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研究報告の概要

日本人献血者をALT高値と正常値の2群に分類し、E型肝炎ウイルス（HEV）感染の実態について調査した。2ヶ所の血液センターにおいて、ALT高値(61～966IU/L)の献血者1,087名、ALT正常値（≦60IU/L）の献血者4,256名の計5,343名から血清検体を採取し、ELISA法によりHEV IgG抗体の存在を検査したところ、ALT高値の献血者32名(2.9%)とALT正常値の献血者168名（3.9%）の計200名（3.7%）がHEV IgG抗体陽性であった。HEV IgG抗体が検出された血清検体については更に、ELISA法によるHEV IgM抗体とRT-PCR法によるHEV-RNAの有無について検査した結果、ALT値が966、62、61 IU/Lであった3名の献血者がHEV IgM抗体およびHEV-RNAが陽性であった。この3名から得られたHEV分離株はgenotype 3であり、ORF-2の412塩基配列において91.5～93.4%の相同性を示し、海外渡航歴のない散発性急性E型肝炎患者から採取したJRA1型分離株とも91.5～94.9%と極めて高い相同性を認めたことから、日本固有のHEV株であることが示唆された。本研究により、少数ではあるものの、一部の献血者はHEVのウイルス血症状態にあり、潜在的には輸血を介したE型肝炎ウイルス感染の原因となり得ることが示唆された。

使用上の注意記載状況・その他参考事項等

クロスエイトM250
クロスエイトM500
クロスエイトM1000
血液を原料とすることに由来する感染症伝播等
理論的なvCJD等の伝播のリスク

報告企業の意見	今後の対応
一部の献血者は、HEVのウイルス血症状態にあることを示唆した報告である。日本赤十字社は、既に国内における輸血を介したHEV感染症例について報告している。	HEVは脂質膜の無いRNAウイルスである。これまで、本製剤によるHEV感染の報告はない。本製剤の製造工程には、平成11年8月30日付医薬発第1047号に沿ったウイルス・プロセスバリデーションによって検証された2つの異なるウイルス除去・不活化工程が含まれていることから、本製剤の安全性は確保されており、念のため情報収集に努めるも、今後特別の対応を必要としない。なお、最終製品10ロットについてはHEV NAT陰性であることを確認している。

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Prevalence of Antibodies to Hepatitis E Virus Among Japanese Blood Donors: Identification of Three Blood Donors Infected With a Genotype 3 Hepatitis E Virus

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Risk factors for acquiring hepatitis E among individuals in industrialized countries including Japan are not fully understood. We investigated whether Japanese blood donors with or without an elevated alanine aminotransferase (ALT) level are likely to have hepatitis E virus (HEV) infection. Serum samples were collected from 5,343 voluntary blood donors including 1,087 donors with elevated ALT of 61–966 IU/L and 4,256 donors with normal ALT (≤60 IU/L) at two Japanese Red Cross Blood Centers, and were tested for the presence of anti-HEV IgG by in-house enzyme-linked immunosorbent assay (ELISA). Overall, 200 donors (3.7%) were positive for anti-HEV IgG, including 32 (2.9%) with elevated ALT and 168 (3.9%) with normal ALT. Serum samples with anti-HEV IgG were further tested for the presence of anti-HEV IgM by in-house ELISA and for HEV RNA by reverse transcription (RT)-polymerase chain reaction (PCR). Three donors with ALT of 966, 62 or 61 IU/L were positive for anti-HEV IgM and HEV RNA. The HEV isolates obtained from the three viremic donors segregated into genotype 3, were 91.5–93.4% similar to each other in the 412 nucleotide sequence of open reading frame 2, and had the highest identity of 91.5–94.9% with the JRA1 isolate which was recovered from a Japanese patient with sporadic acute hepatitis E who had never been abroad, suggesting that these three HEV isolates are indigenous to Japan. This study suggests that a small but significant proportion of blood donors in Japan with or without elevated ALT are viremic and are potentially able to cause transfusion-associated hepatitis E. ***J. Med. Virol. 73:554–561, 2004.*** © 2004 Wiley-Liss, Inc.

KEY WORDS: hepatitis viruses; alanine aminotransferase; PCR; phylogenetic analysis

INTRODUCTION

Hepatitis E is an important public health concern in many developing countries of Asia and Africa where sanitation is suboptimal, and it is also endemic in many industrialized countries including the United States, European countries, and Japan [Harrison, 1999; Purcell and Emerson, 2001; Smith, 2001; Okamoto et al., 2003]. The hepatitis E virus (HEV), the causative agent of hepatitis E, is an unclassified nonenveloped virus. Its genome is a single-stranded, positive-sense RNA of approximately 7.2 kb. It consists of a short 5′ untranslated region (UTR) followed by three partially overlapping open reading frames (ORFs: ORF1, ORF2, and ORF3), and then a short 3′UTR terminated by a poly(A) tract. ORF1 encodes viral non-structural proteins, ORF2 encodes the capsid protein, and ORF3 encodes a small phosphorylated protein [Reyes et al., 1990; Tam

The nucleotide sequence data reported in this study have been assigned DDBJ/EMBL/GenBank accession numbers AB124818, AB154829, and AB154830.

