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医薬品　研究報告　調査報告書

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研究報告の概要 102	問題点（米国調査研究：輸血によるCJD伝播のエビデンス欠如） 米国赤十字社の報告である。2004年以降、英国でのvCJDの輸血による伝播が報告され、古典的CJDの伝播のリスクについての懸念が高まってきた。1995年に米国赤十字社は米国疾病対策センター（CDC）と共同して、輸血によるCJD伝播の懸念を評価する詳細な疫学データを得るために、供血後にCJDと診断された供血者（CJD donor）の長期遡及調査を開始し、CJD donorの供血から製造された血液製剤の受血者の追跡調査を実施した。調査コーディネーターは、共同している血液センター、患者家族、CDCやFDAからの情報によりCJD donorを特定した。血液事業者の記録調査及び医療施設との協力により、CJD donorの血液成分を投与された受血者を特定した。少なくとも受血者の一人が特定され、投与後少なくとも1日以上の生存記録があれば、そのCJD donorは本調査に登録される。受血者の生存状況また死亡の場合は死因を、CDCのNational Death Index (NDI)データベースで調査した。 36人の特定されたCJD donor（供血期間：1970年から2006年まで）のCJDの診断は、神経科医により行われ、その58%（21/36）は脳組織の剖検、生検が実施された。36人のCJD donorのうち、34人（94%）が孤発性CJD、1人が家族性CJD、1人が医原性CJDと特定された。 436人の受血者が本調査に登録され、2006年12月時点で329人（75.4%）が死亡、91人（20.9%）が生存、16人（3.7%）が脱落した。死亡者の平均年齢は70.5歳で、CJDの診断で死亡した人はなかった。 供血後60ヶ月未満にCJDを発症した供血者の血液を投与された受血者260人のうち、47人（18%）が2006年時点で生存していた。 受血者の約三分の一(144人)が輸血後5年以上生存していた。この長期生存者中60人の受血者(46.8%)がCJD発症60ヶ月未満に供血された血液を投与されていた。 米国のCJD発症60ヶ月未満に供血された血液成分を輸血された68人の長期生存者と英国でのvCJD donorの血液成分を輸血された21人の長期生存者のリスクを比較した。米国では死亡例がなく、英国では3例（14%）で有意に差があった（p=0.012、Fisher's exact test）。 CJD Donorは、血液の安全性にとって例えリスクがあったとしても、vCJD Donorと比較してリスクはより少ない。

報告企業の意見	今後の対応
当社製品を製造する原料血漿は、ドイツ、米国、オーストリア由来であり、またCJDの家族歴、英国等の滞在期間等に基づき供血停止基準を設けて収集している。 製造工程において異常プリオンを低減し得るとの報告があるものの、理論的なvCJD等の伝播のリスクを完全には排除できないので、投与の際には患者への説明を十分行い、治療上の必要性を十分検討の上投与することを添付文書に記載し、注意喚起している。	今後とも新しい感染症に関する情報収集に努める所存である。

使用上の注意記載状況・その他参考事項等

Lack of evidence of transfusion transmission of Creutzfeldt-Jakob disease in a US surveillance study

Kerri Dorsey, Shimian Zou, Lawrence B. Schonberger, Marian Sullivan, Debra Kessler, Edward Notari IV, Chyang T. Fang, and Roger Y. Dodd

BACKGROUND: Since 2004, several reported transfusion transmissions of variant Creutzfeldt-Jakob disease (vCJD) in the United Kingdom have reawakened concerns about the possible risk of similar transmissions of nonvariant or classic forms of CJD.

STUDY DESIGN AND METHODS: Patients with a CJD diagnosis and a history of donating blood were reported to the study coordinator. Through review of blood distribution and hospital records, the recipients of blood components from these donors were identified. We then determined each recipient's vital status and, if deceased, the cause(s) of death identified by matching the recipient's personal identifiers with the Centers for Disease Control and Prevention's National Death Index database. We conducted such searches after recipients were enrolled in this study and annually thereafter for those who remained alive.

RESULTS: The study included a total of 36 blood donors who subsequently developed CJD and 436 recipients. Through 2006, 91 of these recipients were still alive, 329 were deceased, and 16 were lost to follow-up. After transfusion, these three groups had survived a total of 2096.0 person-years. A total of 144 recipients survived 5 years or longer after transfusion and 68 of them had received blood donated 60 or fewer months before the onset of CJD in the donor. We identified no recipient with CJD.

CONCLUSIONS: The current results of this large, ongoing lookback study show no evidence of transfusion transmission of CJD. They reinforce the conclusion that the risk, if any, of transfusion transmission of prion disease by CJD donors is significantly lower than the comparable risk of such transmission by vCJD donors.

