医薬品 研究報告 調査報告書

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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	Sato S, Matsubayashi K, Sakata H, Takeda H, Kato T, Ikeda H. XIVth Regional Congress of the ISBT, Asia; Nov 14-18, 2009; Nagoya.	公表国 日本	
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) 赤十字アルブミン20%静注4g/20mL(日本赤十字社) 赤十字アルブミン20%静注10g/50mL(日本赤十字社) 赤十字アルブミン25%静注12.5g/50mL(日本赤十字社)					

研究報告の概要

○E型肝炎ウイルス(HEV)陽性血液の輸血を受けた受血者のルックバック調査

目的:2004年までに輸血によるHEV感染症例を少なくとも2例観察した。それ以来、日本赤十字社では北海道において、HBV/HCV/HIV-1に加えて、HEV NATスクリーニング検査を行っている。本試験の目的は、HEV陽性血液の輸血を受けた受血者のルックバック検査を行うことにより、輸血によるHEV伝播が生じる要因を検討することである。

材料および方法:2005年1月～2006年3月まで、全ての供血者検体について、HEV-NATスクリーニング検査を行った。しかし、一部の血液製剤は検査結果が判明する前に輸血されていた。2006年4月以降、北海道で採血された血液製剤はHEV-NATスクリーニング後に供給されている。過去の供血保管検体のルックバック検査で判明したHEV陽性血液製剤の輸血を受けた受血者の肝機能およびHEVマーカー(抗HEV抗体、HEV-RNA)を検査した。

結果:ルックバック検査により、HEV陽性血液製剤の輸血を受けた受血者13名が判明した。輸血前検体がHEV RNAまたはHEV抗体陽性だった者はいなかった。HEV感染の兆候を示した4名の受血者のうち、3名がE型肝炎を発症し、1名は一過性のALT上昇(ピーク:611IU/mL)を示した。4本の輸血済み血液製剤におけるHEVウイルス量とgenotypeは、5.4 (G4), 5.5 (G3), 5.8 (G4), 6.8 (G3) log/bagだった。HEV感染を起こさなかった受血者4名に輸血された4製剤では、<4.4 (G3)、<4.4 (G3)、4.3 (G4)、5.5 (G3) log/bagであった。5名は輸血直後に亡くなり、評価できなかった。

結論:血液製剤中のHEV高値(>5.4log/bag)がウイルス伝播に関連付けられると思われた。また、遺伝子型4は遺伝子型3より毒性が高い可能性がある。

使用上の注意記載状況・その他参考事項等

赤十字アルブミン20
赤十字アルブミン25
赤十字アルブミン20%静注4g/20mL
赤十字アルブミン20%静注10g/50mL
赤十字アルブミン25%静注12.5g/50mL

血液を原料とすることに由来する感染症伝播等

報告企業の意見

HEV陽性血液の輸血を受けた受血者のルックバック調査から、血液製剤中のHEV高値(>5.4log/bag)がウイルス伝播に関連付けられると考えられたとの報告である。

本剤の製造工程にはコーン分画および液状加熱の2つのウイルス除去・不活化工程が含まれている。最近ある遺伝子型のHEVは耐熱性であるとの成績が発表され、液状加熱の有効性に一部疑念を生じている。しかし、血漿分画製剤で最も長い歴史を持つアルブミンにはHEVの侵淫度が遥かに高い過去から現在に至るまで世界的にHEV感染例がないとの疫学的事実があることから、本剤の安全性は確保されていると考える。

今後の対応

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。

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Monday: Parallel Session S2: TTI

2A-S02-01

PREVALENCE OF HEV INFECTION AMONG JAPANESE BLOOD DONORS

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Hepatitis E virus (HEV) infection had been recognized to be extremely rare in industrialized countries. Recently, however, increasing reports of hepatitis E including transfusion-transmitted cases are reported in Japan and other industrialized countries.

So far, we have experienced four cases of transfusion-transmitted hepatitis E (TTHE). In 2004, we reported the first molecularly confirmed case of TTHEV, where infection route of the causative donor was not very clear. Then surveys of HEV prevalence in blood donors were undertaken and showed that higher prevalence of IgG anti-HEV in eastern Japan, and the positive rates in female donors were lower than that in male donors. There is a clear age-dependency in IgG anti-HEV prevalence in blood donors in Japan.

Meanwhile, we experienced the second case of TTHE. The causative donor had a barbecue party at a restaurant with his family and enjoyed yakiniku dinner including pig liver and/or intestines. Six of whom including the causative donor and his father were positive for IgM anti-HEV. The father died of fulminant hepatitis E after the barbecue party. HEV isolates from the donor also showed 99.9% homology with that from his father based on nearly entire HEV genome and was classified into genotype 4 that was indigenous to Hokkaido.

This case suggest that there are HEV carriers among blood donors in Japan and HEV infection does not necessarily lead to hepatitis symptoms. For this possibility, we decided to implement preliminary HEV NAT screening in Hokkaido in 2005. However, after the start of this preliminary NAT, we experienced two additional cases of TTHE in 2005 and 2006 because of the delay of the results of NAT. It took almost a week to obtain the results and some blood products, especially platelets concentrates, were already transfused before the NAT. In 2006, we implemented real-time HEV NAT screening.

Up to the end of 2008, the frequency of HEV RNA-positive donors is approximately 1/7700. Male positive donors were dominant. Also, genotype 3 was a dominant genotype. About half of the donors showed the elevation of their ALT level above 45 IU/l during follow-up period. In all of the HEV RNA-positive donors, ALT level came down below 45 IU/l within 50 days after their donation. The HEV RNA-positive donors were also followed-up for their HEV RNA. In all of them, HEV RNA became under the detectable level up to 62-76 days after the donation. The significant increase of the virus level after the donation was observed in 43% of the donors. Compared to hepatitis E patients, a) HEV NAT-positive donors were younger; b) genotype 3 is dominant in contrast to genotype 4 dominance in hepatitis patients. Sequence analyses showed that most of the representative strains from HEV NAT-positive blood donors exhibit over 99% sequence homology with the corresponding swine isolates suggesting that most of HEV are from pigs through food-borne routes.

2A-S02-02

EPIDEMIOLOGY OF HEV INFECTION AMONG BLOOD DONORS IN HOKKAIDO, JAPAN

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Background: Recent studies have revealed that indigenous hepatitis E virus (HEV) strains cause domestic hepatitis E in industrialized countries including Japan. Several cases of transfusion-transmitted hepatitis E have been reported there.

Aims: To clarify the characteristics of HEV infection among blood donors in Hokkaido, Japan, and to consider preventive measures for HEV transmission via blood transfusion.

Methods: A total of 1,098,989 serum or plasma samples from blood donors in Hokkaido from January 2005 to December 2008 were tested for the presence of HEV RNA by real-time reverse transcription (RT)-PCR using 20-pooled samples. Blood samples positive for HEV RNA were tested for the presence of IgM and IgG anti-HEV by ELISA, and measured for HEV viral load by real-time RT-PCR. HEV strains from the HEV positive donors were phylogenetically analyzed by direct sequencing of RT-PCR products of regions of HEV ORF1 and ORF2. Questionnaire was mailed to the HEV RNA positive donors to collect the data on their history of intake of animal meats within 2 months previous to the donation. The donors positive for HEV RNA were looked-back and followed-up before and after their positive donations.

