別紙

一般的名称	①人血清アルブミン②人血清アルブミン③人血清アルブミン④人免役グロブリン⑤乾燥ペプシン処理人免疫グロブリン⑥乾燥スルホ化人免疫グロブリン⑦乾燥スルホ化人免疫グロブリン⑧乾燥濃縮人活性化プロテインＣ⑨乾燥濃縮人血液凝固第Ⅷ因子⑩乾燥濃縮人血液凝固第Ⅸ因子⑪乾燥抗破傷風人免疫グロブリン⑫抗ＨＢｓ人免疫グロブリン⑬トロンビン⑭フィブリノゲン加第ＸⅢ因子⑮乾燥濃縮人アンチトロンビンⅢ⑯ヒスタミン加人免疫グロブリン製剤⑰人血清アルブミン⑱人血清アルブミン⑲乾燥ペプシン処理人免役グロブリン⑳乾燥人血液凝固第Ⅸ因子複合体㉑沈降精製百日せきジフテリア破傷風混合ワクチン㉒沈降精製百日せきジフテリア破傷風混合ワクチン㉓沈降精製百日せきワクチン㉔乾燥弱毒生風しんワクチン㉕乾燥弱毒生おたふくかぜワクチン
販売名（企業名）	①献血アルブミン20“化血研”②献血アルブミン25“化血研”③人血清アルブミン“化血研”④“化血研”ガンマーグロブリン⑤献血静注グロブリン“化血研”⑥献血ベニロンーＩ⑦ベニロン⑧注射用アナクトＣ2,500単位⑨コンファクトＦ⑩ノバクトＭ⑪テタノセーラ⑫ヘパトセーラ⑬トロンビン“化血研”⑭ボルヒール⑮アンスロビンＰ⑯ヒスタグロビン⑰アルブミン 20%化血研⑱アルブミン 5%化血研⑲静注グロブリン⑳ノバクトＦ㉑DPT“化血研”シリンジ㉒沈降精製百日せきジフテリア破傷風混合ワクチン㉓沈降精製百日せきワクチン㉔乾燥弱毒生風しんワクチン㉕乾燥弱毒生おたふくかぜワクチン「化血研」
報告企業の意見	弊所の血漿分画製剤に対するウイルス安全性は、原料血漿におけるNAT及び血清学的検査によるスクリーニング、製造工程での効果的なウイルス不活化・除去、更には小分品でのNAT、血清学的検査による確認というステップにより確保されている。製造工程のウイルス除去・不活化能は、「血漿分画製剤のウイルスに対する安全性確保に関するガイドラインについて（医薬発第1047号）」に従い、原料に混入する可能性のあるウイルスを考慮したモデルウイルスを選定し、ウイルスプロセスバリデーションを実施し評価を行っている。 WNVは、エンベロープを持つRNAウイルスであり、このモデルウイルスとしてBVDV（ウシウイルス性下痢ウイルス）が一般的に認められている。弊所においても、このモデルウイルスを用いてウイルスプロセスバリデーションを実施した。弊所の血漿分画製剤は、その製造工程中にウイルス安全対策工程として「ウイルス除去膜工程」や「加熱工程」等が導入されている。この原理が異なるウイルス安全対策工程については、左記ウイルスプロセスバリデーションの結果より、WNVに対する不活化、除去効果が確認されている。また、この様に、ウイルスプロセスバリデーションにより検証されたウイルス除去・不活化工程を経た弊所の血漿分画製剤において、その臨床使用上もWNVの感染報告例はない。 また、ヒト血漿由来のアポセルロプラスミンを沈降精製百日せきジフテリア破傷風混合ワクチンの製造工程において使用しているが、以下の理由により安全と考えられる。 アポセルロプラスミンの製造には、 BMM膜（35n）が用いられているが、フラビウイルスビリオンは本来の状態において直径40-60nmの球状であるとされていることから、同工程において除去されると考えられる。 更に、アポセルロプラスミンは、65℃で18時間加熱工程を行っているが、フラビウイルスは高温で急激に不活化される。５０℃において１０分で５０％の感染性が失われる。実際的処置においては、血液や他の蛋白溶液中の完全な不活化は、５６℃３０分以内に起きるとされている。 これらのことから、仮に原料自体にWNVが混入していたとしても、製造過程で充分にウイルスの不活化はできているものと考えられる。 弊所製品の WNV に対する安全性は高いレベルで保たれていると考えるが、今後とも情報収集に努め、更なる安全性の向上を図っていきたい。