Variant Creutzfeldt-Jakob disease (vCJD) and the nonvariant or classic forms of Creutzfeldt-Jakob disease (CJD) of humans belong to a group of transmissible, fatal degenerative neurologic diseases called transmissible spongiform encephalopathies (TSEs). These diseases are also called prion diseases because of the formation and accumulation of an abnormal form of the prion protein (PrP^{sc}) that is hypothesized to play a central etiologic role in the disease process.[1] TSEs affect both humans and animals (e.g., bovine spongiform encephalopathy [commonly known as mad cow disease] in cattle; scrapie in sheep and goats; and chronic wasting disease in deer, elk, and moose).

Prion diseases in humans have been reported to occur sporadically without an apparent environmental source, through an inherited genetic mutation, or iatrogenically. Cases of familial CJD have occurred due to a mutated prion protein gene (PRNP) located on chromosome 20. More than 30 different mutations of the PRNP have been linked to familial human prion diseases. The most common familial CJD haplotypes are E200K-129M and D178N-129V.[2] Cases of iatrogenic CJD have been associated with exposures to contaminated neurosurgical equipment, human-derived pituitary growth hormone injections, cadaver-derived dura mater grafts, and corneal grafts.[3]

Surveillance of CJD in the United States has shown approximately one case annually per million people in the general population. Over many years, these rates have remained reasonably stable and the median age at death has consistently been approximately 68 years.[4,5]

Since the late 1980s, efforts have been made to minimize the potential risk of transfusion transmission of CJD, and in the 1990s the Food and Drug Administration (FDA) convened a TSE advisory committee, consisting of public interest advocates, ethicists, caregivers, and technical experts. Further, the FDA has issued a number of guidances for industry. These guidances attempt to balance the benefits of reducing the uncertain risks of prion disease transmission by blood products and the potential adverse impact that such preventive policies might have on product availability.[6]

Since 2004, transfusion transmission of the vCJD agent has been well documented. To date, the investigators conducting the UK Transfusion Medicine Epidemiological Review (TMER) study have linked three symptomatic cases of vCJD and one asymptomatic vCJD infection to receipt of blood transfusions from donors who subsequently developed vCJD (vCJD donor).[7,8] One blood donor was linked to two of the vCJD transmissions through donations, 21 and 17 months before the donors' onset of vCJD. These data suggest that once vCJD infectivity appears in blood it probably persists there. In addition to increasing concerns about the transmissibility of vCJD, these transfusion transmissions reawakened concerns and interest in blood safety and CJD. Both vCJD and CJD are invariably fatal and are caused by similar unconventional agents that are unusually resistant to inactivation. Incubation periods for vCJD and iatrogenic CJD are measured in years; there is no practical, licensed screening test to identify those who may be incubating these diseases.[9,10] Because CJD is far more common than vCJD, CJD might potentially affect even more recipients if, in fact, CJD were transmitted by blood transfusion.[11,12]

Surveillance and epidemiologic studies have provided the most reassuring data about blood safety and CJD, although very little long-term lookback data on donations from CJD donors have been reported.[8,13,14] Surveillance of high-exposure recipients, such as persons with hemophilia, and case-control studies show no evidence for transfusion transmission of CJD in humans.[15-17] In contrast, animal models have demonstrated that prion diseases can be transmitted by blood, a finding that aggravates concern about blood safety and CJD.[18,19] For example, studies comparing the infectivity in murine models of vCJD and Gerstmann-Straussler-Scheinker disease, a genetically inherited, classic (not bovine spongiform encephalopathy related) form of prion disease, revealed similarly low levels of infectivity in blood components during both the preclinical and the clinical phases of disease.[19]

In late 1994, a report of CJD in an American Red Cross 10-gallon donor heightened public health concerns in the United States about the possible transfusion transmission risk of CJD. Because of these concerns, in 1995 the Red Cross in collaboration with the Centers for Disease Control and Prevention (CDC) initiated a long-term lookback investigation of blood donors who were later diagnosed with CJD (CJD donors). The purpose of this collaborative study was to provide further epidemiologic data to assess the recurring concerns about the possibility of CJD transmission by blood transfusion. This article reports on the follow-up of the recipients of blood products from reported CJD donors. This study is the largest of its kind reported to date in terms of the number of such recipients identified and the period of time that they were documented to have survived after transfusion.

MATERIALS AND METHODS

CJD patients with a history of blood donation

The study coordinator identified CJD blood donors from reports provided by collaborating blood centers, family members, the CDC, and the FDA. Through searches of blood establishment records on donations made by the CJD donor and with the cooperation of hospitals, we identified recipients of the CJD donors' blood components.