Results: HEV RNA was detected in 142 (105 males and 37 females) donors and the overall prevalence of the HEV infected donors was 0.013% [0.015% in males and 0.009% in females] between 2005 and 2008 in Hokkaido. The yearly prevalence of HEV RNA-positives in male and female donors were 0.018% and 0.011% in 2005, 0.016% and 0.013% in 2006, 0.017% and 0.003% in 2007, and 0.012% and 0.009% in 2008, respectively, suggesting progressive expansion of HEV infection in male donors. No clear seasonality of the infection was observed during the period. Of the 142 donors, 109 (77%) donors had neither IgM nor IgG antibodies against HEV at their HEV RNA-positive donations. The strains detected in the donors were segregated into genotype 3 (132) and genotype 4 (6), which were assumed to be Japan-indigenous strains. Of the 103 donors responding to the questionnaire, 71 (69%) had a history of eating the animal viscera such as intestine and/or liver. Of the 39 donors followed-up at least twice a month after the donation, 21 (54%) showed transient elevations of ALT higher than 45 IU/L.

Conclusions: A total of 142 sporadic HEV infection were observed among blood donors during 2005 through 2008 in Hokkaido with male superiority in the prevalence, which were caused by Japan-indigenous HEV strains and appeared to be associated to ingestion of the animal viscera. HEV NAT screening may be more adequate to exclude the HEV-infected donors than HEV antibody screening.

2A-S02-03

LOOK-BACK STUDY ON RECIPIENTS WHO WERE TRANSFUSED HEPATITIS E VIRUS (HEV)-POSITIVE BLOOD

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Objective: Up to 2004, we observed at least two cases of transfusion-transmitted HEV infection. Since then, we have implemented NAT screening for HEV in addition to HBV/HCV/HIV-1 in Hokkaido area. The purpose of this study is to evaluate the factor(s) that may lead to transfusion-transmission of HEV by looking back the recipients who were transfused with HEV-positive blood.

Materials and methods: From 2002 to 2004, donor samples with high ALT (>200 IU/mL) were tested for HEV-RNA. From 2005.1-2006.3, all donor samples were screened by HEV-NAT. However, a part of blood products were already transfused before the NAT results turned out. Since 2006.4, blood products have been issued after HEV-NAT screening. The recipients of HEV-positive blood products that were disclosed mostly by look-back

study with stored samples at previous donations were tested for HEV markers including antibody to HEV and HEV-RNA as well as liver functions.

Results: Look-back study disclosed 13 recipients who were transfused HEV-positive blood products. None of them was positive for HEV RNA or anti-HEV in pretransfusion samples. Of four recipients showing signs of HEV infection, three developed hepatitis E and one showed a transient elevation of ALT (peak: 61 IU/mL). The amount and genotypes of HEV in the four transfused blood products were 5.4 [G4], 5.5 [G3], 5.8 [G4] and 6.8 [G3] log/bags, while four blood products that did not cause HEV infection in four recipients contained <4.4 [G3], <4.4 [G3], 4.3 [G4] and 5.5 [G3] log/bags. Five of the 13 recipients died soon after transfusion and were not able to be evaluated for HEV transmission.

Conclusion: The higher amount of HEV (>5.4 log/bag) in blood products may be associated with the virus transmission. Also genotype 4 may be more virulent than genotype 3.

2A-S02-04

ESTABLISHMENT OF A KOREAN HBSAG LOW TITER PERFORMANCE PANEL FOR QUALITY CONTROL OF HBV DIAGNOSTIC KITS

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Background: Currently, International Standards or commercially available reference materials are used for the validation or quality assessment of domestic *in-vitro* diagnostic medical devices. However, due to their high cost and limited quantity a sustainable supply cannot be guaranteed. Also, these materials might not reflect the viral characteristics common in Korea. This study was conducted to establish a low titer performance panel to be used for quality control of HBV diagnostic kits.

Materials and methods: 371 plasma units with OD values less than 1.0 on EIA screening and 105 units with S/C ratio less than 10.0 on CIA were collected from Korean Red Cross blood centers. HBsAg testing with three EIA assays [GENEDIA HBsAg EIA 3.0 (Green Cross MS), BIO-RAD Monolisa HBsAg Ultra (BIO-RAD), and Murex HBsAg V.3 (Murex Biotec.)] and one CIA assay [Architect HBsAg (Abbott)] was performed on all units. Units with reactive results on CIA or units that were reactive on more than two assays were further subjected to HBV DNA quantification. HBV genotyping and subtyping. Units reactive on HBV DNA quantification were confirmed for HBsAg by HBsAg neutralization. The reactivity of a commercial low titer performance panel to various HBsAg assays was determined to be used as a selection criterion for candidate materials. Based on these results, 13 HBsAg positive units and two HBsAg negative units were selected as candidates. After addition of Bromidox as a preservative, the candidate materials were distributed into the final containers. Collaborative study with seven participating laboratories was conducted using two CIA assays [Architect HBsAg, Prism HBsAg (Abbott)], one ECA assay [Elecsys HBsAg (Roche Diagnostics)], one MEIA assay [AxSYM HBsAg V.2 (Abbott)], and three EIA assays [Retrieval Enzygnost HBsAg 5.0 (Dade Behring), BIO-RAD Monolisa HBsAg Ultra, Murex HBsAg V.3].

Results: Based on the results of the collaborative study, 11 HBsAg positive units and two HBsAg negative units were selected to constitute the low titer performance panel. The mean S/C ratio of HBsAg positive units was less than 10.0 and mean concentration of HBsAg of ten HBsAg positive units was less than 1.0 IU/mL. The panel members were of genotype C, subtype adr and ayr.

Conclusions: As a result of this study, a low titer HBsAg performance panel for quality control of HBV diagnostics kits has been established. This will enable supply of quality control materials at an affordable cost on a long-term basis.

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2A-S02-05

STATUS OF HEPATITIS VIRAL MARKERS CALCULATED FROM PRETRANSFUSION VIRAL MARKER TEST RESULTS OF PATIENTS AT ASAHIKAWA MEDICAL COLLEGE HOSPITAL

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Background: In October 2004, the Japanese government recommended that six viral markers be tested in patients scheduled for transfusion: hepatitis B surface antigen (HBsAg), antibody to HBsAg (HBsAb), antibody to HBV core antigen (HBcAb), antibody to hepatitis C virus (HCVAb), HCV core antigen (HCVcAg), and antibody to human immunodeficiency virus (HIVAb). At our hospital, we started testing these markers of pretransfusion patients in July 2005.

Aim: Japan is regarded as an endemic area of HBV and HCV. Therefore, it is considered that many Japanese are in a state of asymptomatic or latent HBV or HCV infection. At our hospital, a series of hepatitis marker tests (HBsAg, HBsAb, HBcAb, HCVAb, HCVcAg) was prepared. Physicians used this set menu to evaluate the status of hepatitis viral markers before transfusion. For this study, we calculated the status of hepatitis viral markers at our hospital from results of the pretransfusion viral marker tests conducted routinely before transfusion.

Materials and methods: Hepatitis viral markers of 3353 patients during July 2005 and December 2008 were evaluated. Data were collected from the database of our hospital information system. Measurement methods and positive values were the following: HBsAg (CLIA, >0.5 IU/ml); HBsAb (CLIA, >10 mIU/ml), HBcAb (CLEIA, >70%[NH]), HCVAb (CLIA, >1.0 C.O.I), HCVcAg (CLEIA, >50 fmol/l).

Results: The cases were those of 1721 men and 1632 women. Their average age was 59.9 years (0-96 yrl). The positive rates of HBsAg, HBsAb, HBcAb, HCVAb, and HCVcAg are presented as a table. The rate of positive HBsAb with negative HBcAb was 8.9%, the rate of negative HBsAb with positive HBcAb was 9.9%, the rate of both positive was 20.3%, and the rate of both negative was 60.9%. Among 204 HCVAb positive cases, 118 cases were HCVcAg positive. The others were HCVcAg negative. No HCVcAg positive case was HCVAb negative. Among the 107 cases that were positive for both some HBV marker and some HCV marker, 88 cases were HBcAb positive.