INF2005-021

MMWR

Dispatch

October 5, 2005 / 54(Dispatch);1-3

West Nile Virus Infections in Organ Transplant Recipients --- New York and Pennsylvania, August--September, 2005

In September 2005, West Nile virus (WNV) infection was confirmed in three of four recipients of organs transplanted from a common donor. Two recipients subsequently had neuroinvasive disease, one recipient had asymptomatic WNV infection, and a fourth recipient apparently was not infected. This report summarizes the ongoing investigation. Clinicians should be aware of the potential for transplant-associated transmission of infectious disease.

Organ Donor

The organ donor, a New York City resident, was hospitalized on August 23 after a traumatic head injury and underwent emergency evacuation of an epidural hematoma, during which he received one unit of packed red blood cells (PRBCs). He was declared brain dead on August 26. Liver and associated vessels, one lung, and both kidneys were recovered. On August 28, the liver and kidneys were transplanted into three recipients at two transplant centers in New York City, the lung was transplanted into a recipient at a transplant center in Pittsburgh, and the vessels were discarded.

After unexplained neurologic illness occurred in two organ recipients, an investigation was initiated. Investigators determined that the donor had lived near an area where mosquitoes positive for WNV were collected on August 16, 2005. The donor's wife reported that he had spent time outdoors and felt febrile before sustaining the fatal head injury. Serum and plasma collected from the donor on August 27 were retrieved. The samples tested positive for WNV immunoglobulin M antibodies (IgM) and IgG by enzyme immunoassay but negative for WNV RNA by polymerase chain reaction (PCR). Immunohistochemical analyses of liver, gallbladder, kidney, and epidural hematoma were negative for WNV antigens. The PRBC unit received by the organ donor was donated on July 30 and was negative for WNV RNA by minipool nucleic acid-amplification test (mpNAT). A repeat donation on September 22 was WNV mpNAT and IgM negative.

Liver Recipient

The liver recipient had end-stage liver disease caused by hepatitis C virus infection. She initially did well after the transplantation. She required multiple transfusions of blood products, all of which were WNV RNA negative by mpNAT. On post-transplant day 13, she had a fever and altered mental status. On day 18, she experienced respiratory distress requiring endotracheal intubation. A lumbar puncture revealed mild lymphocytic pleocytosis (8 cells/mm^3) and elevated protein (81 mg/dL). She became comatose and developed acute flaccid paralysis consistent with WNV encephalitis.

Serum and cerebrospinal fluid (CSF) specimens collected on day 23 were positive for WNV IgM, and CSF contained WNV RNA. That day, the patient began treatment with four doses of intravenous Omr-IgG-am™ (Omrix Biopharmaceuticals, Tel Aviv, Israel, supplied by the National Institutes of Health [NIH]), an immune globulin with high antibody titers against WNV under an investigational new drug (IND) compassionate-use protocol; however, the patient had no subsequent clinical improvement and remains in a coma.

Lung Recipient

The lung recipient had end-stage lung disease caused by pulmonary fibrosis. The initial post-transplant course was uneventful aside from blood-product receipt. The patient went home on post-transplant day 16 but was readmitted the following day with fever and dyspnea requiring endotracheal intubation, followed by altered mental status, seizures, and acute flaccid paralysis consistent with WNV encephalitis. On day 23, a lumbar puncture revealed elevated CSF protein (149 mg/dL) but no white blood cells; a brain magnetic resonance image taken the same day was normal. Serum collected on day 19 was negative for WNV IgM, but, by day 23, serum was IgM and IgG positive. CSF from day 24 was negative for WNV IgM and WNV RNA, but CSF from day 27 was positive for WNV IgM and IgG. The patient completed experimental treatment with four doses of Omr-IgG-am, without clinical improvement, and remains in a coma.