Criteria for inclusion of a CJD donor in the study included a diagnosis of CJD made by a neurologist (and preferably confirmed by neuropathologic study of brain tissue at autopsy or biopsy) and a history of at least one documented allogeneic blood donation. (Autologous and therapeutic donations were not included.) We collected results of available diagnostic laboratory tests, cerebrospinal fluid studies, and electroencephalograms on the reported CJD donors. We notified the blood centers about the CJD donors and requested that each center review its records for each of the CJD donor's donations to identify the recipients of each donor's labile blood components. A CJD donor was entered in the study when at least one of these recipients was identified and could be documented to have survived for at least 1 day after receiving the blood components.

Recipients of blood products from donors who developed CJD

We requested that the transfusion service personnel send us information on each recipient of blood from a CJD

ABBREVIATIONS: NDI = National Death Index; TMER = Transfusion Medicine Epidemiological Review; TSE(s) = transmissible spongiform encephalopathy(-ies); vCJD = variant Creutzfeldt-Jakob disease.

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donor. This information included the recipient's name and social security number; data on the transfusion of concern, including date of transfusion and the volume and type of components transfused; and data on the last known vital status of the patient, including the date and cause of death if a recipient was deceased. The institutional review boards of the CDC and the Red Cross approved this protocol. No study-related recipient notification was required by the institutional review boards because of the absence of: 1) compelling evidence of transfusion transmission of CJD in humans, 2) any practical licensed test for preclinical CJD, and 3) any established treatment to prevent or cure CJD.

Follow-up of the recipients

For recipients for whom we had identifiers, we determined each recipient's vital status and cause(s) of death, if deceased, through searching the CDC's National Death Index (NDI) database (National Center for Health Statistics, Hyattsville, MD). We conducted such searches after a recipient was entered in this study and annually thereafter for those who remained alive. Whenever a match between the recipient's personal identifiers and the NDI database occurred, the NDI provided us with the date and codes for the cause(s) of death. The NDI database contains up to 20 codes describing the multiple causes of death. All codes describing the cause of death (underlying and additional contributing causes) were reviewed and recorded. When a code for a neurologic death was identified, the death certificate itself was obtained for review primarily to verify that CJD or some other mention of a prion disease was not listed on the certificate and possibly miscoded. In addition to enabling this verification, the death certificate may provide information on the duration of the illness and whether an autopsy was performed. Codes that triggered a request of the death certificate for a further review are listed in Table 1. The information received from NDI has an 18- to 24-month lag (e.g., the 2006 death index data first became available in 2008) because the vital statistics information is first compiled and coded by the states in which the death occurs, after which it is sent to NDI.

In addition to cross-matching recipient data with the NDI database, we annually queried AutotrackXP (Choicepoint, Inc., Boca Raton, FL) databases. AutotrackXP is a database that provides personal data sourced from multiple public and private databases. They enabled us to confirm the last known state of residence and the survival status of the recipients (e.g., a report of recent activity would indicate that the recipient was alive). For new recipients, we also used the Choicepoint databases to verify the recipients' names and social security numbers. Loss to follow-up occurred when a hospital did not provide us with identifying information for the recipient, but did provide us with the most recent health and vital status available (e.g., patient was alive and healthy at last visit, date of visit).

Statistical analysis

We analyzed the data in terms of the number of recipients of CJD donor blood components multiplied by each recipient's period in years of survival after the date of transfusion. Because the date of each donation was not collected, we used the transfusion date as a surrogate for it when determining the interval from the donation to onset of CJD in the donor. In the few situations where only the month and year were provided, the date was set as the 15th of the month and if only the year was provided the month and day was set to the middle of the year (July 1). Thus, this interval in months was calculated by determining the number of days between the date of onset of the CJD in the donor minus the date of transfusion in the recipient, dividing by 365 and multiplying by 12. This information, in turn, was categorized into seven groups: less than or equal to 12, 13 to 24, 25 to 36, 37 to 48, 49 to 60, 61 to 72, and 73 months and greater.

For recipients, their survival time was calculated by the interval between the date of transfusion and the last known date the recipient was alive or, if the recipient was known to be deceased, the interval between the date of transfusion and the date of death. Person-years were also determined for selected groups of recipients with different lengths of posttransfusion survival, such as recipients who had survived 5 or more years after transfusion ("long-term survivors").

We used Fisher's exact test to assess the difference in risk of blood transfusion transmission of CJD and vCJD among recipients who survived 5 years or longer after transfusion and received blood from a donor whose last donation occurred within 60 months of the onset of symptoms (donation-to-onset interval). The data on CJD were derived from the present study and the data on vCJD from the UK TMER study.[7] In the UK study, the three identified clinical cases of vCJD occurred among 21 recipients known to have survived 5 years or longer and whose donors had an onset-to-donation interval of 60 months or less (R.G. Will, personal communication, 2008).