Summary: We determined the status of hepatitis viral markers of a hospital based on results of pretransfusion viral tests. We assessed the status of nationwide or latent hepatitis viral infection from a hospital level to a nationwide level if a pretransfusion viral marker test were strictly implemented for all patients scheduled for transfusion. Furthermore, these data provide background information for developing preventive measures against hepatitis viral infections, including transfusion-transmitted infections and hospital infections.

Table 1. Age related positive rate of viral marker

age	number of pts.	positive rate of viral marker				
		HBsAg	HBsAb	HBcAb	HCVAb	HCVcAg
0-9 yr	87	1.1%	6.9%	3.4%	0.0%	0.0%
10-19 yr	42	0.0%	2.4%	0.0%	2.4%	0.0%
20-29 yr	130	1.5%	12.3%	4.6%	1.6%	0.0%
30-39 yr	266	2.3%	14.7%	6.6%	1.5%	0.4%
40-49 yr	285	3.2%	26.0%	15.4%	3.5%	1.1%
50-59 yr	535	6.5%	30.1%	32.5%	4.3%	3.1%
60-69 yr	755	7.3%	38.7%	41.3%	8.5%	4.7%
70-79 yr	900	1.6%	32.2%	34.4%	9.1%	6.1%
80-89 yr	323	1.2%	38.4%	40.9%	7.4%	3.1%
over 90 yr	27	0.0%	25.9%	29.6%	0.0%	0.0%
total	3353	3.7%	29.2%	30.2%	6.3%	3.6%

別紙様式第2-1

No. 17

医薬品 研究報告 調査報告書

識別番号・報告回数			報告日	第一報入手日	新医薬品等の区分	総合機構処理欄
				2009. 12. 20	該当なし	
一般的名称	人血清アルブミン		研究報告の公表状況	Iwanaga M, Koga Y, Soda M, Inokuchi N, Sasaki D, Hasegawa H, Yanagihara K, Yamaguchi K, Kamihira S, Yamada Y. 51st ASH Annual Meeting and Exposition; 2009 Dec 5-8; New Orleans.	公表国 日本	
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) 赤十字アルブミン20%静注4g/20mL(日本赤十字社) 赤十字アルブミン20%静注10g/50mL(日本赤十字社) 赤十字アルブミン25%静注12.5g/50mL(日本赤十字社)					

研究報告の概要

○ヒトT細胞白血病ウイルス1型(HTLV-1)有病率の傾向および長崎(日本)の成人T細胞白血病/リンパ腫(ATL)の発症率:病院ベースおよび集団ベース試験

序論:HTLV-1の有病率は、主に献血者の年齢別抗体陽性率により評価されATL発症率が推定されてきたが、献血者集団の特性から過小評価されている可能性がある。献血者以外のHTLV-1キャリアの出生年別ATL発症率データは少ない。

方法:2000～2007年に長崎大学病院を受診した患者10,261名(男性:5,523、女性:4,737)のHTLV-1抗体検査のデータ、及び長崎県がん登録中の長崎市で診断されたATL症例360例(男性:188、女性:172)のデータを評価した。長崎市の2006国勢調査人口に病院ベースの陽性率データを適用して、HTLV-1キャリアの出生年別ATL発症率を推定した。

結果:患者10,261名のうち、HTLV-1抗体陽性者は1,392名(男性:653、女性:739)、陽性率は13.57%(95%CI:12.90-14.23%)であった。陽性率は女性が有意に高かった(15.60%対11.82%、P<0.0001)。出生年別抗体陽性率は、18.69%(1926年以前)、17.83%(1927-1936)、15.91%(1937-1946)、13.80%(1947-1956)、9.19%(1957-1966)、4.07%(1967-1976)、2.07%(1977-1986)、0%(1987年以降)であった(有意な減少傾向:P < 0.0001)。長崎市の出生年別の年間HTLV-1キャリア推定人数は、それぞれ5257、8093、8151、8083、4434、2180、785、0であった。キャリア100,000人あたりの年間ATLL発症率の推定は、それぞれ171、86、41、32、11、0、0、0となった。HTLV-1キャリアの生涯の粗ATL発症リスクは、男性7.29%、女性3.78%と推定された。

結論:本試験の出生年別HTLV-1抗体陽性率は供血者の陽性率より約50%高く、流行地域で高齢者の大規模なキャリア集団が現在も存在することを示唆している。発症予防のためATL発現機序を解明するには更なる試験が必要である。

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

報告企業の意見	今後の対応
長崎大学病院を受診した患者の出生年別HTLV-1抗体陽性率は過去に報告された供血者の陽性率と比べて約50%高く、流行地域において高齢者のHTLV-1キャリアの大規模集団が存在することが示唆されたとの報告である。 HTLV-1は脂質膜を有するRNAウイルスである。垂直感染により日本では古代から広く侵淫しているが、本製剤による感染の報告はない。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とから、本製剤の安全性は確保されていると考える。	日本赤十字社では献血時のスクリーニング法として、より感度の高い化学発光酵素免疫測定法(CLEIA)によるHTLV-1抗体のスクリーニング検査を行っている。今後も引き続き情報の収集に努める。

Blood (ASH Annual Meeting Abstracts) 2009 114: Abstract 1920

Poster Session

NON-HODGKIN'S LYMPHOMA - BIOLOGY, EXCLUDING THERAPY POSTER I

Trends in Human T-Cell Leukemia Virus Type-1 (HTLV-1) Prevalence and the Incidence of Adult T-Cell Leukemia/Lymphoma (ATL) in Nagasaki, Japan: A Hospital-Based and Population-Based Study.

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Abstract 1920

Poster Board I-943

Introduction: The prevalence of HTLV-1 is mostly evaluated by the age-specific seroprevalence in blood donors, and the results have been conventionally used to estimate the age-specific incidence of ATL in Japan. However, the results may be underestimated due to an age limit (16-69 yr) for donation, a healthy donor effect, and a birth cohort effect. Data concerning the birth-year specific incidence of ATL among HTLV-1 carriers other than blood donors are scarce.

Methods: The study evaluated data of the anti-HTLV-1 antibody testing of 10,261 patients (males: 5,523, females: 4,737) who visited the Nagasaki University Hospital during 2000-2007 and data of 360 ATL cases (males: 188, females: 172) who were diagnosed in Nagasaki City (an endemic area in Japan) in a population-based Nagasaki Prefectural Cancer Registry (NPCR). To estimate birth-year specific incidence rates of ATL in population-based HTLV-1 carriers, we used the 2006 census population for Nagasaki City by applying the hospital-based seroprevalence data.

Results: Of 10,261 patients, 1,392 (males: 653, females: 739) were HTLV-1 antibody positive. The overall HTLV-1 seroprevalence was 13.57% (95%CI: 12.90-14.23%). The seroprevalence was significantly higher in females than in males (15.60% vs. 11.82%, P<0.0001). The birth-year specific seroprevalence was 18.69% (before 1926), 17.83% (1927-1936), 15.91% (1937-1946), 13.80% (1947-1956), 9.19% (1957-1966), 4.07% (1967-1976), 2.07% (1977-1986), and 0% (after 1987) (a significantly declining trend: P <0.0001). The estimated annual number of HTLV-1 carriers by birth-year in Nagasaki city was 5257, 8093, 8151, 8083, 4434, 2180, 785, and 0, respectively. Finally, we estimated the annual incidence rate of ATLL per 100,000 HTLV-1 carriers by birth-year; 171 (before 1926), 86 (1927-1936), 41 (1937-1946), 32 (1947-1956), 11 (1957-1966), and 0 (after 1967). The crude lifetime risk of developing ATLL in HTLV-1 carriers was estimated to be 7.29% for males and 3.78% for females.