Kidney Recipient 1

The first kidney recipient had end-stage renal disease attributable to IgA nephropathy. She had no immediate post-transplant complications, received no blood products, and was discharged home on day 3. Serum collected on day 22 was negative for WNV IgM but positive for IgG (consistent with a previous flavivirus infection) and was positive for WNV RNA. The patient was readmitted to the hospital on day 27 for experimental Omr-IgG-am treatment and remains asymptomatic.

Kidney Recipient 2

The second kidney recipient had end-stage renal disease caused by Alport syndrome. He received blood products after the transplant and was discharged home on post-transplant day 7. Serum collected from the patient on day 16 was negative for WNV IgM, IgG, and RNA. As a precaution, the patient was rehospitalized on day 27 for experimental Omr-IgG-am treatment. He remains well.

Reported by: *LW Teperman, MD, T Diflo, MD, A Fahmy, MB, GR Morgan, MD, RE Wetherbee, MD, New York University Medical Center; L Ratner MD, D Cohen MD, Columbia Presbyterian Medical Center; J Ackelsberg, MD, M Campbell, MS, E DeBernardo, PhD, A Fine, MD, E Lumeng, MPH, New York City Department of Health and Mental Hygiene; NP Tavakoli, PhD, New York State Department of Health. B Dixon, MD, A Weltman, MD, Pennsylvania Department of Health. Div of Vector-Borne Infectious Diseases; Div of Viral and Rickettsial Diseases, National Center for Infectious Diseases; B Tsoi, MD, EIS Officer, CDC.*

Editorial Note:

This report describes the second report of WNV transmission associated with organ transplant (*1*). Several important differences exist between this and the previously reported occurrence. The first organ-donor--associated WNV transmission, reported in August 2002, occurred after the donor received a transfusion of WNV-positive blood 1 day before organ recovery. A serum sample collected immediately before organ recovery subsequently tested positive for WNV by PCR and culture but lacked WNV IgM antibodies. All four organ recipients were infected and became ill. In contrast, the current organ donor was likely infected via a mosquito bite rather than

through blood transfusion, and a serum sample obtained 1 day before the organs were recovered had WNV IgM and IgG antibodies but was PCR negative. The lung and liver transplant recipients had severe WNV encephalitis and acute flaccid paralysis with respiratory failure, one kidney recipient had a positive PCR test result in serum 22 days after transplantation and remains asymptomatic, and the other kidney recipient had no evidence of WNV infection.

Serologic and clinical studies indicate that organ-transplant recipients have a risk approximately 40 times that of the general population for neuroinvasive disease after WNV infection (*2*). Infected organ-transplant recipients and other immunosuppressed persons typically have prolonged WNV incubation periods, during which asymptomatic viremia can be detected (*3*). The infected kidney recipient had asymptomatic viremia 22 days after transplant. All of the recipients were treated through a Food and Drug Administration (FDA)-approved IND compassionate-use protocol with Omr-IgG-am, an intravenous immunoglobulin product with high-titered neutralizing antibody to WNV. No proven effective treatment or prophylaxis for WNV infection exists; a randomized placebo-controlled, double-blind trial of Omr-IgG-am is under way (*5*).

Investigation of 30 recognized cases of WNV transmitted by blood transfusion documented to date indicated that the donors' viremias can be of low titer and that all resulted from IgM antibody-negative donations (*4*). Conversely, transfused viremic donations that were recognized only after retrospective testing did not transmit WNV infection if IgM antibody was present (*6*). Since 2003, the U.S. blood supply has been screened for WNV using NAT, which has reduced the risk for transfusion transmission (*4*). The organ-transplant--associated WNV transmission described in this report suggests that transmission through solid organ transplantation can occur from donors with IgM and IgG antibodies and without detectable nucleic acid by PCR in their serum. Experimental evidence in humans and animals suggests that WNV might persist in organs after clearance of viremia (*7*). Further testing of the donor serum using a highly sensitive NAT assay for blood-donor screening is pending.