RESULTS

Study donors

Forty-three blood donors who were subsequently diagnosed with CJD were reported for possible inclusion in this study. Of these 43, 7 were not included due to lack of response from the blood centers, absence of donations on file, or incomplete recipient records.

The CJD illness of all 36 identified study donors was diagnosed by a neurologist, and 58 percent (21/36) of these diagnoses were autopsy and/or biopsy confirmed by examination of brain tissue. Of these 36 CJD donors, 34 (94%) were identified as sporadic CJD, 1 as familial CJD (E200K), and 1 as iatrogenic CJD.

These 36 donors donated blood in 16 states in the United States between 1970 and 2006. The mean age of these donors at onset of their CJD was 60 years (range, 39-74 years). The mean of reported donations made by the donors was 20 (range, 1-76). Not all of the donations yielded an enrolled recipient. Of the units linked to identified study recipients, red blood cells (238 units) were the most commonly received component, followed by platelets (75 units), and plasma (49 units) with the remaining units being other types of components such as whole blood, cryoprecipitate, and granulocytes (35 units).The transfusion service did not report the type of component received for 41 of the recipients.

TABLE 1. Frequency for the top five ICD-9 and ICD-10 codes for the multiple causes of death and for codes that generated further investigation

Code	Grouping or frequency	Number
ICD-9 morbidity/mortality codes for deaths between 1978 and 1998		
ICD-9	*Five most frequent grouping of codes (total diagnosis codes 696 from 252 decedents*)*	
420.0-429.9	Other forms of heart disease	67
410.0-414.9	Ischemic heart disease	58
200.0-208.9	Malignant neoplasms of lymphatic and hematopoietic tissue	45
570.0-579.9	Other diseases of digestive system	37
280.0-289.9	Diseases of blood and blood-forming organs	34
	Frequency of codes that generated further investigation†	
046.1	CJD	0
310.9	Specific nonpsychotic mental disorders following organic brain damage, unspecified	1
331.9	Other cerebral degenerations, unspecified	0
341.9	Other demyelinating diseases of central nervous system, unspecified	0
348.8	Other conditions of brain	0
ICD-10 morbidity/mortality codes for deaths for 1999 through present		
ICD-10	*Five most frequent grouping of codes (total diagnosis codes 182 from 77 decedents*)*	
I30.0-I51.9	Other forms of heart disease (e.g., cardiac arrest, congestive heart failure, endocarditis)	21
I20.0-I25.9	Ischemic heart disease	18
N17.0-N19.9	Renal failure	15
I60.0-I69.9	Cerebrovasular disease	12
I10.0-I13.9	Hypertensive disease	8
	Frequency of codes that generated further investigation†	
A81.0	CJD	0
A81.2	Progressive multifocal leukoencephalopathy	0
A81.9	Atypical virus infection of central nervous system, unspecified	0
B94.8	Sequelae of other specified infectious and parasitic diseases	0
E85.2	Heredofamilial amyloidosis, unspecified	0
F03	Unspecified dementia	3
G20	Parkinson's disease	1
G30.0	Alzheimer's disease with early onset	0
G30.9	Alzheimer's disease, unspecified	1
G31.8	Other specified degenerative diseases of nervous system	0
G47.0	Disorders of initiating and maintaining sleep	0
G90	Disorders of the autonomic nervous system	0
G93.3	Postviral fatigue syndrome	0
G93.4	Encephalopathy, unspecified	0
G93.9	Disorder of brain, unspecified	0
G96.9	Disorder of central nervous system, unspecified	0
G98	Other disorders of nervous system, not elsewhere classified	0
R99	Other ill-defined and unspecified causes of mortality	0

* Mean number of multiple cause of death codes listed per decedent is 3 for both ICD-9 and ICD-10.
† Mean age at death for those decedents that triggered further investigation was 79.5 years (range, 64-101 years).

Study recipients and the results of their follow-up

A total of 436 recipients were included in this lookback. Their median age at transfusion was 66.1 years (range, 4 days to 99 years). They received transfusions in 30 different states between 1970 and 2006.

