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<tr><td>一般的名称</td><td></td><td rowspan="2">研究報告の公表状況</td><td rowspan="2">Variant Creutzfeldt-Jakob disease: risk of transmission by blood transfusion and blood therapies
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<tr><td>販売名（企業名）</td><td></td></tr>
<tr><td>研究報告の概要</td><td colspan="5">このレビュー記事は最新のvCJDに関する知見と英国での罹患率の要旨である。vCJDは感染性海綿状脳症(TSE)である。TSEの原因物質は立体的に構造変化した宿主正常タンパク質(プリオンタンパク質，PrP^{C})であり，異常で毒性を持つタンパク質(PrP^{Sc}：異常プリオンタンパク質)を作り出し中枢神経系に蓄積される。これまで，vCJDの臨床症例はすべてプリオンタンパク遺伝子のコドン129がメチオニン同型の人で発現していた。ウシ海綿状脳症(BSE)の蔓延は1986年の英国に始まり，何千頭ものウシに影響を及ぼした。その一方，ヒトで初のvCJDはその10年後に報告され，汚染牛肉の消費が原因と思われた。その後すぐに，血液を介したプリオン感染が齧歯類で実験的に証明され，同様の血液感染ルートによるヒト間での感染の可能性という懸念が生じた。後に，無症候のドナーから供血を受けた後にvCJDを発現した2症例が実際に報告された。興味深いことに，1症例目の患者はvCJDが原因で死亡し，そのコドン129はメチオニン同型であった。一方，2症例目の患者はvCJDの徴候はなく無関係の状態で死亡し，そのコドン129は異型であった。
ヒトにおけるvCJDの潜伏期間は不明であり，血液中のPrP^{Sc}を検出するスクリーニングテストがないため，英国においてvCJDの無症候段階(供血者になり得る)にある感染者数を知るのは現時点では不可能である。逆に，vCJDの臨床症状は発症しないが，無症候キャリアーとして感染させる可能性のある人々の存在も浮き彫りになった。
衛生局がリスク評価を行った結果，第VIII因子，第IX因子及び抗トロンビン使用患者はvCJDに感染するリスクが最も高くなった。これらの使用患者をこれまで以上に保護するために，異常なPrP^{Sc}の検出に特定する高感度の血液検査を開発し，同様に潜在的感染者の疫学的調査を頻繁に行うことが不可欠である。
2005年10月の時点で，世界中でvCJD184症例が確認されていると報告された：英国158症例，フランス15症例，その他EU諸国7症例，日本1症例，米国1症例，カナダ1症例，サウジアラビア1症例。カナダ，日本，米国の感染者とアイルランドの感染者1名は英国に在住した履歴があった。そのため，日本政府は1980～1996年の間に英国へ渡航したドナーからの献血を禁止した。</td><td rowspan="3">使用上の注意記載状況・その他参考事項等

BYL-2006-0220-2</td></tr>
<tr><td colspan="3">報告企業の意見</td><td colspan="2">今後の対応</td></tr>
<tr><td colspan="3">弊社血漿分画製剤に使用している血漿は，vCJD のリスクが低い米国で採漿されており，また，現在までに血漿分画製剤による vCJD 感染症例は報告されていないことから，弊社の血漿分画製剤におけるリスクは依然低いと考える。</td><td colspan="2">現時点で新たな安全対策上の措置を講じる必要は無いと考える。引き続き関連情報の収集に努める。</td></tr>
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Variant Creutzfeldt–Jakob disease: risk of transmission by blood transfusion and blood therapies

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Summary. In the last decade, a new variant of the human prion disease Creutzfeldt–Jakob disease (now known as variant CJD or vCJD) was identified and causally linked to dietary exposure to bovine spongiform encephalopathy (BSE) during the 1980s and early 1990s. Preliminary studies in animal models suggest that prions can be transmitted by blood. Based on two recent reports of iatrogenic vCJD transmission by blood transfusion in humans, a Department of Health-sponsored risk assessment warned that recipients of plasma therapies are now at risk of contracting vCJD from potentially infected donors. It is believed that all the population may be susceptible to vCJD infection, although clinical cases have so far occurred only in methionine homozygotes at codon 129 in the human prion protein gene. A non-invasive blood-based diagnostic assay is urgently needed. Because the incubation period may be upwards of 40 years and there is no reliable screening test, it is currently unknown how many people may be in an asymptomatic phase of vCJD infection in the UK. However, there remains a distinct possibility that some infected patients may never develop clinical symptoms but will remain asymptomatic carriers who can potentially transmit the disease to other individuals. Therefore, screening of infectious individuals will be a critical component for individuals who rely on blood transfusions and/or blood therapies. In the absence of screening tests or effective therapies to treat this disease, a formidable worldwide public health challenge lies ahead to prevent new infections, accurately assess infection rates and treat infected patients.