Conclusions: The birth-year specific HTLV-1 seroprevalnces in the present study were approximately 50% higher than those previously reported in blood donors1 (for example: 6.22% in those born before 1950). Although it is possible that our results are over-estimated2, the present study suggests that there is still a large pool of elderly HTLV-1 carriers in this endemic area. Further studies are needed to investigate the mechanism of the development of ATL among HTLV-1 carriers for preventing the development. Reference: 1) Iwanaga M et al. Int J Hematol, 2009. 2) Arisawa K et al. Int J Cancer, 2000.

Disclosures: No relevant conflicts of interest to declare.

Footnotes

* Asterisk with author names denotes non-ASH members.

別紙様式第2-1

No. 16

医薬品 研究報告 調査報告書

識別番号・報告回数			報告日	第一報入手日	新医薬品等の区分	総合機構処理欄
				2009. 12. 20	該当なし	
一般的名称	人血清アルブミン		研究報告の公表状況	Sobata R, Matsumoto C, Suzuki K, Uchida S, Suzuki Y, Satake M, Tadokoro K. XIVth Regional Congress of the ISBT, Asia; Nov 14-18, 2009; Nagoya.	公表国 日本	
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) 赤十字アルブミン20%静注4g/20mL(日本赤十字社) 赤十字アルブミン20%静注10g/50mL(日本赤十字社) 赤十字アルブミン25%静注12.5g/50mL(日本赤十字社)					

研究報告の概要

○ヒトT細胞リンパ球向性ウイルス1型(HTLV-1)抗体陽性献血者のプロウイルス量の定量と輸血感染症の感染性ウイルス量の評価

背景:献血血液の抗体スクリーニングと保存前白血球除去は、日本におけるHTLV-1の輸血感染(TTI)リスクを確実に低下させた。しかし、TTIを生じる血液成分中プロウイルス量は不明である。

目的:HTLV-1抗体陽性献血者から白血球除去前に採取した血液検体のプロウイルス量を調べた。献血者のプロウイルス量の分布と過去のデータから、感染性を持つプロウイルス量を推定した。

方法:献血者74名の保管検体の末梢血単核細胞または凝固血液からDNAサンプルを得た。検体は白血球除去前に採取した。HTLV-1pX領域とヒトCD81遺伝子のTaqMan PCRでプロウイルス量を測定し、細胞DNA量を推定した。過去のデータでは、抗体陽性献血者由来の赤血球濃厚液1単位の輸血を受けた患者約80%にセロコンバージョンが起こったことから、血液検体の80%に感染リスクがあると仮定し、輸血感染力を持つウイルス量を推定した。

結果:献血者のHTLV-1プロウイルス量は、100白血球につき、0.01～4.9コピー(平均0.83)だった。評価した検体の80%には、100白血球あたり少なくとも0.06コピーのプロウイルスが含まれていた。赤血球濃厚液1単位あたりの白血球数を白血球除去前は1×10^9と仮定すると、TTIを生じた製剤には最低6×10^5のHTLV-1感染細胞が含まれる。

結論:2007年、日本のすべての血液製剤に保存前白血球除去が導入され、残存白血球数は製剤の99%で1×10^6未満と確認されている。スクリーニング未実施でもHTLV-1感染細胞の最大数は1製剤につき4.9×10^4と考えられ、推定される感染性ウイルス量(6×10^5の感染細胞)よりかなり低い。抗体スクリーニングと白血球除去は、日本におけるHTLV-1のTTIリスクを事実上排除した。

使用上の注意記載状況・その他参考事項等

赤十字アルブミン20
赤十字アルブミン25
赤十字アルブミン20%静注4g/20mL
赤十字アルブミン20%静注10g/50mL
赤十字アルブミン25%静注12.5g/50mL

血液を原料とすることに由来する感染症伝播等

報告企業の意見	今後の対応
HTLV-1抗体陽性供血者の血液成分中のHTLV-1感染細胞の最大数は推定される感染性ウイルス量よりかなり低く、血清学的スクリーニングと白血球除去によって輸血感染リスクは事実上排除されているとの報告である。 HTLV-1は脂質膜を有するRNAウイルスである。垂直感染により日本では古代から広く侵淫しているが、本製剤による感染の報告はない。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とから、本製剤の安全性は確保されていると考える。	日本赤十字社では献血時のスクリーニング法として、より感度の高い化学発光酵素免疫測定法(CLEIA)によるHTLV-1抗体のスクリーニング検査を行っている。今後も引き続き情報の収集に努める。

MedDRA/J Ver.12.0J

JRC2009T-068

P-141

QUANTIFICATION OF HUMAN T-CELL LYMPHOTROPIC VIRUS TYPE 1 (HTLV-1) PROVIRUS LOAD IN SEROPOSITIVE BLOOD DONORS AND ESTIMATION OF INFECTIOUS VIRAL LOAD FOR TRANSFUSION-TRANSMITTED INFECTION

Sobata R[1], Matsumoto C[1], Suzuki K[1], Uchida S[1], Suzuki Y[2], Satake M[1], Tadokoro K[1]

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Background: Serological screening and prestorage leukocyte reduction for donated blood have undoubtedly decreased the risk of transfusion-transmitted infection (TTI) for HTLV-1 in Japan. However, the provirus load in blood component that would cause TTI is still unclear.

Aims: HTLV-1 provirus load was measured in blood samples collected before leukocyte reduction that were obtained from seropositive blood donors. From the distribution of provirus load among blood donors, provirus load for infectivity was estimated using the historical data on the frequency of transfusion-transmitted infection.

Methods: DNA samples were obtained from peripheral blood mononuclear cells or blood clots of stored samples obtained from 74 HTLV-1-seropositive individuals. All blood samples were obtained before leukocyte reduction. HTLV-1 provirus load was determined using TaqMan PCR for the HTLV-1 pX region and human CD81 gene to estimate the amount of cellular DNA. Previous data showed that seroconversion occurred in approximately 80% of patients transfused with one unit of fresh red-cell concentrate from HTLV-1-seropositive blood donors (Okochi K et al. ADS Res 1986;2:157–61). It is, therefore, expected that 80% of our blood samples will be in the category of units with infectious risk, which allows us to estimate the viral load for infectivity by transfusion.

Results: The HTLV-1 provirus loads in HTLV-1-seropositive blood donors ranged from less than 0.01 to 4.9 copies (average 0.83) per 100 leukocytes. Eighty per cent of blood samples evaluated contained at least 0.06 copies of HTLV-1 provirus per 100 leukocytes. Assuming that the number of leukocytes per unit of red-cell concentrate was $1\text{-}10^9$ before leukocyte reduction, a minimum of $6\text{-}10^5$ HTLV-1-infected cells would have been found in the unit that caused TTI.

Conclusions: In 2007, universal prestorage leukocyte reduction was introduced for all blood components in Japan. The number of residual leukocytes after leukocyte reduction is confirmed to be less than $1\text{-}10^6$ in 99% of unit currently issued from Japanese Red Cross Blood Center. If serological screening is omitted, the maximum number of HTLV-1-infected cells found in blood components would be $4.9\text{-}10^4$ per unit. This figure is substantially lower than the infectious virus load estimated ($6\text{-}10^5$ infected cells). The combination of serological screening and universal leukocyte reduction virtually eliminated the TTI risk for HTLV-1 in Japan.