As of the end of December 2006, 329 recipients (75.4%) were deceased, 91 (20.9%) were alive, and 16 (3.7%) were lost to follow-up. For those who died, the median age at death was 70.5 years (range, 8 months-101 years). None died with a diagnosis of CJD. The top five causes of death for the reported combined underlying cause and multiple causes of death groupings are listed in Table 1; ICD-9 codes were used for deaths occurring before 1999 and ICD-10 codes were used for deaths occurring for 1999 through present and the complete list can be found in Table 1. On average, the decedents had three multiple causes of death

TABLE 2. Distribution of recipients by vital status and the interval between their transfusion and their donor's onset of CJD

Interval between recipient's transfusion and donor's onset of CJD symptoms (months)	Alive	Deceased	Lost to follow-up	Total
≤12	17	44	5	66 (15.1%)
13-24	5	32	3	40 (9.2%)
25-36	12	50	1	63 (14.5%)
37-48	5	35	0	40 (9.2%)
49-60	8	43	0	51 (11.7%)
61-72	15	26	0	41 (9.4%)
≥73	29	99	7	135 (30.9%)
Total	91 (21%)	329 (75%)	16 (4%)	436 (100%)
Person-years followed	1199.25	832.25	64.5	2096.00

TABLE 3. Distribution of recipients by years of posttransfusion survival and the interval between transfusion and onset of CJD in donor

Interval between recipient's transfusion and donor's onset of CJD symptoms (months)	Posttransfusion survival (years)									
	≤4	5	6	7	8	9	10	≥11	≥5, subtotal	Total
≤12	47	2	0	0	7	1	3	6	19	66
13 to 24	31	0	0	1	1	1	2	4	9	40
25 to 36	51	0	2	1	0	0	1	8	12	63
37 to 48	27	0	2	2	0	1	2	6	13	40
49 to 60	36	1	3	2	0	1	0	8	15	51
61 to 72	19	1	3	0	2	2	2	12	22	41
≥73	81	3	1	5	4	4	1	36	54	135
Total	292	7	11	11	14	10	11	80	144	436

listed. Codes that triggered further investigation were 310.9, F03, G20, and G30.9 and occurred six times. Review of each of the six death certificates verified that none included any mention of prion diseases. The mean age of the six decedents was 79.5 years (range, 64-101 years; Table 1). Almost half (49%) of the recipients died within the first year after transfusion. The 2006 NDI results indicated that 91 recipients (all but 2 were adults) were still alive at the end December 31, 2006. Of these 89 adults, AutotrackXP subsequently provided further evidence that at least 85 percent of them were alive.

Recipients in the study were documented to have survived for a total of 2096.0 person-years after receipt of a blood component from a CJD donor (Table 2). The 329 deceased recipients contributed 832.25 of these person-years and the 91 recipients who were alive as of December 2006 contributed 1199.25 person-years. The remaining 16 recipients who were lost to follow-up had contributed 64.5 person-years.

A majority (60%) of the 436 recipients in this study received blood and components from CJD donors that were donated 60 months or less before their onset of CJD (Table 2). A total of 66 recipients received their units within 12 months or less of the donor's onset of CJD. Of the 260 recipients who received blood from donors 60 months or less before their donor's onset of CJD, 47 (18%) were still alive as of 2006.

Approximately one-third of the recipients survived 5 or more years after transfusion (Table 3). Within this group of long-term survivors, 68 recipients (46.8%) received blood that had been donated 60 months or less before onset of CJD in the donor.

We compared the risk associated with receipt of blood components donated 60 months or less before the onset of the prion disease in the CJD donors in the United States and the vCJD donors in the United Kingdom. Whereas in the United States, no case of CJD was identified among the 68 long-term surviving recipients of the blood components donated by the CJD donors within the 60-month period before their onset, in the United Kingdom 3 cases of vCJD (14%) were identified among 21 long-term surviving recipients of the blood components donated by the vCJD donors ($p = 0.012$, Fisher's exact test).

DISCUSSION

This study evaluates the risk of transfusion transmission of CJD in US blood recipients and compares the risk to that reported for vCJD in the United Kingdom. Overall, the US recipients survived for a total of 2096.0 person-years after receipt of a blood component from a CJD donor. No recipient was found to have been diagnosed with CJD. These results indicate that for the period studied, the risk, if any of transfusion transmission of CJD by CJD donors is significantly lower than the risk of transfusion transmission of vCJD by vCJD donors.

Although the incubation period for prion diseases can be very long, about 30 years or longer as observed

when environmental exposures can be reasonably estimated (e.g., Kuru, dural graft-associated CJD, and pituitary hormone-associated CJD), it is noteworthy that at least one case for each of these prion diseases has been observed within 10 years of an exposure. The present plan for evaluating transfusion transmission of CJD is to continue the current surveillance efforts and to continue to identify new recipients for at least another 5 years.

There could be a variety of reasons for not seeing a case of CJD in our recipient population. One of the most likely reasons is that CJD may not be transmitted by blood transfusion, unlike its variant counterpart. If the agent that causes CJD were present in human blood, its concentration might be too low to transmit an infection by the intravenous route. It is also possible that this study has not yet included enough donors and recipients to observe an infection or followed up on the study recipients long enough for them to have completed their incubation period.

