0.49–1.07)	0.22 (0.16–0.40)	0.004
Platelet count — $\times 10^{-3}/mm^3$	261 (190–285)	155.5 (75.0–250.0)	0.01
Serum creatinine — mg/dl*	2.15 (1.31–2.84)	1.33 (1.08–1.89)	0.01
At last follow-up			
Aspartate aminotransferase — IU/liter	25.5 (7–35)	55.5 (39.0–238.0)	0.002
Alanine aminotransferase — IU/liter	25 (13–45)	108.0 (59.0–298.0)	0.002

* To convert values for creatinine to micromoles per liter, multiply by 88.4.

DISCUSSION

HEV infection is transmitted by the fecal–oral route and may be a zoonosis in industrialized countries. It has a mortality rate of about 1% in the general population and 30% in pregnant women.[13] HEV-induced acute hepatitis may be fulminant,[14] but we are not aware that any cases of chronic hepatitis have previously been reported. Recently, the diagnosis of many cases of acute HEV hepatitis in nonimmunocompromised patients in southwest France[15] prompted us to look systematically for HEV in recipients of solid-organ transplants who had unexplained hepatitis. Of the 14 patients with acute HEV infection whom we report on here, 8 underwent progression to chronic hepatitis. In addition, in this issue of the *Journal*, Gérolami et al. report a case of HEV-related cirrhosis in a kidney-transplant recipient.[16]

After all other causes of hepatitis had been ruled out, the serum of 14 patients, none of whom had traveled outside France in the previous year, was found to be positive for HEV RNA. We did not identify any source of contamination. The peak aminotransferase levels were lower than in nonimmunocompromised patients.[17,18] Histologic lesions (mainly spotty lobular necrosis) that are characteristic of classic acute viral hepatitis were seen; these lesions were less severe than those typically seen in nonimmunocompromised patients. These findings could be related to the immunosuppressive therapy in transplant recipients.

HEV infection resolved in 6 of the 14 patients within 6 months after the end of the acute phase. In contrast, HEV infection in eight patients evolved to chronic hepatitis, as indicated by persistently elevated liver-enzyme levels and detectable serum HEV RNA at a median of 15 months (range, 10 to 24) after the end of the acute phase. Liver biopsies performed at a median of 12.5 months (range, 10 to 18) after the acute phase revealed signs of chronic viral hepatitis. The histologic lesions — dense lymphocytic portal infiltrate with constant piecemeal necrosis — were similar to those observed in patients chronically infected with hepatitis C virus. None of the patients received any specific therapy; in particular, none received antiviral therapy. Immunosuppressive therapy was not modified after the diagnosis of HEV. In the absence of available therapeutic recommendations for patients infected with HEV, we only performed close monitoring of liver-enzyme levels.

There were no significant differences between patients with resolving HEV infection and those with chronic HEV infection in demographic or clinical features, including treatment with immunosuppressive agents before the acute phase. However, the immunologic status of the patients may have had a role in the evolution to chronic dis-

ease. In patients in whom the infection became chronic, the time from transplantation to the development of infection was significantly shorter — and consequently, the total lymphocyte counts and the CD2, CD3, and CD4 lymphocyte counts were significantly lower — than in patients in whom HEV infection resolved. Hence, the T-cell response seems to have a role in HEV clearance, as does the B-cell response.

HEV seroconversion occurred later in patients with chronic infection than in those with resolving infection. This difference may be related to the reduction in the humoral immune response caused by treatment with mycophenolate, inhibitors of mTOR, or both. These drugs are known to decrease the synthesis of antibodies[19,20] and to inhibit the cell-cycle progression and differentiation of human B lymphocytes.[21] The humoral immune response is necessary to clear HEV and to prevent hepatitis. Bryan et al. have shown that antibodies to the HEV capsid can be protective against hepatitis E.[22] Passive immunoprophylaxis studies in cynomolgus monkeys have confirmed that the antibody to the HEV capsid may prevent HEV infection in humans.[23] Recently an HEV recombinant protein vaccine was found to be effective in preventing HEV infection.[24]

Further studies are required to determine the incidence of chronic HEV infection in transplant recipients who live in areas where the disease is not endemic. Vaccination against HEV could be proposed to patients before or after organ transplantation. However, the efficacy of vaccination in these populations should be addressed.

In conclusion, our data suggest that HEV should be considered an etiologic agent of hepatitis in organ-transplant recipients. We have demonstrated that HEV infection can evolve to chronic hepatitis, at least in organ-transplant recipients. A longer follow-up is required to assess the outcome of HEV infection in organ-transplant recipients.

No potential conflict of interest relevant to this article was reported.

We thank Mrs. Martine Dubois for her technical assistance.

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