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et al., 1991; Huang et al., 1992; Zafrullal et al., 1997; Wang et al., 1999, 2000]. Although only one serotype has been recognized, extensive genomic diversity has been noted among HEV isolates and HEV sequences have tentatively been classified into four genotypes (genotypes 1–4). The majority of HEV infections in developing countries are caused by genotype 1; one epidemic of infection with HEV of genotype 2 has been documented in Mexico; and only isolated cases of infection with HEV of genotype 3 or 4 have been described in industrialized nations [Schlauder and Mushahwar, 2001].

Transmission of HEV occurs primarily by the fecal-oral route through contaminated water supplies in developing countries. Recent studies have indicated that zoonosis is involved in the transmission of HEV, especially in industrialized countries where hepatitis E had been believed to be non-endemic [Meng et al., 1997, 1998; Harrison, 1999; Erker et al., 1999; Meng, 2000; Halbur et al., 2001; Okamoto et al., 2001; Smith, 2001; Nishizawa et al., 2003; Takahashi et al., 2003; Tei et al., 2003; Yazaki et al., 2003]. Numerous strains of HEV have been isolated from pigs in both developing and industrialized countries [Clayson et al., 1995; Chandler et al., 1999; Hsieh et al., 1999; Pina et al., 2000; Garkavenko et al., 2001; van der Poel et al., 2001; Arankalle et al., 2002; Huang et al., 2002; Pei and Yoo, 2002; Wu et al., 2002; Choi et al., 2003; Takahashi et al., 2003]. Increasing lines of evidence indicate that pigs are animal reservoirs for HEV and hepatitis E may be zoonotically transmitted from viremic animals to humans [Meng et al., 1997; Harrison, 1999; Meng, 2000; Smith, 2001]. In Japan, it has recently been reported that food-borne transmission of HEV may occur through ingestion of raw or undercooked meat including liver and intestine from infected swine, deer, or boar [Matsuda et al., 2003; Tei et al., 2003; Yazaki et al., 2003]. However, the modes of HEV transmission are still unclear for most patients with sporadic acute or fulminant hepatitis E in Japan [Takahashi et al., 2001, 2002a,b; Aikawa et al., 2002; Mizuo et al., 2002; Suzuki et al., 2002]. It has been reported that a substantial proportion of blood donors (3/200 or 1.5%) were positive for HEV RNA and viremic blood donors are potentially able to cause transfusion-associated hepatitis E in areas of high endemicity [Arankalle and Chobe, 1999, 2000]. Therefore, in the present study, we investigated whether Japanese blood donors with or without an elevated alanine aminotransferase (ALT) level are likely to have HEV infection in an attempt to gain insight into the possible blood-borne transmission of HEV in Japan which is now considered to be endemic.

MATERIALS AND METHODS

Serum Samples

Serum samples were collected from a total of 5,343 voluntary blood donors including 560 donors (age, 31.6 ± 10.5 [mean ± standard deviation, SD] years; 503 men and 57 women) with an elevated ALT level of 61–966 (range: 108 ± 59, mean ± SD) IU/L and 2,071 donors (38.3 ± 15.8 years; 1,030 men and 1,041 women) with a normal ALT level at the Japanese Red Cross Tochigi Blood Center (Center T) between April 2002 and June 2003, and 527 donors (37.0 ± 9.9 years; 480 men and 47 women) with an elevated ALT of 61–472 (96 ± 40) IU/L and 2,185 donors (39.1 ± 15.2 years; 1,121 men and 1,064 women) with a normal ALT at the Japanese Red Cross Yamaguchi Blood Center (Center Y) between May 2002 and October 2003. Blood Center T is located in a city in the northern part of mailand Honshu of Japan (Tochigi Prefecture) and Blood Center Y is located in a city in the southernmost part of mainland Honshu (Yamaguchi Prefecture). Additionally, periodic serum samples were obtained from three donors with transient HEV viremia. Stored serum samples that had been obtained from one donor were also used for retrospective analysis.

All 5,343 donors were negative for hepatitis B surface antigen, and antibodies to hepatitis C virus (HCV), human immunodeficiency virus (HIV) types 1 and 2, and human T-lyimphotropic virus type 1, as well as for hepatitis B virus DNA, HCV RNA, and HIV type 1 RNA by the nucleic acid amplification test using Roche's Multiplex reagent [Mine et al., 2003].

Detection of Antibodies to HEV

To detect anti-HEV IgG and anti-HEV IgM, enzyme-linked immunosorbent assay (ELISA) was carried out using purified recombinant ORF2 protein of HEV genotype 4 that had been expressed in the pupae of silkworm, as described previously [Mizuo et al., 2002]. The optical density (OD) of each sample was read at 450 nm. Using control sera from 200 healthy individuals (100 males and 100 females; age range: 16–24 years), the cut-off value was determined for the anti-HEV IgG assay as 0.180, and that for the anti-HEV IgM assay as 0.353 by the method described previously [Mizuo et al., 2002]. Samples with OD values for anti-HEV IgG or IgM equal to or greater than the respective cut-off value were considered to be positive for anti-HEV IgG or IgM, respectively. The specificity of the anti-HEV assays was verified by absorption with the same recombinant ORF2 protein that was used as the antigen probe or a mock protein obtained from the pupae of silkworm infected with nonrecombinant baculovirus. Briefly, when the OD value of the tested sample was less than 30% of the original value after absorption with the recombinant ORF2 protein and was greater than 70% of the original value after absorption with a mock protein, the sample was considered to be positive for anti-HEV.