Organ donors are screened to identify infectious risks on the basis of national organ-procurement standards (*8*). Screening of all organ donors with WNV NAT is not currently required or routinely performed because of 1) NAT availability only through IND applications for blood screening, 2) the length of turnaround time to obtain WNV NAT testing, and 3) the unproven test performance on donated organs. One analysis suggested that WNV NAT screening might result in a net loss of years of life among certain types of potential transplant recipients (*9*) by excluding healthy donors from an already limited donor pool. National guidelines for organ-donor screening are continuously reevaluated by the Health Resources and Services Administration in consultation with FDA, CDC, and organ-procurement organizations (*10*).

Clinicians should be aware that transplant-associated infectious disease transmission can occur and should be vigilant for unexpected outcomes in transplant recipients, particularly when they occur in clusters. Cases of suspected WNV infection through organ transplant should be reported promptly to local and state health departments and CDC.

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別紙様式第 2-1

9

医薬品
医薬部外品　研究報告　調査報告書
化粧品

別紙 3-7

識別番号・報告回数		回	報告日 年　月　日	第一報入手日 2005 年 7 月 29 日	新医薬品等の区分 該当なし	厚生労働省処理欄
一般的名称			研究報告の公表状況	Variant Creutzfeldt-Jakob Disease Death, United States, Belay E.D. et al. Emerging Infectious Disease (CDC) Vol. 11, No. 9 September 2005	公表国 米国	
販売名（企業名）						

研究報告の概要

米国における唯一の変異型クロイツフェルト・ヤコブ病(vCJD)の女性患者が 2004 年に死亡し，剖検により診断が確定された。この女性は 1979 年に英国で生まれ，1992 年に米国に移住した。2001 年 11 月に最初の症状(記憶障害および抑うつ)が認められてから様々な神経症状が進行し，32 ヶ月後に死亡した。この患者は米国で手術・輸血・血液製剤の使用歴はなく，英国に住んでいる間に BSE に曝露されたと考えられている。
また 2004 年 2 月時点で，英国で輸血により感染した vCJD 症例が 2 例報告されている。
米国で発生した vCJD 症例はなく，また FDA は英国および周辺国に BSE 曝露の可能性が高かった期間中の居住あるいは長期滞在した人を供血者から除外したため，輸血による vCJD のリスクは低い。2005 年 6 月に，米国テキサス州において最初の BSE 感染ウシが発見された。カナダ産ウシを含め現在 4 例の BSE が報告されており，米国における vCJD の発生を監視しつづける必要性が高まっている。vCJD が疑われる症状を呈した患者については地域および州の保健局に届け出が義務付けられている。現在，国立プリオン病病理研究センターでは，最新のプリオン診断検査が無料で受けられる。プリオン病疑いまたは診断例における神経症状の変化を見逃さないために医師らがこのサービスを利用することが推奨される。

使用上の注意記載状況・その他参考事項等

報告企業の意見	今後の対応
本論文は，米疾病管理センター(CDC)が公表した，米国における BSE と vCJD の様々な状況をまとめたものである。米国における vCJD のリスクは，英国滞在を供血除外基準としたため，極めて低いことが確認される。しかしながら，本論文は，vCJD が疑われるあらゆる症例の報告を奨励している。弊社の血漿分画製剤は，vCJD 症例が殆ど報告されていない北米にて採取された血漿を用いているため，vCJD 伝播の理論的リスクは非常に低いと考えられる。	現時点で弊社が新たな安全対策上の措置を講じる必要はないと考える。引き続き関連情報の収集に努める。

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Variant Creutzfeldt-Jakob Disease Death, United States

Ermias D. Belay,* James J. Sejvar,* Wun-Ju Shieh,* Steven T. Wiersma,† Wen-Quan Zou,‡ Pierluigi Gambetti,‡ Stephen Hunter,* Ryan A. Maddox,* Landis Crockett,† Sherif R. Zaki,* and Lawrence B. Schonberger*

The only variant Creutzfeldt-Jakob disease (vCJD) patient identified in the United States died in 2004, and the diagnosis was confirmed by analysis of autopsy tissue. The patient likely acquired the disease while growing up in Great Britain before immigrating to the United States in 1992. Additional vCJD patients continue to be identified outside the United Kingdom, including 2 more patients in Ireland, and 1 patient each in Japan, Portugal, Saudi Arabia, Spain and the Netherlands. The reports of bloodborne transmission of vCJD in 2 patients, 1 of whom was heterozygous for methionine and valine at polymorphic codon 129, add to the uncertainty about the future of the vCJD outbreak.

