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TABLE I. Patients' Clinical Details and Laboratory Results of Hepatitis E^{IDC} Cases as Obtained From the First Serum Sample Tested

	Age (years)	Sex	Peak ALT[a] (IU/L)	INR	Bilirubin[b] (μmol/L)	Jaundice	Comorbid condition(s)	Hospital admission	HEV IgG	HEV IgM	HEV genotype
1	68	F	6,210	1.6	75	Yes	NIDDM and hypertension	Yes	+	+	3
2	61	M	951	1.1	28	No	None	No	+	+	3
3	71	M	1,037	1	10	No	NIDDM	No	+	+	ND
4	75	M	2,733	1	123	Yes	Bladder carcinoma, pharyngeal pouch	No	+	+	3
5	82	M	6,777	2.6	154	Yes	AF, IBS, THR	Yes	−	+	3
6	85	M	656	1	172	Yes	Aortic stenosis, hypertension	Yes	+	+	ND
7	76	M	1,705	>8[c]	320	Yes	AVR, CABG	Yes	+	+	3
8	80	F	945	1	94	Yes	Hypertension	No	+	+	3
9	47	M	630	1	28	No	None	No	+	+	ND
10	69	M	959	1.1	115	Yes	NIDDM, CABG, hypertension, hypercholesterolemia	No	+	−	3
11	83	M	3,554	1.2	115	Yes	NIDDM	No	+	+	3
12	56	M	300	NP[b]	68	Yes	Non-alcoholic fatty liver	No	+	+	NP
13	56	M	551	NP[b]	228	Yes	IHD	No	+	+	NP

NIDDM, non-insulin dependent diabetes mellitus; AF, atrial fibrillation; IBS, irritable bowel syndrome; THR, total hip replacement; AVR, aortic valve replacement; CABG, coronary artery by-pass graft; IHD, ischemic heart disease; INR, international normalized ratio; ND, not detected; NP, not performed.
[a]ALT normal value 10–40 IU/L.
[b]Bilirubin normal value 0–20 μmol/L.
[c]On warfarin since 1998.

TABLE II. Published Cases of Acute Hepatitis E^{IDC} in England and Wales

	Location	Period	Number of cases	Age (years)	Sex
Cases detected in single Centers	Southampton, Hampshire [McCrudden et al., 2000]	1999	4	41, 44, 70, 71	1 Male, 3 females
	Truro, Cornwall [Levine et al., 2000]	1999	1	61	Male
	Hull, East Yorkshire [Jary, 2005]	2005	1	54	Male
	Birmingham, Midlands [Sadler et al., 2006]	2005 (5-month period)	8[a]	Median age 60	4 Males, 3 females
	Cornwall and South-West Devon [Dalton et al., 2007]	March 1999–September 2005	21[b]	Median age 67	15 Males, 6 females
Cumulative data of England and Wales	National survey [Ijaz et al., 2005]	1997–2003	17[c]	Median age 70	13 Males, 4 females
	National survey [Lewis et al., 2006]	January–June 2005	24[d]	Median age 59	20 Males, 4 females

[a]2/8 Patients were RT-PCR positive, one patient with genotype 3 while the other with genotype 1 (the latter had been in recent contact with a jaundiced individual returning from Pakistan).
[b]HEV genotype 3 detected in 16/21 (76%) cases.
[c]HEV genotype 3 detected in 11/17 (65%) patients.
[d]10/25 (40%) cases were HEV RT-PCR positive, of which 9 were genotype 3.

demographic feature was previously documented in a nation-wide UK study [Ijaz et al., 2005] of 17 hepatitis E^{IDC} cases diagnosed between 1997 and 2003 in individuals, 14 of whom (82%) lived in coastal and estuarine areas, as are the ones found in our study in the South Hampshire region. Ijaz et al. [2005] pointed out the confounding effect of older age on the place of residence. This bias might not be relevant to this study where the elderly patients affected by acute hepatitis E belonged to a population which, on average, appears younger compared to that in the rest of England and Wales (www.statistics.gov.uk/census2001, Fig. 1).

Although documented in other European countries, Asia, and USA [van der Poel et al., 2001; Clemente-Casares et al., 2003; Widdowson et al., 2003; Buti et al., 2004; Amon et al., 2006; Peron et al., 2006], hepatitis E^{IDC} is still considered an uncommon disease. A recent report by Lewis et al. [2006] suggests that hepatitis E^{IDC} in UK is under diagnosed. However, implementation of routine serology for hepatitis E is hampered by the fact that currently available antibody assays, based on HEV genotypes 1 and 2, lack sensitivity [Lin et al., 2000; Myint et al., 2006]. This has been attributed to several factors of which the main one is likely to be that the currently available recombinant HEV proteins used in the assay systems may not include all relevant immunogenic B cell epitopes encoded within the HEV genome [Wang et al., 2001; Zhang et al., 2003; Zhou et al., 2004]. Additionally, the genetic diversity between HEV genotypes [Lu et al., 2006] warrants the inclusion of each HEV genotype in future diagnostic kits.