Detection of HEV RNA

Reverse transcription (RT)-polymerase chain reaction (PCR) was carried out for detection of HEV RNA in serum samples. Total RNA was extracted from 100 μl of serum, reverse transcribed, and then subjected to nested PCR with the ORF2 primers as described previously [Mizuo et al., 2002]. The size of the amplification product of the first-round PCR was 506 base pairs

(bp), and that of the second-round PCR was 457 bp. The nested RT-PCR assay was performed in duplicate, and reproducibility was confirmed. The specificity of the RT-PCR assay was verified by sequence analysis as described below. The sensitivity of the RT-PCR assay was assessed as described previously [Mizuo et al., 2002].

Sequence Analysis of PCR Products

The amplification products were sequenced directly on both strands using the BigDye Terminator Cycle Sequencing Ready Reaction Kit on an ABI PRISM 3100 Genetic Analyzer (Applied Biosystems, Foster City, CA). Sequence analysis was performed using Genetyx-Mac version 12.2.0 (Genetyx Corp., Tokyo, Japan) and ODEN version 1.1.1 from the DNA Data Bank of Japan (DDBJ: National Institute of Genetics, Mishima, Japan) [Ina, 1994]. Sequence alignments were generated by CLUSTAL W (version 1.8) [Thompson et al., 1994]. A phylogenetic tree was constructed by the neighbor-joining method [Saitou and Nei, 1987] based on the partial nucleotide sequence of the ORF2 region (301 nucleotides [nt]). Bootstrap values were determined on 1,000 resamplings of the data sets [Felsenstein, 1985]. The final tree was obtained using the TreeView program (version 1.6.6) [Page, 1996].

Statistical Analysis

Statistical analyses were performed using the χ^2-test for comparison of proportions between two groups. Differences were considered to be statistically significant at $P < 0.05$.

RESULTS

Prevalence of Anti-HEV IgG Among Voluntary Blood Donors in Two Distinct Geographic Regions in Japan

A total of 5,343 serum samples obtained from apparently healthy blood donors at two Red Cross Blood Centers (T and Y), located in cities in the northern part and southernmost part, respectively, of Honshu Island of Japan, were tested for the presence of anti-HEV IgG. At Blood Center T, anti-HEV IgG was detected in 5.5% (144/2,631) of the tested population; it was detected in 4.1% of the 560 donors with elevated ALT of 61–966 IU/L and in 5.8% of the 2,071 donors with normal ALT. On the other hand, the detection rate of anti-HEV IgG among the 2,712 donors at Blood Center Y was 2.1%, which was significantly lower than that at Blood Center T ($P < 0.0001$). Anti-HEV IgG was detected in 1.7% in the 527 donors with an elevated ALT level of 61–472 IU/L ($P = 0.0193$ in comparison with the respective parameter in Center T), and in 2.2% of the 2,185 donors with normal ALT ($P < 0.0001$) (Table I). The age-dependent prevalence of anti-HEV IgG was compared among blood donors in relation to gender and ALT at the two blood centers (Table I). The prevalence of anti-HEV IgG increased with age among both the male and female

TABLE I. Age-Specific Prevalence of Anti-HEV IgG Among Apparently Healthy Individuals With or Without an Elevated ALT at Two Blood Centers in Japan

	Blood center T				Blood center Y			
	ALT ≤60 IU/L		ALT ≥61 IU/L		ALT ≤60 IU/L		ALT ≥61 IU/L	
Age (year)	Male	Female	Male	Female	Male	Female	Male	Female
16–19	2/185 (1.1%)	1/173 (0.6%)	2/91 (2.2%)	0/16	1/157 (0.6%)	1/173 (0.6%)	0/13	0/4
20–29	7/195 (3.6%)	3/208 (1.4%)	2/113 (1.8%)	0/13	5/209 (2.4%)	2/200 (1.0%)	0/99	0/6
30–39	7/175 (4.0%)	5/189 (2.6%)	8/183 (4.4%)	0/13	3/196 (1.5%)	2/180 (1.1%)	3/196 (1.5%)	0/14
40–49	19/175 (10.9%)	15/156 (9.6%)	6/89 (6.7%)	0/10	6/212 (2.8%)	2/194 (1.0%)	5/120 (4.2%)	0/10
50–59	23/152 (15.1%)[a]	10/157 (6.4%)[a]	4/24 (16.7%)	0/4	9/183 (4.9%)	7/168 (4.2%)	1/45 (2.2%)	0/11
60–69	18/148 (12.2%)	11/158 (7.0%)	1/3 (33.3%)	0/1	6/164 (3.7%)	3/149 (2.0%)	0/7	0/2
Subtotal	76/1,030 (7.4%)[b,d]	45/1,041 (4.3%)[b,e]	23/503 (4.6%)[b]	0/67[f]	30/1,121 (2.7%)[a,d]	17/1,064 (1.6%)[c,e]	9/480 (1.9%)[a,b]	0/47[g]
Total	121/2,071 (5.8%)[j,k]		23/560 (4.1%)[j]		47/2,185 (2.2%)[j,k]		9/527 (1.7%)[j]	
Grand total	144/2,631 (5.5%)[m]				56/2,712 (2.1%)[m]			