Variant Creutzfeldt-Jakob disease (vCJD) was first reported in 1996 in the United Kingdom and has been causally linked to eating cattle products contaminated with the bovine spongiform encephalopathy (BSE) agent (1–3). Both vCJD and BSE are rapidly progressive neurodegenerative disorders classified as transmissible spongiform encephalopathies (TSEs) or prion diseases. TSEs are characterized by 1) incubation periods measured in years, 2) presence in the brain of an unconventional agent called a prion, 3) absence of inflammatory reaction, and 4) a neuropathologic feature consisting typically of spongiform lesions, astrogliosis, and neuronal loss. vCJD is distinguished from the more common TSE in humans, sporadic CJD, by the younger median age (28 years and 68 years, respectively) of the patients and by its clinical and neuropathologic manifestations.

In 2002, the likely occurrence of vCJD was reported in a 22-year-old woman living in Florida and represented the first detection of the disease in North America (4). In this report, we describe this patient's illness and provide an update on the epidemiologic features of the ongoing vCJD outbreak worldwide, including recent reports of bloodborne transmission of vCJD.

*Centers for Disease Control and Prevention, Atlanta, Georgia, USA; †Florida Department of Health, Tallahassee, Florida, USA; and ‡Case Western Reserve University, Cleveland, Ohio, USA

Case Report

In early November 2001, the patient in Florida was evaluated for depression and memory loss that adversely affected her work performance and may have contributed to a traffic ticket she received for failure to yield the right of way at a traffic sign. In December 2001, the patient developed involuntary movements, gait disturbances, difficulty dressing, and incontinence. The following month, she was taken to a local emergency department; a computed tomographic scan of her brain showed no abnormalities, a diagnosis of panic attack was made, and antianxiety medications were prescribed.

In late January 2002, the patient was transported to the United Kingdom, where her mother resided. During the ensuing 3 months, the patient's motor and cognitive deficits worsened, which caused falls resulting in minor injuries; she had difficulty taking care of herself, remembering her home telephone number, and making accurate mathematical calculations. She also experienced confusion, hallucination, dysarthria, bradykinesia, and spasticity. An electroencephalogram evaluation showed no abnormalities, but a brain magnetic resonance imaging (MRI) study showed the characteristic signal abnormalities in the pulvinar and metathalamic regions suggestive of vCJD. Western blot and immunohistochemical analyses of tonsillar biopsy tissue demonstrated the presence of protease-resistant prion protein, which supported the diagnosis of vCJD. By September 2002, the patient was bedridden. An experimental treatment with quinacrine was given to the patient for 3 months, but she showed little

improvement. She remained in a state of akinetic mutism and died in June 2004, ≈32 months after illness onset.

The patient was born in Great Britain in 1979 and immigrated to the United States with her family in 1992. She had no history of surgery or receipt of blood or blood products, and she was never a blood donor. Consistent with findings for vCJD patients in the United Kingdom associated with potential foodborne exposure, this patient was homozygous for methionine at polymorphic codon 129 of the prion protein gene. A full autopsy was performed, and neuropathologic examination of brain tissue showed the presence of florid plaques and severe cortical atrophy (*Figure 1*). Immunohistochemical staining for the prion protein showed numerous plaquelike formations along with a synaptic staining pattern similar to that previously described in other vCJD patients (Figure 2).

This patient is the only US resident with a confirmed diagnosis of vCJD. She was likely exposed to BSE while growing up in the United Kingdom from 1980 to 1992, which suggests an incubation period of 9–21 years (Table). The illness duration in this patient (≈32 months) was much longer than the median illness duration for patients in the United Kingdom with vCJD (14 months, range 6–40 months).