Keywords: blood transfusion, factor replacement, haemophilia, prion, transmission, variant Creutzfeldt–Jakob disease

Introduction

Variant Creutzfeldt–Jakob disease (vCJD) is a recently identified member of the transmissible spongiform encephalopathies (TSE) or prion diseases [1,2]. These disorders are fatal neurodegenerative conditions occurring in humans and other mammals, the best known examples in non-human species being bovine spongiform encephalopathy (BSE) in cattle, scrapie in sheep and chronic wasting disease in deer and elk [3]. Prion diseases are transmissible under both experimental and natural conditions. For many years, the nature of the transmissible agent was the subject of intense debate, and in 1982 the prion hypothesis was proposed by Prusiner [4]. This postulated that the transmissible agent was composed entirely of a modified host protein (prion protein) that was partially resistant to proteolytic degradation, without a nucleic acid component.

The normal form of the prion protein (PrP^{C}) is expressed in many cells and tissues in the body, but is present at highest levels in neurones within the central nervous system [3]. The precise function of PrP^{C} is uncertain, but it has a short half life and is readily degraded by proteolytic enzymes [5]. An abnormal isoform of PrP (PrP^{Sc}) accumulates in the central nervous system in prion diseases. PrP^{Sc} has an identical amino acid sequence to PrP^{C}, but a different conformation, with an increased beta-sheet content that is associated with infectivity and neurotoxicity [3]. This abnormal conformation also confers a relative resistance to degradation by proteolytic enzymes. The precise cellular mechanisms that result in this conformational change, and their locations, have not yet been fully determined.

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The BSE epidemic in the UK

In 1987, a novel progressive neurological condition in cattle was reported in the UK [6]. The new disease was named bovine spongiform encephalopathy (BSE, or 'mad cow' disease) because of its similarity to other prion diseases by pathology and immunohistochemistry. By the early 1990s thousands of cattle were diagnosed with BSE and millions were incinerated to prevent the disease from spreading [7,8]. However, BSE has still not been fully eradicated in the UK. The BSE epidemic in the UK has been attributed to TSE-infected feeds made of meat and bone meal prepared from rendered sheep offal [9]. With the prohibition of specific feeding practices and specified offals, however, the number of reported cases declined to fewer than 500 by 2003 in UK (Fig. 1) [7,8].

Since the UK continued to export cattle offals after 1986, the BSE agent spread to over 20 European countries, as well as to Japan, Russia, Canada, Israel and the USA. Thus, the exportation of contaminated animal feed from the UK to many other countries across the world resulted not only in the spread of BSE but potentially widespread human exposure to BSE-positive animals through the consumption of BSE-contaminated meat products [10]. Public health concerns about the safety of meat products around the world since the BSE epidemic two decades ago have not diminished. On 24, June 2005, the US Department of Agriculture confirmed BSE in a cow that had conflicting screening test results the previous year. Fortunately, no part of the animal had entered the human or animal food supply; however, this case heightened the awareness of the need for better testing in this country and ongoing surveillance [8,11].

Table 1. Classification of human prion diseases [12].

Class	Diseases
Idiopathic	Sporadic Creutzfeldt–Jakob disease
	Sporadic fatal insomnia
Familial	Familial Creutzfeldt–Jakob disease
	Gerstmann–Sträussler–Scheinker syndrome
	Fatal familial insomnia
Acquired	
Human origin	Kuru, iatrogenic Creutzfeldt–Jakob disease
Bovine origin	Variant Creutzfeldt–Jakob disease

Classification of human prion diseases

Human prion diseases are categorized into three distinct groups that reflect their different origin and range: idiopathic, inherited and acquired [2] (Table 1). The commonest of the idiopathic disorders is sporadic CJD (sCJD). Sporadic CJD is distributed worldwide and is the most common of all human prion diseases, accounting for around 85% of all cases [13]. It is associated with a highly aggressive clinical course with a mean duration of illness of approximately 4.5 months. Sporadic CJD occurs most frequently in middle-aged or elderly individuals and appears to be triggered by a somatic mutation of the prion gene, or by a spontaneous conformational change of the host prion protein from its normal cellular form (PrP^{C}) to its abnormal and pathogenic form (PrP^{Sc}) [3,14].