[a] $P = 0.0127$.
[b] $P = 0.0024$.
[c] $P = 0.0824$ (not significant [NS]).
[d] $P < 0.0001$.
[e] $P = 0.0002$.
[f] $P = 0.1068$ (NS).
[g] $P = 0.3437$ (NS).
[h] $P = 0.0247$.
[i] $P = 0.0717$ (NS).
[j] $P = 0.5207$ (NS).
[k] $P < 0.0001$.
[l] $P = 0.0193$.
[m] $P < 0.0001$.

donors at the two blood centers regardless of the ALT level, although none of the female donors with elevated ALT tested positive for anti-HEV IgG at both blood centers, probably due to the small number of female donors tested in all age groups. At Blood Center T, the prevalence of anti-HEV IgG was significantly higher among donors with normal ALT aged ≥40 years than among those aged <40 years in the males (12.6% vs. 2.9%, $P < 0.0001$) and females (7.6% vs. 1.6%, $P < 0.0001$), and among male donors with elevated ALT aged ≥40 years than among those aged <40 years (9.5% vs. 3.1%, $P = 0.0039$). Similar age-specific differences in the prevalence of anti-HEV IgG were observed at Blood Center Y, as indicated in Table I. Upon comparison of donors with normal ALT at Blood Center T, HEV infection was significantly more frequent among the male donors than among the female donors (7.4% vs. 4.3%, $P = 0.0024$). The prevalence of anti-HEV IgG was also higher among the male donors with normal ALT than among the female donors with normal ALT at Blood Center Y and higher among the male donors with elevated ALT than among female donors with elevated ALT at both blood centers.

Prevalence of Anti-HEV and HEV RNA Among Blood Donors in the Two Blood Centers in Japan, Stratified by ALT Level

Twenty-one donors with anti-HEV IgG of high OD_{450} value (>1.000) were found at Blood Center T, including one (50%) with an ALT of >500 IU/L, two (1.0%) with an ALT of 101–200 IU/L, seven (2.0%) with an ALT of 61–100 IU/L, and 11 (0.5%) with normal ALT (Table II). At Blood Center Y, only seven donors (0.3%) with anti-HEV IgG of high OD_{450} value (>1.000) were found, in which all seven donors had a normal ALT. The 200 donors who were positive for anti-HEV IgG were tested for the presence of anti-HEV IgM. No donor at Blood Center Y was seropositive for anti-HEV IgM, regardless of the ALT level. In contrast, at Blood Center T, three donors (3/560 or 0.5%) with an elevated ALT level of 61, 62, or 966 IU/L were positive for anti-HEV IgM, all of whom had anti-HEV IgG of high OD_{450} value (>1.000), and all 121 donors with normal ALT who were positive for anti-HEV IgG, were negative for anti-HEV IgM. Two of the three donors with anti-HEV IgG and anti-HEV IgM had detectable HEV RNA. No other donor with anti-HEV IgG of high OD_{450} value (>1.000) was positive for HEV RNA.

Detection of Anti-HEV and HEV RNA in Periodic Serum Samples Obtained From Three Donors With Anti-HEV IgM

Periodic serum samples were obtained from the three donors (Donors 1–3) with elevated ALT who had been found to be positive for anti-HEV IgM in the above-mentioned screening test after informed consent, and tested for anti-HEV IgG, anti-HEV IgM, and HEV RNA (Table III). None of the three donors had signs or symptoms of HEV infection during the observation period. Donor 1 was a 54-year-old male with a history of >100 donations. His blood screening tests including liver function tests were exclusively normal at the previous donations. On the initial sampling day of the present study (September 12, 2002), his liver enzyme levels were markedly elevated (ALT, 966 IU/L; AST, 815 IU/L), he was positive for both anti-HEV IgG and anti-HEV IgM, and HEV RNA was detectable. Thereafter, his liver enzyme levels were within the normal range and HEV RNA was undetectable. The anti-HEV IgG level continued to be high until the end of the observation period (November 26, 2003), at which time the OD_{450} value was 2.632. The relative titer of IgM antibody was highest on day 61 (OD_{450} value, 2.279) and then gradually decreased, and it continued to be positive

TABLE II. Prevalence of Anti-HEV and HEV RNA Among Blood Donors at Two Distinct Blood Centers in Japan, Stratified by ALT Level

ALT level (IU/L)	No. of donors tested	No. of donors with anti-HEV IgG (OD_{450} value) of		No. of donors with anti-HEV IgM[b]	No. of donors with HEV RNA[c]
		≥0.180[a]	>1.000		
Blood center T					
>500	2	1 (50%)	1 (50%)	1 (50%)	1 (50%)
201–500	21	0	0	0	0
101–200	193	5 (2.6%)	2 (1.0%)	0	0
61–100	344	17 (4.9%)	7 (2.0%)	2 (0.6%)	1 (0.3%)
Total	560	23 (4.1%)	10 (1.8%)	3 (0.5%)	2 (0.4%)
5–60	2,071	121 (5.8%)	11 (0.5%)	0	0
Blood center Y					
>500	0	0	0	0	0
201–500	13	0	0	0	0
101–200	149	0	0	0	0
61–100	365	9 (2.5%)	0	0	0
Total	527	9 (1.7%)	0	0	0
5–60	2,185	47 (2.2%)	7 (0.3%)	0	0

[a]Cut-off value for anti-HEV IgG was 0.180.
[b]Positivity for anti-HEV IgM was tested in blood donors with anti-HEV IgG.
[c]Positivity for HEV RNA was tested in blood donors with anti-HEV IgG of >1.000.

