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一般的名称	人血清アルブミン	研究報告の公表状況	Marisuy JM, Huynh A, Abravanel F, Recher C, Peron JM, Izopet J. Clin Infect Dis. 2009 Feb 1;48(3):373-4.	公表国 フランス
販売名（企業名）	赤十字アルブミン20（日本赤十字社） 赤十字アルブミン25（日本赤十字社）			

研究報告の概要

○病棟におけるE型肝炎ウイルスの患者間感染の分子学的エビデンス
血液疾患病棟で急性白血病の33才の男性が急性肝炎を発症し、患者の血漿及び糞便検体からE型肝炎ウイルス（HEV）遺伝子が検出されHEV感染症と診断された。患者にHEV流行地域への旅行歴、野生動物・ペットとの接触歴及び生肉・貝類の摂食歴はなく、また、複数回の輸血を受けていたが供血者検体の検査結果はHEV RNA陰性であった。
この病棟には、急性E型肝炎を発症し、ほぼ1年間にわたって血液と糞便の両方にHEVを排出した44才のリンパ腫の男性患者がおり、最後の病棟滞在時期がHEVに感染した患者と重なった。
PCRの結果、2人の患者のHEVはいずれもgenotype 3fに属し、シーケンスの同一性は97.8% ～98.6%であった。
2人の患者は地理的に異なった地域に住み、HEVの共通感染源に暴露されていなかったため、2人が同時に病棟に滞在した間に感染が起こったことが示唆される。
病棟での遡及的調査で一般的な衛生予防措置上の重大な違反は確認されなかったが、(1) 免疫抑制患者はウイルスに感染しやすい、(2) 感染患者は長期間にわたり二次感染につながるHEVを排出する、(3) ウイルスは無機物表面で長期間生存する、(4) HEVに対してワクチンは利用できないことから、我々は、免疫抑制患者が治療される病棟でE型肝炎の症例が発生した場合には、一般的な衛生予防措置は強化されなければならないと結論する。

報告企業の意見	今後の対応
急性白血病の33才の男性がE型肝炎を発症し、HEV遺伝子検査の結果、重複する時期に同じ病棟に入院していた別のE型肝炎患者から感染したことが示唆されたとの報告である。 免疫抑制状態にある患者では、食物、輸血以外の経路によるHEV伝播の可能性についても、配慮する必要があるものと考える。 HEVは脂質膜のないRNAウイルスである。本剤の製造工程にはコーン分画及び液状加熱の2つのウイルス除去・不活化工程が含まれている。疫学的に見て、血漿分画製剤で最も長い歴史を持つアルブミンでは世界的にHEV感染の報告はないことから、本剤の安全性は確保されていると考える。	本剤の安全性は確保されていると考えるが、今後もHEV感染の実態に関する情報の収集及び安全対策に努める。なお、日本赤十字社では、北海道における輸血後HEV感染報告を受け、献血者の疫学調査や、北海道で研究的NATを実施している。

使用上の注意記載状況・その他参考事項等

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血液を原料とすることに由来する感染症伝播等

6

ceftriaxone, and benzylpenicillin were administered empirically. MRI revealed meningeal enhancement around the brain stem, contiguous with a markedly edematous cervical cord and "sugar coating" of the entire cervico-thoraco-lumbar cord (figure 1). A clinical diagnosis of necrotizing varicella myelitis with meningoencephalitis was made. Progressive bulbar palsy and respiratory failure developed. Because of the extremely poor prognosis, the patient was palliated, and she died 60 h after arrival at our institution.

Varicella-zoster virus (VZV) was detected by PCR of the patient's CSF and skin vesicle specimens. Postmortem examination confirmed extensive infarction and necrosis of the entire spinal cord due to necrotizing vasculitis in association with a lymphocytic meningitis.

This fulminant presentation of VZV necrotizing myelitis has been reported infrequently in profoundly immunosuppressed HIV-infected individuals in the pre-ART era [1–4]. To our knowledge, this is the first occurrence in a moderately immunosuppressed individual in the post-ART era. Its occurrence shortly after a change in ART raises the possibility that this is a manifestation of VZV immune restoration disease (IRD).