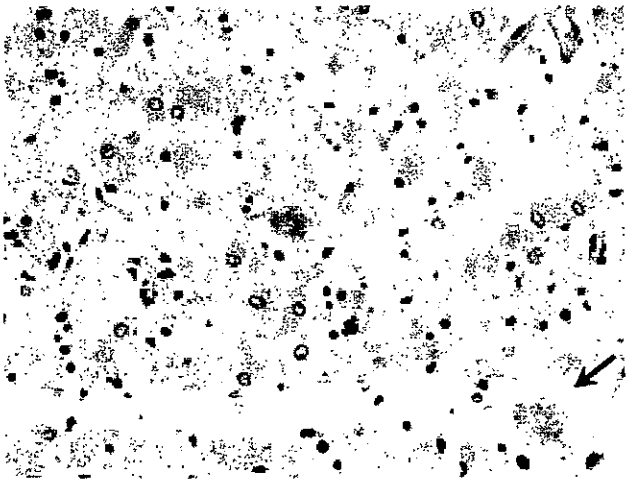

Figure 1. Histopathologic changes in frontal cerebral cortex of the patient who died of variant Creutzfeldt-Jakob disease in the United States. Marked astroglial reaction is shown, occasionally with relatively large florid plaques surrounded by vacuoles (arrow in inset) (hematoxylin and eosin stain, original magnification ×40).

Updates on vCJD

As of early August 2005, 157 vCJD patients were reported from the United Kingdom: 13 have been reported from France, 3 from Ireland, and 1 each from Canada, Italy, Japan, Portugal, Spain, the Netherlands, and the United States (Figure 3). Similar to the vCJD patient from the United States, 1 patient from Ireland and the patients from Canada and Japan were likely exposed to the BSE agent during their residence in the United Kingdom. Preliminary information indicates that the Japanese patient spent only ≈24 days in the United Kingdom. In addition, the US National Prion Disease Pathology Surveillance Center confirmed a vCJD diagnosis by analyzing a brain biopsy sample from a 33-year-old Saudi man admitted to a hospital in Saudi Arabia. Although detailed information on this patient was not available, he may have visited the United Kingdom, if at all, only for several days. Thus, the patient likely contracted the disease in Saudi Arabia after eating BSE-contaminated cattle products imported from the United Kingdom.

Certain characteristics distinguishing vCJD from classic CJD raised early concerns about possible secondary bloodborne spread of vCJD, especially in light of the lack of experience with this newly emerged disease. Of specific concern was the detection of the agent in lymphoid tissues and the possibility of prionemia as the agent spreads from the gut to the brain. In 1997, to monitor for the possible bloodborne transmission of vCJD, researchers in the United Kingdom began investigating recipients of blood components obtained from donors who subsequently died of vCJD (5). As of February 2004, 48 recipients were identified, including 18 who had survived for ≥4 years after transfusion. Two of these 18 recipients had evidence of bloodborne transmission of vCJD. One of the 2 recipients was 62 years of age and had received 5 units of erythrocytes in 1996 (5). One of these units was traced to a 24-year-old donor in whom vCJD developed >3 years after the blood was donated. In 2002 (6.5 years after the transfusion), vCJD developed in the recipient, who died 13 months after illness onset. An autopsy confirmed the diagnosis of vCJD.

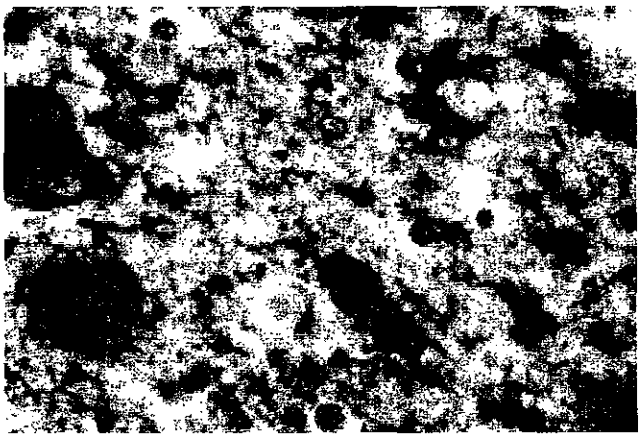

Figure 2. Immunohistochemical staining of cerebellar tissue of the patient who died of variant Creutzfeldt-Jakob disease in the United States. Stained amyloid plaques are shown with surrounding deposits of abnormal prion protein (immunoalkaline phosphatase stain, naphthol fast red substrate with light hematoxylin counterstain; original magnification ×158).