TABLE III. Laboratory Parameters, Anti-HEV Antibody Levels and HEV RNA in Periodic Serum Samples Obtained From Three Blood Donors With Transient HEV Viremia at Blood Center T

Blood donor	Date of sampling	ALT (IU/L)	AST (IU/L)	OD_{450} value in anti-HEV assay[a] IgM-class	IgG-class	HEV RNA
1	**2002/9/12[b]**	**966**	**815**	**0.940 (+)**	**>3.000 (+)**	+
	2002/10/27	25	26	2.020 (+)	>3.000 (+)	–
	2002/11/12	20	20	2.279 (+)	>3.000 (+)	–
	2002/12/15	22	24	1.127 (+)	>3.000 (+)	–
	2003/1/29	17	20	0.937 (+)	>3.000 (+)	–
	2003/2/16	19	24	0.838 (+)	>3.000 (+)	–
	2003/3/8	16	21	0.732 (+)	>3.000 (+)	–
	2003/4/6	24	27	0.676 (+)	>3.000 (+)	–
	2003/6/28	12	18	0.571 (+)	>3.000 (+)	–
	2003/7/29	18	25	0.460 (+)	2.684 (+)	–
	2003/9/1	14	21	0.302 (–)	2.592 (+)	–
	2003/11/11	14	20	0.217 (–)	2.362 (+)	–
	2003/11/26	12	22	0.255 (–)	2.632 (+)	–
2	**2002/4/22[b]**	**61**	**22**	**>3.000 (+)**	**>3.000 (+)**	+
	2002/8/14	19	16	0.390 (+)	>3.000 (+)	–
	2003/8/13	20	15	0.135 (–)	2.181 (+)	–
3	2002/11/14	49	51	0.025 (–)	0.008 (–)	–
	2003/3/10	68	35	0.030 (–)	0.014 (–)	+
	2003/6/10[b]	**62**	**37**	**0.792 (+)**	**2.611 (+)**	–

[a]Cut-off values for anti-HEV IgM and IgG were 0.353 and 0.180, respectively.
[b]Index sample that was first found to be positive for anti-HEV IgM and IgG is indicated in boldtype.

until day 320 after the initial testing. Donor 2 was a 35-year-old male with normal liver enzyme levels (ALT, 24 IU/L; AST, 16 IU/L) at the time of his previous donation 126 days before the initial sampling day of April 22, 2002. On the first sampling day, the ALT was slightly elevated (61 IU/L), but the AST was within the normal range (22 IU/L). He was highly positive for anti-HEV IgG and anti-HEV IgM, and HEV RNA was detectable on the initial sampling day. After 16 months, he remained positive for anti-HEV IgG antibody with an OD_{450} value of 2.181, but he was negative for IgM antibody. Donor 3 was a 41-year-old male. On the initial testing, he had a slightly elevated ALT level of 62 IU/L and was positive for both anti-HEV IgG and anti-HEV IgM, but HEV RNA was undetectable. Two stored serum samples that had been obtained 92 and 208 days before the initial testing, were tested for the presence of anti-HEV IgG, anti-HEV IgM, and HEV RNA. Although the two serum samples were negative for both anti-HEV antibodies, the serum sample obtained 3 months before the initial testing was repeatedly positive for HEV RNA and the donor had an elevated ALT level of 68 IU/L at that time. Fortunately, this blood was not utilized for transfusion due to an abnormal ALT level. Consequently, three blood donors with anti-HEV IgG and anti-HEV IgM were found to be transiently viremic.

Genetic Analysis of HEV Isolates Recovered From Three Viremic Donors

The three HEV isolates recovered from the transiently viremic donors (Donors 1–3) were named HE-JBD1, HE-JBD2, and HE-JBD3, respectively. The 412 nt sequence of ORF2 of these HEV isolates were determined and compared with each other and with that of known human and swine HEV isolates of genotypes 1–4. These three HEV isolates were 91.5–93.4% similar to each other, and were most closely related to the prototype Japanese isolate of genotype 3 (JRA1 [accession no. AP003430]) with nucleotide sequence identity of 91.5–94.9%, and were only 78.3–79.6%, 74.3–77.4%, and 78.8–79.9% similar to the B1 isolate (M73218) of genotype 1, MEX-14 isolate (M74506) of genotype 2, and T1 isolate (AJ272108) of genotype 4, respectively. The phylogenetic tree constructed based on the common 301 nucleotides within the ORF2 sequence confirmed that the HE-JBD1, HE-JBD2, and HE-JBD3 isolates obtained in the present study belonged to genotype 3, and that they segregated into the cluster consisting of Japanese HEV strains of the same genotype that had been recovered from humans (JRA1, HE-JO-1982, HE-JA5, HE-JA6, HE-JA9, HE-JA11, HE-JA21, HE-JA23, and HE-JF2) and swine (swJ570 and swJ681), supporting the indigenous nature of these three blood donor isolates.