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医薬品 研究報告 調査報告書

識別番号・報告回数			報告日	第一報入手日	新医薬品等の区分	総合機構処理欄
				2009. 11. 19	該当なし	
一般的名称	新鮮凍結人血漿				公表国	
販売名(企業名)	新鮮凍結血漿「日赤」(日本赤十字社) 新鮮凍結血漿-LR「日赤」(日本赤十字社) 新鮮凍結血漿-LR「日赤」成分採血(日本赤十字社)		研究報告の公表状況	Agapova M, Custer B. AABB Annual Meeting and TXPO; 2009 Oct. 24-27; New Orleans.	米国	

研究報告の概要

○米国の血液供給における*T. cruzi*スクリーニングの費用対効果

背景:シャーガス病の病原体である*Trypanosoma cruzi* (*T. cruzi*)は、輸血の安全性を脅かしている。現在、米国の供血血液の75～80%に*T. cruzi*のスクリーニング検査が行われており、29,000名当たり1名が陽性と考えられる。病原体の輸血による感染性とシャーガス病の拡大については特徴が十分に分かっておらず、全国的なスクリーニングの費用対効果は報告されていない。

方法:*T. cruzi*の脅威とその制圧にかかる費用を評価するために、疾患の進行モデルを用いて受血者の仮想集団の生涯コストと健康アウトカムを異なるスクリーニング計画下で比較した。以下の7つの供血者・供血血液検査方法を分析し、スクリーニング非実施と比較した:1)ラテンアメリカで生まれた供血者、2)血小板供血、3)初回供血者、4)全供血者を1回、5)全供血者を2回、6)全血と血小板供血、7)すべての供血。モデルパラメータは、スクリーニング・データまたは文献レビューより得た。一元感度分析および確率的感度分析を用いて、影響力のあるパラメータと全体の不確実性を評価した。

結果:各方法の費用対効果は、1)170,000、2)330,000、3)370,000、4)760,000、5)970,000、6)1,070,000、7)1,360,000(単位:ドル/QALY)となった。モデルにおける最も影響力のあるパラメータは、受血者の特徴と関連がある(生存率、健康状態ユーティリティ、将来の健康状態の低下率)。最も影響が強かったのは*T. cruzi*の血清陽性率と伝播効率だった。CE比率は、米国が報告した血清陽性率1/3,333と1/100,000の範囲ではそれぞれ、92%低く(よい)、215%高かった(悪い)。このモデルは、シャーガス病に伴う変数に無関係だった。

結論:本分析では、選択的*T. cruzi*スクリーニング検査は、全数検査とほぼ同等の効果があり、コストが低いことを示している。これらの所見は、輸血による伝播が観察されなかった、2年間の試験およびルックバック・データと整合している。

使用上の注意記載状況・その他参考事項等

新鮮凍結血漿「日赤」
新鮮凍結血漿-LR「日赤」
新鮮凍結血漿-LR「日赤」成分採血

血液を介するウイルス、細菌、原虫等の感染
vCJD等の伝播のリスク

報告企業の意見

米国の血液供給における*T. cruzi*検査において、選択的スクリーニングは全数検査とほぼ同等の効果があり、コストが低いことが示されたとの報告である。

今後の対応

日本赤十字社は、輸血感染症対策として献血時に海外渡航歴の有無を確認し、帰国(入国)後4週間は献血不適としている。また、シャーガス病の既往がある場合には献血不適としている。日本在住の中南米出身献血者については、厚生労働科学研究「献血血の安全性確保と安定供給のための新興感染症等に対する検査スクリーニング法等の開発と献血制限に関する研究」班と共同して検討する予定である。今後も引き続き情報の収集に努める。

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time. Finally, for donors with previously negative donations and recent travel to Latin America, there was no evidence of incident infection. **Conclusion:** While country of birth is the best predictor of *T. cruzi* infection, these data indicate that selective testing based solely on donor responses to any question or combination of questions would be insufficient to identify all RIPA+ *T. cruzi* infections. These data also have helped in guiding the development of a large incidence study to accompany conversion to selective 1-time testing of all donors in most of the US.

Disclosure of Commercial Conflict of Interest

M. Agapova: Nothing to disclose; H. H. Biswas: Nothing to disclose; M. P. Busch: Nothing to disclose; B. Custer: Nothing to disclose; H. Kamel: Nothing to disclose; P. Tomasulo: Nothing to disclose

Disclosure of Grants Conflict of Interest

M. Agapova: Nothing to disclose; H. H. Biswas: Nothing to disclose; M. P. Busch: Gen-Probe, Inc., Grants or Research Support, Travel Support or Honorarium Chiron / Novartis, Grants or Research Support, Travel Support or Honorarium Ortho, Travel Support or Honorarium Abbott, Travel Support or Honorarium; B. Custer: Nothing to disclose; H. Kamel: Nothing to disclose; P. Tomasulo: Nothing to disclose

Birth Country or Region	Allogeneic Donors Number (%) N = 703,725	*T.cruzi* RIPA+ Number (%) N = 34	*T.cruzi* RIPA+ Prevalence by Birth Country or Region
USA	546,230 (77.2)	10 (29.4)	1:54,623
Mexico	18,511 (2.6)	10 (29.4)	1:1,851
Central or South America	2,235 (0.3)	8 (23.5)	1:279
All other countries	13,254 (1.9)	1 (2.9)	1:13,254
Missing/Unreported	123,495 (17.5)	5 (14.7)	1:24,699

S39-020D

Sensitivity of Selective Testing for Antibody to *Trypanosoma cruzi* (*T. cruzi*)

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Background: Donor screening for *Trypanosoma cruzi* antibody began in 2007 at the American Red Cross by testing each donation (dn) from every donor (universal testing). Data for the 22-month experience with universal testing (Jan 27 07-Nov 30 08) were examined to determine the sensitivity of selective testing. Donor data collected included: risk factors related to direct or indirect exposure in a non-US endemic country, US-derived infection, ELISA false negativity (neg) and potential incident infection. **Methods:** The Ortho *T. cruzi* ELISA was used to screen each dn. Repeat reactive (RR) dns were further tested using a research radioimmunoprecipitation assay (RIPA); RIPA-pos donors were considered confirmed. RR donors were followed and tested by repeat serologic/parasitologic tests (PCR/ hemoculture-HC). Donors were also asked to respond to a detailed survey regarding risk factors; RIPA-pos donors were defined as cases and RIPA-unconfirmed as controls. **Results:** Prevalence for ~13 million dns screened was 1:36,000 (RR rate = 0.014%) and identified 394 RIPA-pos donors of which 4-14% were pos for the presence of the parasite by PCR/HC. Of 157 pos donors who completed a risk survey, all but 40 were born in an endemic area compared to 5/457 controls ($p < 0.0001$; OR 256 by univariate and 32 by multivariate analyses). The 40 US-derived cases came from 18 states; 6 had congenital infection and 7 others had identified risks (2 due to residence in an endemic area prior to *T. cruzi* screening and 5 with outdoor activities in the Southern US); 16/394 (4%) ELISA RR/RIPA pos donors had prior ELISA false-neg donation results of which 11 had one prior neg dn and 5 had >1 prior neg dn; 8/16 had prior neg reactivity within 20% of the ELISA cutoff. A 20% reduction in the assay cutoff would increase the RR rate by 0.025%. None of the 16 was PCR/HC pos, and of those followed (13/16), all ELISA signals were stable and none represented incident cases. No incident donors were identified in 2.5 million donors with >2 neg dns during the 22 months (>2.3 million person years of observation; neg dn interval = 0.9 years). Sensitivity by method is provided in the Table. **Conclusions:** A selective testing strategy based on qualifying a donor by a single direct or indirect test had high sensitivity. A protocol to further determine *T. cruzi* donor incidence is under development with collaborators from Blood Systems.