VZV complications involving the CNS are estimated to occur in 2% of patients with HIV/AIDS, with 4 other recognized variants, including multifocal encephalitis, ventriculitis, focal necrotizing myelitis, and vasculopathy that leads to cerebral infarction [2, 4–6]. Prognosis of VZV necrotizing meningomyelitis is extremely poor, with a median survival of 16 days [7].

The diagnosis of IRD is usually contingent on a clear response to ART with ≥1-log reduction in HIV RNA level [8]. Assessment of HIV RNA level was not performed, but a significant decrease is highly likely, given the initiation of 2 new classes of ART 2 weeks before presentation. The patient's moderate immunosuppression and decrease in $CD4^+$ T cell count after the change of ART regimen does not preclude IRD [9]. Compartmentalization of VZV IRD in the CNS has been suggested and may explain the profound CNS changes in the absence of significant rash or systemic symptoms [10].

Necrotizing myelitis is a devastating complication of VZV. In the context of immunosuppression, necrotizing myelitis may represent a new manifestation of VZV IRD.

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Christina C. Chang,[1] Catriona McLean,[2] Olga Vujovic,[1] Adam J. Jenney,[1] Martin Short,[3] Stuart Lyon,[4] Elsdon Storey,[5] and Sharon R. Lewin[1,5]

[1]Infectious Diseases Unit and Departments of [2]Anatomical Pathology, [3]Neurology, and [4]Radiology, The Alfred Hospital, and [5]Department of Medicine, Monash University, Melbourne, Victoria, Australia

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Reprints or correspondence: Prof. Sharon R. Lewin, Infectious Diseases Unit, The Alfred Hospital, Commercial Rd., Melbourne 3004, Victoria, Australia (Sharon.lewin@med.monash.edu.au).

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Molecular Evidence of Patient-to-Patient Transmission of Hepatitis E Virus in a Hematology Ward

To the Editor—A 33-year-old man receiving treatment for acute leukemia in a hematological ward developed acute hepatitis (aspartate aminotransferase level, 1215 IU/L; alanine aminotransferase level, 2960 IU/L). Test results for viral markers (i.e., anti–hepatitis A virus IgM, hepatitis B virus surface antigen and DNA, anti–hepatitis C virus antibodies, and hepatitis C virus RNA) were negative; nonviral causes of liver disease, such as autoimmunity, toxic or iatrogenic hepatitis, and metabolic disorders, were excluded. A diagnosis of hepatitis E virus (HEV) infection was made after the detection of the HEV genome in plasma and stool samples from the patient [1]. Anti-HEV IgG was detected 2 weeks after the onset of the illness and persisted throughout.

The patient had not traveled in areas where HEV was endemic and declared that he had had no contact with wild or domestic animals. He had not eaten raw meat or shellfish. No symptomatologic cases of hepatitis E had been reported in his family or in nurses and medical staff during the same period. The patient had received many transfusions from blood

donors. Because HEV can be transmitted through transfusion [2], all donors' samples were tested and had negative results for HEV RNA.

Medical records from the hematology ward indicated that a 44-year-old man with lymphoma had developed acute hepatitis E 1 year earlier. This patient was hospitalized repeatedly for short periods during that year until his lymphoma was cured. The patient did not recover after the acute phase of hepatitis, and he excreted HEV in both blood and stool for almost a year. His last stay in the ward overlapped with that of the other patient who was infected with HEV.

We therefore looked for a link between the HEV strains from the 2 patients with use of samples that were collected at the time of diagnosis of acute hepatitis E. PCR products amplified from 3 distinct regions of the HEV genome were sequenced. Both strains belonged to HEV genotype 3f. Phylogenetic analyses including HEV sequences from local and GenBank reference strains indicated that the strains from the 2 patients were closely related. The nucleotide identity of the 3 HEV sequences from the 2 patients was 97.8%–98.6%. Both strains also harbored the same insertion in the ORF1 hypervariable region that differed from the reference sequences. Because the 2 patients lived 250 km apart in 2 geographically distinct areas and had not been exposed to a common source of HEV, transmission probably occurred during their overlapping stays in the hospital that occurred 3 weeks prior to the onset of hepatitis E in the patient with acute leukemia.