DISCUSSION

HEV is a significant cause of epidemic and sporadic acute viral hepatitis in developing countries of Asia and Africa, and HEV-associated hepatitis also occurs sporadically in some industrialized countries including the United States, European countries, and Japan. Transmission of HEV occurs primarily by the fecal-oral route through contaminated water supplies in many developing countries. However, in industrialized countries where sanitation and hygiene are well established, the chance of fecal-oral transmission of HEV may be negligible, and the risk factors for acquiring hepatitis

E among individuals in industrialized countries are not fully understood [Harrison, 1999; Meng, 2000; Purcell and Emerson, 2001; Smith, 2001; Emerson and Purcell, 2003; Okamoto et al., 2003]. As reviewed by Smith [2001], it is likely that several forms of HEV transmission other than fecal-oral transmission occur in industrialized countries with no or low HEV endemicity: (a) zoonotic infection, (b) transmission by food, and (c) transmission via blood transfusion. Accumulated evidence indicates that pigs are animal reservoirs for HEV and hepatitis E may be zoonotically transmitted from viremic animals to humans [Meng et al., 1997, 1998; Erker et al., 1999; Harrison, 1999; Meng, 2000; Pina et al., 2000; Halbur et al., 2001; Smith, 2001; Wang et al., 2002]. In Japan where hepatitis E had been believed to be non-endemic but is now considered to be endemic [Okamoto et al., 2001; Takahashi et al., 2001, 2002a,b, 2003; Mizuo et al., 2002; Nishizawa et al., 2003], evidence for food-borne transmission of HEV through the consumption of HEV-contaminated food has been accumulating; HEV contamination was found in various foods including raw pig livers that are available in grocery stores in Hokkaido, which is located in the northern part of Japan and where hepatitis E is most prevalent in Japan [Yazaki et al., 2003]; and raw meat from a wild deer in Hyogo Prefecture which is located in the southern part of mainland Honshu [Tei et al., 2003]. Japanese people have a peculiar habit of eating uncooked seafood (sushi or sashimi), and less frequently, raw or undercooked meat including liver and intestine from pigs and other animals. These eating habits may explain, at least partly, the cryptic endemicity of HEV in Japan. However, the source and route of HEV transmission remain unclear for most cases of sporadic acute or fulminant hepatitis E in areas other than the above-mentioned areas of Japan [Takahashi et al., 2001, 2002a,b; Aikawa et al., 2002; Mizuo et al., 2002; Suzuki et al., 2002; Tokita et al., 2003].

In the present study, in an attempt to gain insight into the possible blood-borne transmission of HEV in Japan, we investigated the prevalence of anti-HEV IgG among voluntary blood donors who donated blood in two distinct geographic regions that are located in the northern and southernmost parts of mainland Honshu (Blood Center T in Tochigi Prefecture and Blood Center Y in Yamaguchi Prefecture, respectively). At least two cases of sporadic acute hepatitis E with unknown transmission mode(s) have been recognized thus far in Tochigi Prefecture [Takahashi et al., 2002b; Kuno et al., 2003], although no case has been reported in Yamaguchi Prefecture, reflecting the observed higher prevalence of anti-HEV IgG among blood donors at Blood Center T (5.5% vs. 2.1%, $P < 0.0001$). The prevalence of anti-HEV IgG was clearly associated with age among the blood donors at both blood centers, corroborating the previous report on the prevalence of anti-HEV IgG antibody among 900 Japanese patients in that the anti-HEV prevalence of anti-HEV among patients over 30 years of age was associated with age and increased in a cumulative fashion in all three geographical regions (northern, central, and southern prefectures of Japan) [Li et al., 2000]. HEV infection was associated with male sex in all age groups studied in at the two blood centers in the present study, consistent with the observed higher prevalence of clinical HEV infection among male patients in Japan [Mizuo et al., 2002].

In the current study, three viremic blood donors who all had an elevated ALT, were identified among the donors with a high level of anti-HEV IgG (>1.000) at Blood Center T which is located in a region where the prevalence of anti-HEV IgG is high, although none of the donors with normal ALT and a high level of anti-HEV IgG had detectable HEV RNA. In contrast, at Blood Center Y which is located in a region where HEV infection is less prevalent, none of the blood donors who had a high level of anti-HEV IgG with or without an elevated ALT were positive for HEV RNA. These results suggest that a proportion of blood donors in areas where HEV infection is prevalent in Japan are viremic and are potentially able to cause transfusion-associated hepatitis E, as has been reported in India which has high endemicity of HEV; in two studies of Arankalle and Chobe [1999, 2000], three (1.5%) of 200 voluntary blood donors were positive for HEV RNA. As the three viremic donors identified in the present study had an elevated ALT, the blood from the three donors were not used for transfusion. As the majority of donors with elevated ALT and the donors with normal ALT were not tested for HEV viremia in the present study, we cannot conclude that the serum ALT level could be a surrogate marker for exclusion of blood donors with ongoing HEV infection. Based on the current study, however, we would like to consider that ALT testing is useful for exclusion of donors with HEV viremia, at least partially, with the aim of preventing transfusion-associated hepatitis E. As two of the three infected donors had only a slightly elevated ALT level of 61 or 62 IU/L, it seems likely that even donors with a normal ALT level ($\leq$60 IU/L) may have detectable HEV RNA, although the proportion of such donors may be significantly small. In support of this speculation, it has been reported in a newspaper (ABC Newsletter January 24, 2003; accessible at http://www.americasblood.org) that a Japanese man in his 60s contracted hepatitis E from a blood transfusion that he had received during heart surgery at a city hospital in Hokkaido in 2002, where hepatitis E is most prevalent in Japan as described above.