The observation of zero cases of CJD among recipients in this study is consistent with the considerable additional data in the medical literature on the risk of transfusion transmission of human prion diseases that has recently been reviewed.[8] In addition to the UK TMER study, we are aware of a German lookback investigation of one blood donor who died of CJD. The donor had 27 definite recipients and 8 probable recipients (total, 35). None of the deceased recipients died from dementia or neurologic causes. Of the 14 who were alive at publication, none exhibited signs of dementia; the longest period of follow-up was 21 years.[14]

Through 2007, the proportion of vCJD cases among the long-term surviving recipients who received blood from a vCJD donor 60 months or less before onset of the donors' illness was 14 percent in the United Kingdom. In contrast, the present study identified no case of CJD among the 68 long-term surviving recipients of the blood components donated by the CJD donors within the 60-month period before their onset. In addition, the smaller UK study of blood components donated by CJD donors in the United Kingdom revealed no transfusion transmissions of CJD. Thus, the results of the present study in combination with the results from the TMER study in the United Kingdom strongly support the conclusion that the risk, if any, associated with receipt of blood components from CJD donors is significantly lower than that associated with receipt of blood components from vCJD donors.

The limitations of this study include the fact that 15 (42%) of the CJD donors enrolled in this study did not have their diagnosis confirmed neuropathologically. The CJD illness of each of these 15 donors was diagnosed by a neurologist and at least 11 of these donors had an electroencephalogram characteristic of CJD and/or a positive cerebrospinal fluid test for the neuron-specific enolase or 14-3-3 proteins. Nevertheless, it is possible that not all the recipients received blood from a true CJD donor.

Another limitation of this study is that we relied upon the US multiple cause of death data to identify CJD in recipients. The sensitivity of such data was assessed by a CDC study conducted in 1996, shortly after vCJD was first announced in the United Kingdom. Although this latter study did not allow for sufficient time for complete filing of all death records, it nevertheless found that the sensitivity of the death records compared to very active, alternative surveillance efforts was 86 percent.[4] In addition to this study, Davanipour and colleagues[20] found the false-positive rate of the death certificates to be 8.3 percent.

Assessment of risks of blood-borne transmission of diseases with potentially long latent periods is inherently limited by the poor survival of transfusion recipients. In the present study, for example, approximately 26 percent[21] of the recipients were alive 10 years after transfusion. Although this survival rate is low, it is consistent with another report of lookback investigations in which only 26 percent of the recipients had survived 10 or more years posttransfusion. Lookback investigations may be more inclined to have lower posttransfusion survival rates because they overrepresent recipients that receive multiple transfusions.[22,23] This relatively low survival rate contributes to the limited statistical power of the present study despite its being the largest study of its kind reported to date to assess the risk of transfusion transmission of CJD. Further detection and enrollment of donor/recipient clusters will continue to increase the power, and, if recipients remain free of CJD, will continue to provide the most direct evidence for the absence of CJD transmission by transfusion. Finally, another limitation encountered in this and other lookback investigations is the increasing difficulty in obtaining identifying information on all recipients. As hospital personnel have become more concerned about remaining in compliance with the federal medical privacy rule of the Health Insurance Portability and Accountability Act (HIPAA), our ability to obtain patient information has been reduced.

In addition to providing public health surveillance data on CJD and blood transfusions, our study provides important evidence demonstrating that compared to vCJD donors, CJD donors pose much less of a risk, if any, to blood safety. Precisely why this difference exists, however, is not fully understood, although clearly CJD and vCJD are different prion diseases. They are most prevalent in different age groups, their pathology and etiologic prion disease agents differ, and they are characterized by a different pattern and duration of clinical signs and symptoms.[5,6] As pointed out by the authors of the TMER study, the observed increased lymphoreticular involvement in vCJD compared to CJD is consistent with an increased transfusion-transmissibility of vCJD.[7,24] Further research may shed additional light on the pathophysiologic

mechanisms that account for the greater transfusion transmissibility of vCJD compared to CJD.