Disclosure of Commercial Conflict of Interest

J. P. Brodsky: Abbott Laboratories, Stocks or Bonds; R. Y. Dodd: Nothing to disclose; G. A. Foster: Nothing to disclose; D. Krysztof: Nothing to disclose; D. A. Leiby: Nothing to disclose; B. A. Lenes: Nothing to disclose; C. Rouault: Nothing to disclose; S. L. Stramer: Nothing to disclose; R. L. Townsend: Nothing to disclose

Disclosure of Grants Conflict of Interest

J. P. Brodsky: Nothing to disclose; R. Y. Dodd: Nothing to disclose; G. A. Foster: Nothing to disclose; D. Krysztof: Nothing to disclose; D. A. Leiby: Nothing to disclose; B. A. Lenes: Nothing to disclose; C. Rouault: Nothing to disclose; S. L. Stramer: Nothing to disclose; R. L. Townsend: Nothing to disclose

Method	# Detected/Tested	% Sensitivity (95% CI)
Universal Testing (Ortho)	860/861	99.88 (99.35-100)
Endemic birth question	117/157	74.52 (67.83-81.87)
1 × neg	378/394	95.94 (93.49-97.66)
2 × neg	389/394	98.73 (97.06-99.59)

S39-020D

Cost-Effectiveness of Screening for *T. cruzi* in the US Blood Supply

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Background: *Trypanosoma cruzi* (*T. cruzi*), the etiologic agent of Chagas disease is a safety threat to transfusion. Currently, 75-80% of US donations are screened for *T. cruzi*. Overall, 1 donor out of 29,000 is expected to be confirmed *T. cruzi* positive. The transmissibility of the pathogen by transfusion and progression to Chagas disease are not well characterized in the US, and the cost-effectiveness of nation-wide screening has not been reported. **Methods:** To evaluate the threat of *T. cruzi* as well as costs associated with intercepting this threat, we used disease progression modeling to compare lifetime costs and health outcomes of a hypothetical cohort of blood recipients under different screening strategies. We analyzed 7 donor or donation testing strategies: 1) donors born in Latin America; 2) platelet donations; 3) first-time donors; 4) all donors one time; 5) all donors from laboratory screening data or literature review. One-way and probabilistic sensitivity analyses were used to assess influential parameters and overall uncertainty. **Results:** Costs, effectiveness and the cost-effectiveness (CE) of each strategy compared to no testing, are provided in the table. The cost-effectiveness of testing all donors one time is $760,000/QALY, all donors two times is $970,000/QALY and universal testing is $1.36MQALY. The most influential parameters in the model are related to characteristics of the transfused population: survival rate, health state utilities and discount rate for future health states. With respect to *T. cruzi* seroprevalence and transmission efficiency are the most influential. CE ratios were 92% lower (better) and 215% higher (worse) between the limits of US-reported seroprevalence, 1/3333 and 1/100,000, respectively. The model was insensitive to variables associated with Chagas disease. **Conclusions:** This analysis suggests that selective *T. cruzi* screening generates nearly the same effectiveness as universal screening, but at reduced cost. These findings are consistent with 2-years of testing and lookback data, where incident infections or substantial transmission by transfusion have not been observed.

Disclosure of Commercial Conflict of Interest

M. Agapova: Nothing to disclose; B. Custer: Nothing to disclose

Disclosure of Grants Conflict of Interest

M. Agapova: Nothing to disclose; B. Custer: Nothing to disclose

Testing Strategy	Cost ($)	Effectiveness (QALYs)	CE Ratio ($/QALYs)	CE Ratio 95% range ($/QALYs)
No testing	0.06	8.56605503	-	-
Born in Latin America	0.48	8.56605609	170,000	55,000-380,000
Platelets	0.81	8.56605772	330,000	120,000-690,000
First time	1.36	8.56605906	370,000	160,000-710,000
One time all	3.54	8.56606013	760,000	350,000-1,410,000
Two time all	4.61	8.56606024	970,000	450,000-1,810,000
Whole Blood/Platelets	5.41	8.56605027	1,070,000	500,000-2,010,000
Universal	6.56	8.56606030	1,360,000	640,000-2,530,000

別紙様式第2-1

No. 9

医薬品 研究報告 調査報告書

識別番号・報告回数			報告日	第一報入手日	新医薬品等の区分	総合機構処理欄
				2009. 11. 5	該当なし	
一般的名称	人血清アルブミン		研究報告の公表状況	Azevedo RSS, Silva EVP, Carvalho VL, Rodrigues SG, Nunes Neto JP, Monteiro HAO, et al. Emerg Infect Dis. 2009 Nov;15(11):1830-2.	公表国 ブラジル	
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) 赤十字アルブミン20%静注4g/20mL(日本赤十字社) 赤十字アルブミン20%静注10g/50mL(日本赤十字社) 赤十字アルブミン25%静注12.5g/50mL(日本赤十字社)					

研究報告の概要

○マヤロ熱ウイルス、ブラジル・アマゾン

マヤロウイルスはアルファウイルス属トガウイルス科で、ジェノタイプDとLの2系統が確認されている。流行地は南米の熱帯地域で、発疹、発熱、重い関節痛などのデング様の疾患と関連している。関節痛は数週間持続することもある。

2008年2月、マヤロ熱ウイルス(MAYV)のアウトブレイクが、ブラジル北部、パラー州サンタバーバラ県のベレム近郊の村で発生した。村の住民は150名程度で多くは貧しく、密林の真ん中の木製の家に住んでいた。発熱を訴えた105名のうち53名は村の住民、52名は農学専攻の学生で村の近隣の施設に1週間滞在していた。

患者は発疹、発熱、重い関節痛の症状を呈し最長7日間持続した。患者の血清検体のIgMをELISAで検査したところ、36検体からIgMが検出された。MAYV分離株3株がジェノタイプDと確認され、系統発生解析では、1991年にブラジル北部で分離された株と近縁であることが明らかとなった。

また、村で蚊を捕獲したところ、832匹のうち188匹がMAYVの主要な媒介蚊である*Haemagogus janthinomys*だった。蚊から採取された検体及び患者の急性期血清検体がマウスに感染性を持つことが確認された。

使用上の注意記載状況・その他参考事項等

赤十字アルブミン20
赤十字アルブミン25
赤十字アルブミン20%静注4g/20mL
赤十字アルブミン20%静注10g/50mL
赤十字アルブミン25%静注12.5g/50mL

血液を原料とすることに由来する感染症伝播等

報告企業の意見	今後の対応
ブラジル北部、パラー州サンタバーバラ県のベレム近郊の村で、マヤロ熱ウイルスの流行が見られたとの報告である。 マヤロ熱ウイルスは脂質膜を持つ中型のRNAウイルスで、これまで本製剤によるマヤロ熱発症の報告はない。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、本剤の安全性は確保されていると考える。	日本赤十字社では、輸血感染症対策として問診時に海外渡航歴の有無を確認し、帰国(入国)後4週間は献血不適としている。また、発熱などの体調不良者を献血不適としている。今後も引き続き、新興・再興感染症の発生状況等に関する情報の収集に努める。

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JRC2009T-059

DISPATCHES

Mayaro Fever Virus, Brazilian Amazon

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In February 2008, a Mayaro fever virus (MAYV) outbreak occurred in a settlement in Santa Barbára municipality, northern Brazil. Patients had rash, fever, and severe arthralgia lasting up to 7 days. Immunoglobulin M against MAYV was detected by ELISA in 36 persons; 3 MAYV isolates sequenced were characterized as genotype D.

Mayaro virus (MAYV) is a member of the family *Togaviridae* and the genus *Alphavirus*. Recent molecular studies have recognized 2 MAYV lineages: genotypes D and L (*1*). MAYV has been associated with a dengue-like illness with rash, fever, and severe arthralgia in tropical South America. Arthralgia lasts for several weeks and affects principally ankles, wrists, and toes, but also can affect major joints. MAYV causes a mild to moderately severe acute febrile illness of 3–5 days' duration with uneventful recovery (*2*).

The Study

In February 2008, an outbreak of a dengue-like illness was reported in the Pau D'arco settlement, 38 km from Belém, Para state, in the Brazilian Amazon (online Appendix Figure, available from www.cdc.gov/EID/content/15/11/1830-appF.htm). This rural community has 48 houses with ≈150 inhabitants, many of whom live in poor conditions. They reside in the middle of a native forest, in softwood houses, in the municipality of Santa Barbara (2007 population ≈14,439).