A retrospective audit of the ward identified no major breaches of universal hygiene precautions. However, a lapse in strict hygiene procedures could be the cause of HEV contamination through enteric transmission, because HEV can persist for weeks on inanimate surfaces [3]. Parenteric iatrogenic transmission has also been suggested [4].

We conclude that universal hygiene precautions must be reinforced when cases of hepatitis E occur in medical wards where immunosuppressed patients are treated. There are several reasons for reinforced precautions: (1) immunosuppressed patients are highly susceptible to viral infections; (2) infected patients excrete HEV for a prolonged time, which results in a high risk of secondary transmission; (3) the virus persists for long periods on inanimate surfaces; and (4) no vaccine is available against HEV, although a phase-2 vaccine trial has had recent success [5].

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Jean-Michel Mansuy,[1] Anne Huynh,[2] Florence Abravanel,[1,4] Christian Recher,[2] Jean Marie Peron,[3] and Jacques Izopet[1,4]

Departments of [1]Virology, [2]Hematology, and [3]Hepatogastroenterology, and [4]Institut National de la Santé et de la Recherche Médicale U563, Centre Hospitalier Universitaire Purpan, Toulouse, France

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Reprints or correspondence: Dr. Jean-Michel Mansuy, Dept. of Virology, Centre Hospitalier Universitaire Purpan, 330 ave. de Grande Bretagne, 31059, Toulouse cedex, France (mansuy.jm@chu-toulouse.fr).

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販売名(企業名)	赤十字アルブミン20(日本赤十字社) 赤十字アルブミン25(日本赤十字社)			日本

研究報告の概要

○日本のALT高値献血者のE型肝炎ウイルス陽性率についての全国調査
背景:我々は日本における輸血後E型肝炎感染症例2例を報告したが、日本の献血者のE型肝炎ウイルス(HEV)陽性率は十分明らかになっていない。
試験デザインおよび方法:すべての赤十字血液センターから、ALT高値のため献血不適となった献血者の血液検体を収集し、HEV試験に供した。
結果:北海道のALT高値(500 IU/L超)献血者41名では、8検体(19.5%)にHEV RNAが検出された。日本全土のALT高値(200 IU/L超)献血者1,389名では、HEV RNA、IgM-HEV抗体、IgG-HEV抗体陽性検体数が、それぞれ15(1.1%)、14(1.0%)、45(3.2%)であった。RNA陽性献血者はほとんど男性であり、日本のどの地域にも認められたが、北海道を含む東日本の方が多く、西日本の方が少ない傾向であった。HEV RNA陽性であった23検体のうち、19検体はgenotype 3、4検体はgenotype 4であった。分離株9株のDNA配列は、既知のブタHEV分離株と98.5%以上の相同性を示した。ALT値61～199IU/Lの献血者1,062名では、IgM-HEV抗体およびIgG-HEV抗体陽性検体の割合はそれぞれ0.1および2.7%であったが、これらの検体はHEV RNA陰性であった。
結論:日本各地のALT高値献血者にHEVマーカー(HEV RNAおよび抗HEV抗体)が認められ、いずれのマーカーとも、東日本の方が西日本より高かった。

使用上の注意記載状況・その他参考事項等

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報告企業の意見	今後の対応
日本全国でALT高値のため献血不適となった献血者の血液検体に、HEVマーカー(HEV RNAおよび抗HEV抗体)が認められ、いずれのマーカーとも東日本の方が西日本より高かったとの報告である。 HEVは脂質膜のないRNAウイルスである。本剤の製造工程にはコーン分画及び液状加熱の2つのウイルス除去・不活化工程が含まれている。疫学的に見て、血漿分画製剤で最も長い歴史を持つアルブミンでは世界的にHEV感染の報告はないことから、本剤の安全性は確保されていると考える。	本剤の安全性は確保されていると考えるが、今後もHEV感染の実態に関する情報の収集及び安全対策に努める。なお、日本赤十字社では、北海道における輸血後HEV感染報告を受け、献血者の疫学調査や、北海道で研究的NATを実施している。