Multiple HEV strains of genotype 3 or 4 have been isolated from Japanese patients with sporadic acute or fulminant hepatitis E as well as from farm pigs in Japan [Okamoto et al., 2003]. Reflecting the polyphyletic nature of human and swine HEV isolates of Japan origin, the HEV isolates recovered from three viremic donors in the present study, differed by 6.6–8.5% from each other, although they belonged to the same genotype (genotype 3) with the highest nucleotide sequence identity of 91.5–94.9% with the JRA1 isolate that is believed to be indigenous to Japan [Takahashi et al., 2001]. Three distinct swine HEV strains (swJ570, swJ681, and swJ791 in Fig. 1) of genotype 3 [Okamoto

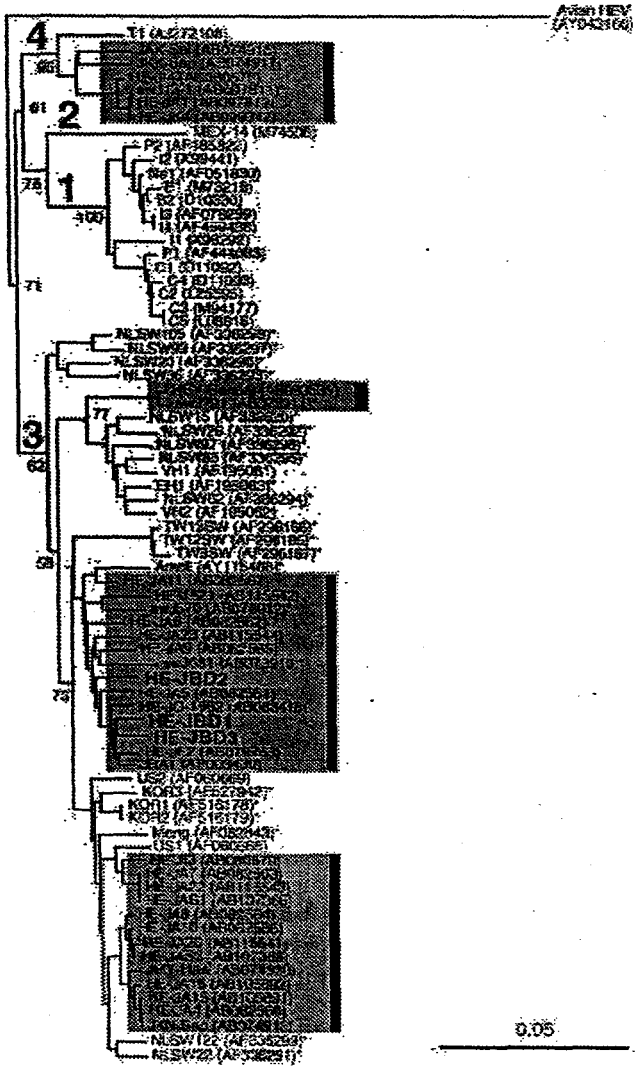

Fig. 1. Phylogenetic tree constructed by the neighbor-joining method based on the partial nucleotide sequence of the ORF2 region (301 nt) of 75 HEV isolates, using a chicken HEV (AY043166) as an outgroup. In addition to the HE-JBD1, HE-JBD2, and HE-JBD3 isolates found in the present study which are indicated in bold type, 72 reported HEV isolates of genotypes 1–4 whose common 301 nt sequence is known are included for comparison and their accession nos. are shown in parentheses. The previously reported HEV sequences of genotype 1 are indicated with abbreviations in accordance with the recent review article by Schlauder and Mushahwar [2001]: B1 and B2 in Burma; C1, C2, C3, C4, and C5 in China; I1, I2, I3 and I4 in India; Ne1 in Nepal; and P1 and P2 in Pakistan. Asterisks denote swine HEV strains. The human and swine HEV isolates of Japan origin are shaded and indicated with vertical bars for visual clarity. Bootstrap values are indicated for the major nodes as a percentage obtained from 1,000 resamplings of the data.

et al., 2001] and three different human HEV strains (HE-JI3, HE-JI4, and HE-JK4 in Fig. 1) of genotype 3 or 4 [Kuno et al., 2003; Takahashi et al., 2002b] have been isolated in the same prefecture as that of the three viremic donors, and they all share only up to 90.7% identity with the HE-JBD1, HE-JBD2, and HE-JBD3 isolates obtained from the viremic donors in the present study. These results further support the marked heterogeneity of the HEV genome and its wide distribution in Japan, even within a certain prefecture in this country.