A total of 105 persons were examined in a house-to-house survey. They reported a febrile illness within the past 30 days, had a current febrile illness, or reported contact with persons with febrile illness. Fifty-three resided in the settlement (50 were agricultural workers), and 52 were agronomy students at a public university in Belém and had been training for a week at a field station adjacent to the settlement. The students slept in the station for a week; their activities included periodic visits to the settlement and sporadic ingression to the forest. Students and agricultural workers were bled weekly by convenience from March 17 through April 4, 2008. All serum samples were processed by ELISA for detection of immunoglobulin (Ig) M (*3*).

During the same diurnal period (9:00 AM–3:00 PM), mosquitoes were captured in the settlement by using human bait on the ground and in the forest canopy (≈15 m high) near the residences. A total of 832 (49 lots) *Culicidae* mosquitoes were collected and frozen before being used for virus isolation. Of these, 188 (11 lots) were *Haemagogus janthinomys*, the main vector of MAYV; the remaining 644 (38 lots) were mainly members of the genera *Wyeomyia, Aedes, Sabethes*, and *Limatus*.

Newborn mice (*Mus musculus*) and C6/36 cells were inoculated with acute-phase serum from samples collected from febrile patients and pooled mosquitoes, as previously described (*4*,*5*). The inoculated animals and cells were observed daily, and the presence of virus was confirmed by complement fixation and immunofluorescent assays (*4*). Three MAYV strains were isolated: 2 from febrile persons and 1 from a pool with 2 *H. janthinomys* mosquitoes collected at ground level. All 3 strains were isolated with both assays.

IgM was detected in 36 (34%) serum samples (Figure 1, panel A). Of those 36 samples, 23 (64%) were collected from residents of the settlement, and 13 (36%) were from residents of Belém and Ananindeua municipalities; these persons had visited the settlement area for a week (Figure 2, panel B). Persons with Mayaro fever ranged in age from 4 to 55 years, and 21 (58%) were male (Figure 1, panel C). Fifty-two percent of MAYV-positive persons were students, 31% were agriculturists, and 17% participated in other activities (Figure 1, panel D).

Of the 36 MAYV-infected persons, 33 were symptomatic. Illness was characterized by sudden onset of fever (100% of patients), arthralgia (89%), myalgia (75%), headache (64%), articular edema (58%), rash (49%), and retroocular pain (44%). Other less frequent symptoms were itching (33%), dizziness (25%), anorexia (22%), swollen lymph nodes (17%), and vomiting (4%).

Other common exanthematic illnesses in Brazil included in the differential diagnoses were dengue fever, rubella, B19 parvovirus, human herpesvirus 6, infectious mononucleosis, malaria, and yellow fever. Serologic results excluded these illnesses.

RNA was extracted by using the TRIZOL LS (Invitrogen, Carlsbad, CA, USA) reagent method according to the manufacturer's instructions. Envelope (E)2 and E1 genes of the MAYV genome were amplified by using a standard 1-step reverse transcription–PCR protocol, as pre-

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DOI: 10.3201/eid1511.090461

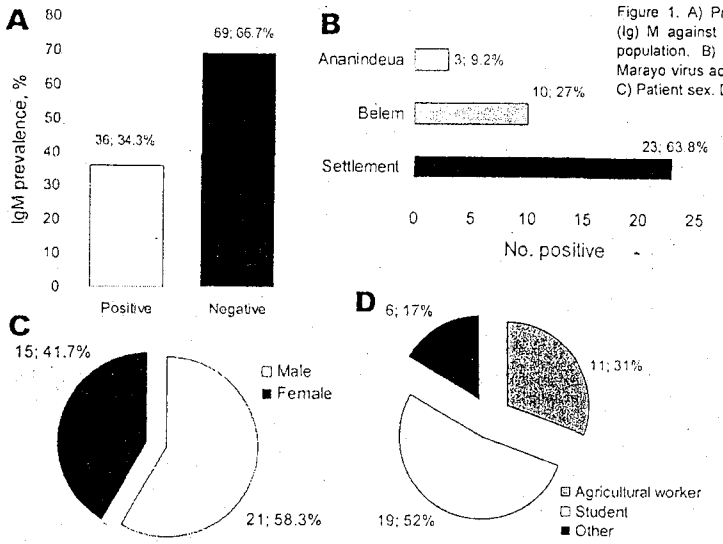

Figure 1. A) Prevalence of immunoglobulin (Ig) M against Mayaro virus in the studied population. B) Prevalence of IgM against Marayo virus according to area of residence. C) Patient sex. D) Patient work activities.

viously described (*1*). The cDNA products were directly sequenced (*6*).

We conducted phylogenetic analysis by using the maximum parsimony (heuristic algorithm), neighbor-joining (Kimura 3-parameter and F84 corrections), and maximum-likelihood methods (*7*) implemented in the PAUP software (*8*) for the nucleotide sequences obtained for the isolates and representative members of other Mayaro-related viruses belonging to the genus *Alphavirus* available at GenBank (www.ncbi.nlm.nih.gov). Bootstrap resample method (1,000 replicates) and outgoup definition were used to provide confidence for the phylogenetic groups (*9*).

The 3 MAYV isolates were successfully sequenced, and the nucleotide sequences covering the 3′ E1 region, the entire E2 gene, and 3′ noncoding region (≈2,000 nt) were phylogenetically compared with other MAYV and Mayaro-related viruses isolated during different periods (1954–2008) and from different hosts (human and arthropods) in Brazil, Peru, French Guiana, Trinidad and Tobago, Suriname, and Bolivia (Figure 2).

The phylogram depicted a clear segregation of MAYV strains into 2 major groups: genotypes D and L (*1*). The strains isolated in Santa Barbara municipality were grouped together in genotype D within clade I. Genetically, these strains were closely related to a 1991 isolate from Tocantins state in northern Brazil. The strains isolated in Santa Barbara were similar to those isolated in Belém during the same period. Interestingly, the Santa Barbara and Belém strains differed from the Brazilian and prototype strains isolated in 1955 (Figure 2).

Conclusions

MAYV has been isolated only in northern South America. Probably because of the short viremic period, it is sporadically isolated only during enzootic periods. However, during epidemics or epizootics, the number of isolates increase sharply (*10,11*). The few isolates obtained are intriguing and contrast with the high prevalence of specific antibodies in Pan-Amazonia; previous studies have shown widespread immunity in the Amazon, ranging from 5% to 60%. Positivity increases with age and is higher in rural and neighboring communities, as observed for the Amerindians (*2,12,13*).

In a previous outbreak in Belterra, several patients were too ill to continue their daily activities while febrile, and some even became prostrate. Moreover, these patients frequently reported severe arthralgia that led to temporary incapacitation (*13,14*).

Our data confirmed the occurrence of a Mayaro fever outbreak in the Pau D'Arco settlement. Clinically, the disease was similar to other outbreaks and characterized mainly by fever, arthralgia, myalgia, headache, rash, and dizziness (*2,13–15*). This outbreak was reported 17 years after the last episode of the disease described in the municipality of Benevides, which is closer (≈10 km) to Santa Barbara (P.F.C. Vasconcelos, unpub. data). The clinical and laboratory data from this MAYV outbreak caused by genotype D confirmed in Santa Barbara provide a better understanding of the MAYV molecular epidemiology in the Brazilian Amazon region.