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医薬品
医薬部外品　研究報告　調査報告書
化粧品

別紙様式第
番号 11

識別番号・報告回数			報告日	第一報入手日 2009年5月26日	新医薬品等の区分 該当なし	厚生労働省処理欄
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研究報告の概要

Health Protection Agencyによる扁桃腺組織の大規模な研究結果によれば、vCJDの無症候の人数の最新の推定値は非常に低いままである（2009年5月22日）。
63,000のサンプルのいずれにもvCJDと関連している異常プリオン・タンパク質の証拠は見つからなかった。
2004年、Health Protection Agencyは抽出された扁桃腺からvCJDと関連しているプリオンタンパク質をさがすことによって、無症候性vCJDの保有率を確定するためにNational Anonymous Tissue Archive（NATA）を開始した。
扁桃腺は一度感染するとvCJDプリオンが蓄積する部位の一つである（その他の部位は、脾臓、虫垂、リンパ節、脊椎及び脳）。
集団でのvCJD保有率を認識することは、集団に対するリスクのレベルを決定する、感染の影響を限定する、あるいは疾患を発病する可能性がある人々のために健康管理介入を計画するために重要である。
調査はすでに63,000の扁桃腺組織の収集と解析を行っており、合計100,000まで検体を収集し続ける予定である。
当初100,000のサンプルのうちの最高50検体が異常プリオン・タンパク質を含むことが推定されたが、現在までのところ陽性サンプルは一つもなかった。調査結果は集団中の無症候性のvCJDは予想より少ない可能性があることを示唆する。

使用上の注意記載状況・その他参考事項

2. 重要な基本的注意
(1) 略
1) 略
2) 現在までに本剤の投与により変異型クロイツフェルト・ヤコブ病（vCJD）等が伝播したとの報告はない。しかしながら、製造工程において異常プリオンを低減し得るとの報告があるものの、理論的なvCJD等の伝播のリスクを完全には排除できないので、投与の際には患者への説明を十分行い、治療上の必要性を十分検討の上投与すること。

報告企業の意見

2004年にHPAは、摘出された扁桃腺におけるvCJD関連プリオン蛋白質を検出することにより、無症候性vCJD有病率を確定するためにNATAを開始したが、無症候性vCJD症例は当初予想されていたよりも少ない可能性があることを示唆する報告である。
血漿分画製剤は理論的なvCJD伝播リスクを完全には排除できないため、投与の際には患者への説明が必要である旨を2003年5月から添付文書に記載している。2009年2月17日、英国健康保護庁(HPA)はvCJDに感染した供血者の血漿が含まれる原料から製造された第Ⅷ因子製剤の投与経験のある血友病患者一名から、vCJD異常プリオン蛋白が検出されたと発表したが、弊社の原料血漿採取国である日本及び米国では、欧州滞在歴のある献（供）血希望者を一定の基準で除外し、また国内でのBSEの発生数も少数であるため、原料血漿中に異常型プリオン蛋白が混入するリスクは1999年以前の英国に比べて極めて低いと考える。また、製造工程においてプリオンが低減される可能性を検討するための実験を継続して進めているところである。

今後の対応

本報告は本剤の安全性に影響を与えないと考えるので、特段の措置はとらない。

ハプトグロビン

BENESIS2009-011

Protecting people
Preventing harm
Preparing for threats

Latest research into prevalence of vCJD consistent with findings of existing studies

22 May 2009

Latest estimates of the number of people asymptomatic for variant Creutzfeldt-Jakob disease (vCJD) in the population remain very low, according to results from a large scale study of tonsil tissue by the Health Protection Agency, published in today's BMJ (Friday 22nd May 2009).

No evidence of the abnormal prion protein associated with vCJD was found in any of the 63,000 samples analysed.

In 2004, the Health Protection Agency launched the National Anonymous Tissue Archive (NATA) to determine prevalence of asymptomatic vCJD in the population, by looking for the prion protein associated with vCJD in extracted tonsils. The tonsils are one of the sites in the body where, once infected, vCJD prions can accumulate (other sites include the spleen, appendix, lymph nodes, spinal cord and brain).

Awareness of the prevalence of vCJD in the population is important to determine the level of risk to the population and to limit the impact of infection or plan healthcare interventions for people who may develop the disease.

The survey has already involved collection and analysis of 63,000 discarded tonsils, and will continue on until a total of 100,000 samples of leftover tonsil tissue have been examined.

When the archive was established it was estimated that up to 50 of the 100,000 samples could contain the abnormal prion protein, however so far none of the samples are positive.

The findings suggest there may be fewer undetected asymptomatic cases of vCJD in the population than were previously expected. However, only by testing a larger number of tonsils and continuing and expanding on the current survey, will scientists be confident that the prevalence is lower than earlier estimates.

Dr Jonathan Clewley, an expert on vCJD at the Health Protection Agency, said: "It may be that we have seen the worst of vCJD already, although we need to keep vigilant and implement appropriate public health measures to prevent any possible secondary spread of disease.

"Estimating the prevalence of people who are carrying vCJD unknowingly is important in guiding our public health response to this disease and ensuring all necessary precautions are taken to reduce this risk of further transmission of the agent through surgical operations and other healthcare settings.