In conclusion, three blood donors with HEV viremia were identified among voluntary blood donors with an elevated ALT at a blood center located in the northern part of mainland Honshu of Japan where HEV infection is prevalent. Our study supports the possibility of transfusion-associated hepatitis E in countries like Japan where HEV is circulating and where there are symptom-free HEV RNA-positive donors. A much larger study with a greater number of blood donors with or without an elevated ALT level is needed to assess the frequency of HEV-viremic blood donors and the usefulness of ALT testing for excluding viremic donors, although the major contributing factors to an elevated ALT level in blood donors are known to be alcohol consumption and obesity, and to elucidate whether or not a screening test for HEV infection is required for blood donors, taking into consideration the geographic region in Japan.

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一般的名称	乾燥濃縮人血液凝固第Ⅷ因子	研究報告の公表状況	第52回日本輸血学会総会(札幌、2004年6月23日～25日), P17-0	公表国 日本
販売名(企業名)	クロスエイトM250　(日本赤十字社) クロスエイトM500　(日本赤十字社) クロスエイトM1000　(日本赤十字社)			

研究報告の概要

2002年に北海道で、本邦初の輸血後E型肝炎症例が確認されたことから、非B非C型の肝炎ウイルスによるリスクは今なお否定できない。今回、北海道内の肝機能異常献血者を対象に各種肝炎ウイルス感染の実態について調査を行った。北海道で献血されたB型およびC型肝炎の血清学的マーカー陰性の献血者検体のうち、2000年4月から2003年9月までの期間に、肝機能検査でALT値500 IU/L以上（47例）、および200 IU/L以上500 IU/L未満（90例）を示した検体について、Real-time PCR法およびRT-PCR法により検査した。更に陽性となった検体については、遺伝子解析および各種抗体検査を行った。ALT値500 IU/L以上の47例中、A，B，CおよびE型肝炎ウイルス核酸は、各々1例(2.1%)，0例(0%)，1例(2.1%)および9例(19.1%)検出された。またALT値200 IU/L以上500 IU/L未満の90例については、いずれの肝炎ウイルスも検出されなかった。HEV RNA陽性9例を解析した結果、genotypeⅢが6例、genotype IVが3例であった。輸血用血液に対するALT検査は、現在スクリーニング検査が導入されていないA型およびE型肝炎ウイルスの輸血感染リスクの低減に有効であることが示唆された。

使用上の注意記載状況・その他参考事項等

クロスエイトM250
クロスエイトM500
クロスエイトM1000
血液を原料とすることに由来する感染症伝播等
理論的なvCJD等の伝播のリスク

報告企業の意見	今後の対応
北海道内の肝機能異常献血者を対象に各種肝炎ウイルス感染の実態について調査を行ったところ、ALT値500IU/L以上の47例中からA，B，CおよびE型肝炎ウイルス核酸が、各々1例(2.1%)，0例(0%)，1例(2.1%)および9例(19.1%)ずつ検出された。したがって、ALT高値の献血者血液を除外することにより各種肝炎ウイルスの輸血感染を未然に防止可能であることが示唆される。	HEVは脂質膜の無いRNAウイルスである。これまで、本製剤によるHEV感染の報告はない。本製剤の製造工程には、平成11年8月30日付医薬発第1047号に沿ったウイルス・プロセスバリデーションによって検証された2つの異なるウイルス除去・不活化工程が含まれていることから、本製剤の安全性は確保されており、念のため情報収集に努めるも、今後特別の対応を必要としない。なお、最終製品10ロットについてはHEV NAT陰性であることを確認している。

P17-O　北海道内の肝機能異常献血者における肝炎ウイルス感染調査

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【目的】輸血用血液のスクリーニング検査としての alanine aminotransferase（ALT）検査は，当初非A非B型肝炎検査を補うものとして導入されてきたが，血清学的検査法の開発改良や核酸増幅検査（NAT）の導入等により，欧米では最近その必要性について議論されてきている．しかしながら，一昨年に当センターで本邦初の輸血後E型肝炎症例が確認され，非B非C型の肝炎ウイルスについてのリスクは今なお否定できない現状である．今回，北海道内の肝機能異常献血者を対象に各種肝炎ウイルス感染の実態について調査を行ったので報告する．
【方法】北海道で献血されたB型およびC型肝炎の血清学的マーカーが陰性の献血者検体のうち，2000年4月から2003年9月までの期間に，肝機能検査でALT値500IU/L以上(47例)，および200IU/L以上500IU/L未満(90例)を示した検体について，Real-time PCR法およびRT-PCR法によりHAV RNA，HBV DNA，HCV RNAおよびHEV RNAの検査を実施した．さらに陽性となった検体については，遺伝子解析および各種抗体検査を行った．
【結果】ALT値500IU/L以上の47例中，A，B，CおよびE型肝炎ウイルス核酸は，各々1例（2.1%），0例（0%），1例（2.1%）および9例（19.1%）検出された．またALT値200IU/L以上500IU/L未満の90例については，いずれの肝炎ウイルスも検出されなかった．HEV RNA陽性9例を解析した結果，genotype IIIが6例，genotype IVが3例であった．
【総括】輸血用血液のALT検査は，現在スクリーニング検査が行われていないA型およびE型肝炎ウイルスの感染リスクの減少に有効であることが示唆された．