In spite of their limitations, currently available antibody assays have been capable of detecting a significant number of hepatitis E^{IDC} cases, leading to the recognition of this emerging disease. This consideration guided the decision to routinely include hepatitis E testing in our laboratory. Cases with a significantly deranged ALT value were tested, in order to target acute hepatitis of clinical importance. By adherence to this algorithm, a pick up rate of 9.3% was obtained.

In a situation of suboptimal performance of currently available antibody assays, RT-PCR represents a useful complementary diagnostic tool [Jothikumar et al., 2006]. Although the duration of viraemia is variable (from few days to few weeks) (1, 10) a serum sample collected at the peak of ALT values has a high chance to be RT-PCR positive thus clarifying cases of acute hepatitis E with atypical serological profiles, as found in two of our patients (Table II), including HEV seronegative cases [Lin et al., 2000; Mansuy et al., 2004].

The incidence of hepatitis E^{IDC} in our center exceeded the frequency of acute hepatitis A (two cases) and hepatitis B (five cases). In UK, where high standards of sanitation and vaccination programs have significantly reduced exposure to hepatitis A and B viruses, hepatitis E^{IDC} may emerge as a major cause of acute viral hepatitis [Lewis et al., 2006]. The high frequency observed in our uncontrolled series may in part be a reflection of a better ascertainment of hepatitis E^{IDC}, which had previously remained undiagnosed, as well as a true increase in incidence in recent time.

In conclusion, it is considered that these findings support the case for more widespread HEV testing according to clearly defined criteria and we propose an effective algorithm for this purpose. This is crucial not only for surveillance purposes and to clarify the epidemiology of HEV in UK, but also for the appropriate management of affected patients. In cases of acute hepatitis, where initial history and viral marker results are negative, autoimmune hepatitis, and idiosyncratic drug reactions are important to consider in the differential diagnosis, with implications for management and prognosis. Thus, in the absence of HEV testing, patients with unexplained raised transaminases may unnecessarily progress to liver biopsy, empirical trial of steroids, or withdrawal of presumed offending drugs. Consideration of HEV infection in individuals without travel-associated risk factors for acute hepatitis may have a major impact on clinical management.

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一般的名称	①乾燥抗HBs人免疫グロブリン ②ポリエチレングリコール処理抗HBs人免疫グロブリン	研究報告の公表状況	The New England Journal of Medicine 2008; 358: 811-817	公表国 フランス
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研究報告の概要

HEVは急性肝炎の原因となる病原体であって、慢性肝炎に進展することはないと考えられている。我々は、HEV急性肝炎の14症例を確認したが、3名の患者は肝臓、9名の患者は腎臓、2名は腎臓と膵臓を移植されていた。患者は全員、血清HEV RNAが陽性であった。8名の患者が慢性肝炎になり、確認はアミノトランスフェラーゼ値上昇の持続、血清HEV RNA、慢性肝炎の組織学的特徴によって行われた。移植から診断までの時間は極めて短く、リンパ球数並びにCD2、CD3及びCD4 T細胞の数は、慢性肝炎に進展した患者では著しく低かった。

使用上の注意記載状況・その他参考事項等

代表として静注用ヘブスブリンーIHの記載を示す。
2. 重要な基本的注意
(1) 本剤の原材料となる血液については、HBs抗原、抗HCV抗体、抗HIV-1抗体、抗HIV-2抗体陰性で、かつALT（GPT）値でスクリーニングを実施している。更に、プールした試験血漿については、HIV-1、HBV及びHCVについて核酸増幅検査(NAT)を実施し、適合した血漿を本剤の製造に使用しているが、当該NATの検出限界以下のウイルスが混入している可能性が常に存在する。本剤は、以上の検査に適合した高力価の抗HBs抗体を含有する血漿を原料として、Cohnの低温エタノール分画で得た画分からポリエチレングリコール4000処理、DEAEセファデックス処理等により抗HBs人免疫グロブリンを濃縮・精製した製剤であり、ウイルス不活化・除去を目的として、製造工程において60℃、10時間の液状加熱処理及びろ過膜処理（ナノフィルトレーション）を施しているが、投与に際しては、次の点に十分注意すること。

報告企業の意見	今後の対応
少なくとも免疫抑制剤を投与されている臓器移植患者においては、HEV感染が慢性肝炎に進展し得るとの報告である。 本剤からHEVが伝播したとの報告はない。万一、原料血漿にHEVが混入したとしても、EMCおよびCPVをモデルウイルスとしたウイルスバリデーション試験成績から、本剤の製造工程において十分に不活化・除去されると考えている。	本報告は本剤の安全性に影響を与えないと考えるので、特段の措置はとらない。

The NEW ENGLAND JOURNAL of MEDICINE

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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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		