"Further studies are planned to strengthen prevalence estimates, these will involve large scale anonymous tissue surveys, and continuation with the testing of tonsil specimens especially in the older age groups."

Ends

Notes to editors

1. The National Anonymous Tissue Archive (NATA) is managed by the CJD Team at the Health Protection Agency and the Transmissible Spongiform Encephalopathies Unit for the Department of Health.

2. The findings are published in the BMJ paper, *Prevalence of disease related prion protein in anonymous tonsil specimens in Britain: a cross-sectional opportunistic survey*, J Clewley *et al. BMJ* 2009; 338: b1442.

3. 63,007 samples were taken, of which 12,763 were from the birth cohort where most cases had arisen (1961-1985), 19,908 were in the 1985-1995 cohort who would have also been exposed to BSE from infected meat or meat products. None of the samples that were investigated by immunohistochemistry or immunoblotting were positive for the presence of PrP^{CJD}.

4. The archive is completely anonymous; after tonsils are removed, they are separated from any identifiable patient

Information before going into the archive. Therefore if abnormal prion proteins are found in a tonsil sample, the results cannot be passed back to the patient.

This anonymous procedure is used because the significance for an otherwise well person of finding abnormal prion protein in their tonsil tissue is unknown at present. The Research Ethics Committee that reviewed the study supported the view that the tonsils should be tested anonymously.

5. Since 1995 there have been 168 definite or probable cases of vCJD in Britain, resulting in 115 deaths from vCJD and 49 deaths thought likely to be due to vCJD. Back calculation based on these cases would suggest between 10 and 190 further clinical cases over the next ten years.

6. The NATA study is able to detect presence of the prion protein regardless of the genotype of the prion protein gene.

7. For further information on this press release please contact the Health Protection Agency's Centre for Infections press office on:

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No. 23

医薬品 研究報告 調査報告書

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研究報告の概要

○稀なBSE突然変異により公衆衛生リスクが懸念される
最近、非定型(H-型、L-型)のウシ海綿状脳症(BSE)が、日本、カナダ、米国に加え、複数のヨーロッパ諸国で発生した。これにより、ヒトの変異型クロイツフェルトヤコブ病(vCJD)が増加するというありがたくない可能性が浮上している。これまで検査された非定型BSE症例のうち、プリオンタンパク遺伝子(PRNP)の突然変異が検出されたのは1例(アラバマ州のBSE牛)のみで、このウシの健常な仔ウシにも突然変異が存在した。これは当該疾患が遺伝性である可能性を示す。実際、2000年のUK BSE Inquiryの報告では、英国のBSE流行はこうした変異による可能性が高いことが示され、スクレイピー関連とする仮説に反対の見解を示した。
非定型BSEを発症させる可能性のある稀なPRNP変異は、オーストラリアとニュージーランドのようなBSEが発生していないと考えられている国々でも起こる可能性がある。このため、ウシに対する厳しいBSE調査を継続し、反すう動物の厳密な飼料規制を行うことが重要である(現在でも多くの国がブタに反すう動物性タンパク質を与えている)。食肉処理時にウシの特定危険部位(脳や脊髄など)を除去することで、感染部位がヒトの食物連鎖に入り込むことを回避できる。
現在利用可能なウシのPRNP突然変異を調べるルーチン遺伝子スクリーニング検査により、公衆リスクについてさらなるデータが得られるだろう。アラバマのウシに同定された点突然変異は、ヒトで最も一般的な型の家族性(遺伝的)CJDの原因と同一であるため、これによって生じる感染性プリオンタンパク質は、より容易にウシ-ヒト関門を通過する可能性が考えられる。vCJD患者の特定は今後も続くだろう。発症頻度が減少しているからといって、将来のアウトブレイクの防止に必要な規制を緩和すべきではない。

使用上の注意記載状況・その他参考事項等

解凍赤血球濃厚液「日赤」
照射解凍赤血球濃厚液「日赤」
解凍赤血球-LR「日赤」
照射解凍赤血球-LR「日赤」

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	今後の対応
非定型ウシ海綿状脳症(BSE)が、日本、カナダ、米国に加え、複数のヨーロッパ諸国で発生し、オーストラリアとニュージーランドのようなBSEが発生していないと考えられている国々でも起こる可能性があるとの報告である。	日本赤十字社は、vCJDの血液を介する感染防止の目的から、献血時に過去の海外渡航歴(旅行及び居住)を確認し、欧州36ヶ国に一定期間滞在したドナーを無期限に献血延期としている。また、英国滞在歴を有するvCJD患者が国内で発生したことから、平成17年6月1日より1980～96年に1日以上の英国滞在歴のある人の献血を制限している。今後もCJD等プリオン病に関する新たな知見及び情報の収集に努める。

(18)