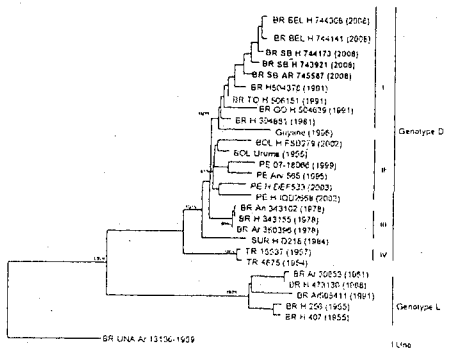

Figure 2. Comparison of genetic relationships among the Mayaro virus strains sequenced in this study with those isolated in different areas of South America, periods of time, and hosts. Numbers above and within parentheses correspond to bootstrap support values for the specific clades. The Una virus was used as an outgroup to root the tree. BR, Brazil (BEL, Belém; SB, Santa Barbara [bold]; TO, Tocantins state); BOL, Bolivia; PE, Peru; SUR, Suriname; H, human; Ar, arthropod. Numbers in parentheses correspond to the year of isolation of each strain. Items in **boldface** indicate strains isolated in this study.

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Dr Azevedo is a physician working with arboviruses and rodent-borne viruses at Instituto Evandro Chagas. Her research interests include epidemiology of these and other emerging infectious diseases.

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No. 10

医薬品 研究報告 調査報告書

識別番号・報告回数			報告日	第一報入手日	新医薬品等の区分	総合機構処理欄
				2010. 1. 26	該当なし	
一般的名称	人血清アルブミン		研究報告の公表状況	Pecorari M, Longo G, Gennari W, Grottola A, Sabbatini A, Tagliazucchi S, Savini G, Monaco F, Simone M, Lelli R, Rumpianesi F. Euro Surveill. 2009 Dec 17;14(50). pii: 19446.	公表国 イタリア	
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) 赤十字アルブミン20%静注4g/20mL(日本赤十字社) 赤十字アルブミン20%静注10g/50mL(日本赤十字社) 赤十字アルブミン25%静注12.5g/50mL(日本赤十字社)					

研究報告の概要

○ウスツウイルス神経浸潤感染の初のヒト症例:イタリア2009年8～9月

ウスツウイルス(USUV)はフラビウイルス科の節足動物媒介性ウイルスで、日本脳炎ウイルスと近縁である。過去10年間に、中央ヨーロッパで脳炎、心筋変性、肝臓・脾臓壊死を発症した鳥類から検出された。これまでにヒトにおいて重症もしくは死に至る疾患を発症した例はなかった。ここでは、発熱と神経症状を呈し髄膜脳炎と診断された、世界初となるUSUV神経浸潤感染の症例を報告する。

患者はイタリア在住の60代女性で、2009年5月にびまん性大細胞型B細胞リンパ腫のため半結腸切除術を受けた。同年8月21日までに6回の化学療法を受けた。その数日後、性器ヘルペスの再燃がありバラシクロビルを投与された。9月1日に39.5℃の発熱と安静時振戦を発症し、抗菌薬を投与されたものの高熱は持続した。9月5日に高熱と静注抗菌薬治療のため入院し、重度の貧血のため輸血を受けた。9月11日に採取された脳脊髄液はUSUV陽性であり、RT-PCRと塩基配列決定によって血清および血漿検体にもUSUVが示された。premembraneの部分配列とウイルス-ゲノムのNS5領域は、USUV Vienna株およびBudapest株と相同していた。髄膜脳炎の急性期前と後の血清(5月26日、10月13日)及び血漿(10月19日)検体からはウイルスは検出されなかった。

使用上の注意記載状況・その他参考事項等

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血液を原料とすることに由来する感染症伝播等

報告企業の意見	今後の対応
発熱と神経症状を呈し髄膜脳炎と診断された、世界初となるウスツウイルス神経浸潤感染の症例報告である。 ウスツウイルスは脂質膜を持つ中型のRNAウイルスで、これまで本製剤によるウスツウイルス感染症の報告はない。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、本剤の安全性は確保されていると考える。	日本赤十字社では、輸血感染症対策として問診時に海外渡航歴の有無を確認し、帰国(入国)後4週間は献血不適としている。また、発熱などの体調不良者を献血不適としている。今後も引き続き、新興・再興感染症の発生状況等に関する情報の収集に努める。

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JRC2010T-001

Rapid Communications

First human case of Usutu virus neuroinvasive infection, Italy, August-September 2009

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We report the first worldwide case of Usutu virus (USUV) neuroinvasive infection in a patient with diffuse large B cell lymphoma who presented with fever and neurological symptoms and was diagnosed with meningoencephalitis. The cerebrospinal fluid was positive for USUV, and USUV was also demonstrated in serum and plasma samples by RT-PCR and sequencing. Partial sequences of the premembrane and NS5 regions of the viral genome were similar to the USUV Vienna and Budapest isolates.

Introduction

Usutu virus (USUV) is an arthropod-borne virus of the family *Flaviviridae*, genus *Flavivirus*. It is included in the Japanese encephalitis virus (JEV) group [1] being closely related to human pathogens such as JEV and West Nile virus (WNV). In the last decade, USUV was detected in a variety of central European birds with encephalitis, myocardial degeneration, and necrosis in liver and spleen [2-5]. As far as we know, the virus had never been associated with severe or fatal disease in humans [6]; it was isolated once in the Central African Republic in a man with fever and rash [7]. Here we report evidence of a neuroinvasive infection clinically related to USUV in Italy.

Case report

In May 2009, a woman in her 60s from Emilia Romagna region, Italy, underwent hemicolectomy because of a diffuse large B cell lymphoma. Six courses of chemotherapy were administered (including rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone), with last administration on 21 August 2009. Some days later, there was a reactivation of genital herpes treated with valacyclovir. On 1 September, a fever of 39.5°C with resting tremor appeared and antibiotic (moxifloxacine and amoxicilline clavulanate) therapy started however the temperature persisted. On 5 September, the patient was admitted to hospital for hyperpyrexia resistant to antipyretic and intravenous antibiotic treatment (meropenem and teicoplanine). Once admitted, the patient received blood transfusion because of a critical anaemia.

Examination of blood, urine and stool cultures and virological assessment for herpes virus simplex (HSV1/2) and cytomegalovirus (CMV) antigen were negative. A total body computerised tomography was performed without evidence of lymphoma. Suspicion of meningoencephalitis was addressed by neurological examination which showed distal resting tremor, positivity to the Romberg test, dysmetry and weakness at four limbs without cranial nerve affection. Magnetic resonance imaging (MRI) of the brain showed a signal alteration of the substantia nigra of the parietal and frontal subcortical areas that did not change after injection of contrast medium. On 11 September, the cerebrospinal fluid (CSF) was therefore collected and examined. The CSF was limpid without any alteration detected in the clinical-chemical analysis, activated lymphocytes were evident in the sediment. As further analysis of the same CSF specimen revealed the presence of flaviviruses (see below), steroid treatment was started. This therapy resolved the fever but did not lead to any improvement of the neurological symptoms. The electroencephalogram still registered diffuse slow theta waves and slow spike prevalent in left frontal parietal area. The neurological functions, mainly the resting tremor, improved following the administration of levodopa and carbidopa.

Virological analysis

When tested for the presence of viral agents, the CSF collected on 11 September was negative in molecular tests for CMV, HSV1/2, Epstein-Barr virus, adenoviruses, parvovirus B19, polyomavirus JC and BK, enteroviruses, mumps virus and WNV and positive to a heminested RT-PCR specific for the NS5 region of the *Flavivirus* genus [8]. The amplicon was directly sequenced and analysed by BLAST (http://www.ncbi.nlm.nih.gov/blast), revealing a 98% identity with both the USUV Budapest (gbIEF206350.1) and Vienna (gbJAY453411.1) isolate.

To confirm the identification of the species Usutu virus, we performed two USUV-specific RT-PCRs targeting the NS5 [2] and premembrane (preM) regions (primer sequences available on request) of the USUV genome on two plasma specimens collected on 8 and 11 September 2009 and one serum specimen collected on 14 September. The amplified products were sequenced (583 bp of NS5 and 602 bp of preM) and aligned with the corresponding sequences deposited in Genbank (gbJAY453411.1;