A nationwide survey for hepatitis E virus prevalence in Japanese blood donors with elevated alanine aminotransferase

Hidekatsu Sakata, Keiji Matsubayashi, Hiromi Takeda, Shinichiro Sato, Toshiaki Kato, Satoru Hino, Kenji Tadokoro, and Hisami Ikeda

BACKGROUND: Although we reported two cases of transfusion-transmitted hepatitis E in Japan, the prevalence of hepatitis E virus (HEV) in Japanese blood donors is not very clear.

STUDY DESIGN AND METHODS: Blood samples of donors who were deferred from donation because of elevated alanine aminotransferase (ALT) levels were collected from all Japanese Red Cross Blood Centers and subjected to HEV tests.

RESULTS: Among the 41 donors with elevated ALT levels higher than 500 IU per L in Hokkaido, HEV RNA was detected in 8 (19.5%) samples. In 1389 donor samples with ALT levels of higher than 200 IU per L in nationwide Japan, the numbers of positive HEV RNA, immunoglobulin M (IgM) anti-HEV, and immunoglobulin G (IgG) anti-HEV samples were 15 (1.1%), 14 (1.0%), and 45 (3.2%), respectively. Although RNA-positive donors were predominantly male and found in any geographic area of Japan, they tended to be higher in number in eastern Japan including Hokkaido and lower in number in western Japan. Of the 23 HEV-positive samples, 19 were Genotype 3 and 4 were Genotype 4. DNA sequences of the 9 isolates showed more than 98.5 percent homology with the known swine HEV isolates. In 1062 donor samples with ALT levels of 61 to 199 IU per L, the percentages of IgM and IgG anti-HEV–positive samples were 0.1 and 2.7 percent, respectively, although there was no HEV RNA–positive sample.

CONCLUSION: HEV markers (HEV RNA and anti-HEV) were detected in donors with elevated ALT levels who were widely distributed over Japan. The prevalence and incidence were higher in eastern Japan than in western Japan.

Although hepatitis E virus (HEV) is an emerging pathogen of enterically transmitted viral hepatitis in endemic areas, its infection is now recognized as a form of zoonosis in which swine, wild boar, and deer act as reservoirs for human infection in Japan.[1-8] HEV subgenomic sequencing studies have revealed a close relationship between the strains infecting humans and those infecting pigs. Accumulating evidence suggests that eating undercooked meat and viscera of pig and other animals is associated with a high risk of acquiring HEV infection. The HEV-infected individuals show transient viremia, which suggests the potential risk of a blood-borne route of HEV infection.[9-12] We previously reported two cases of transfusion-transmitted acute hepatitis E in Hokkaido, Japan.[9,12] In both cases, sequence analyses showed that the isolates of both donors and patients appeared to be identical. Moreover, HEV RNA has been reported to be present among some blood donors with elevated alanine aminotransferase (ALT) levels in Japan.[9,13,14] Although HEV was previously considered to be endemic only in developing countries, approximately 13 percent of the non-A, non-B, and non-C acute hepatitis cases were caused by HEV in Japan, a developed country.[15] However, no report has been available on a nationwide survey for HEV prevalence in Japan.

ABBREVIATIONS: B19 = human parvovirus B19; EBV = Epstein-Barr virus; HAV = hepatitis A virus; HEV = hepatitis E virus; JRC = Japanese Red Cross; RT = room temperature.

From the Japanese Red Cross Hokkaido Blood Center, Sapporo; and the Blood Service Headquarters, Japanese Red Cross Society, Tokyo, Japan.

Address reprint requests to: Hidekatsu Sakata, Hokkaido Red Cross Blood Center, 2-2 Yamanote, Nishi-ku, Sapporo 063-0002, Japan; e-mail: sakata@hokkaido.bc.jrc.or.jp.

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