Inherited (familial) forms of prion diseases comprise up to 15% of all cases and are strongly linked to a series of pathogenic mutations and insertions in the prion protein gene [15,16]. The clinical course of these TSEs is characterized by a slow degeneration of the central nervous system, resulting in dementia, ataxia, motor difficulties and death. The inherited human prion diseases comprise three main groups of

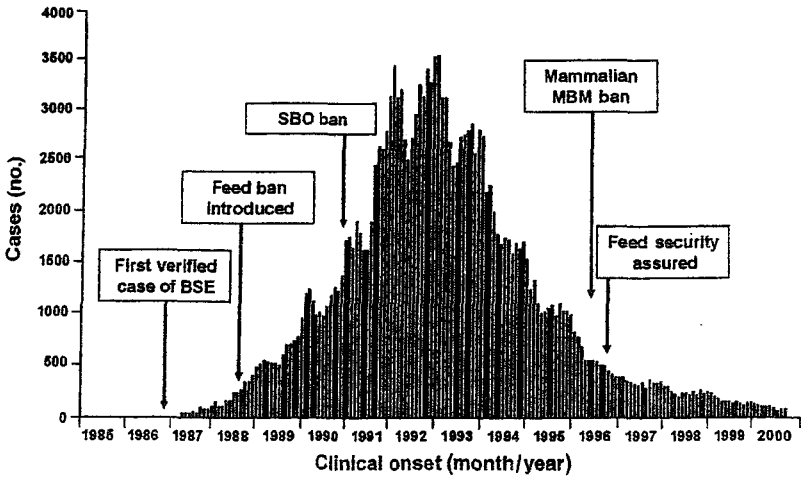

Fig. 1. Bovine spongiform encephalopathy epidemic in the UK [7].

disorders, each with a characteristic clinical and pathological phenotype: familial CJD, the Gerstmann–Sträussler–Scheinker syndrome and fatal familial insomnia [16]. All occur as autosomal dominant disorders [15].

The third group of human prion diseases, the acquired disorders, comprise <1% of all cases and are characterized by exposure to infectivity in brain or nervous system tissue either through human-to-human contact via contaminated neurosurgical instruments, tissue grafts or extracts (iatrogenic CJD) [17], or via the consumption of contaminated bovine meat products (vCJD). Experimental transmission studies have shown that the transmissible agent in vCJD has identical properties to the BSE agent, confirming the link between these 2 disorders [18,19].

Variant CJD was first described in the UK in 1996, but has now been identified in 10 other countries. Variant CJD tends to affect young adults, with a mean age of approximately 29 years (age range 12–74 years at disease onset) [1]. Interestingly, this corresponds with the general age group at which people become blood donors. The duration of the clinical illness is longer (mean duration of 13 months) than that of sCJD, and is characterized by psychiatric features and sensory symptoms at onset, followed by ataxia, myoclonus and other movement disorders; rapidly progressive dementia is very uncommon in this disease [1]. Thus, sCJD and vCJD are distinct disorders that are characterized by different geographical distributions, durations of illness, ages of onset and clinical course, and, most importantly, the causal association of vCJD with BSE.

Transmission of prion diseases by blood

While the transmission of prion infectivity through blood in rodent models of scrapie is well established, recent reports have also found evidence of infectivity in the blood of a rodent model of vCJD and in sheep experimentally infected with BSE [20,21]. These findings have raised questions over the potential transmission of vCJD by blood or blood components. Therefore, concern over safeguarding the blood supply has been gradually mounting given the potentially large number of asymptomatic carriers of vCJD who may unknowingly donate blood. This threat to the blood supply poses a unique challenge to public health officials and raises concerns for patients – especially individuals with haemophilia and other bleeding disorders – who routinely rely on the blood supply and blood therapies. Retrospective studies of haemophilia patients who died from other diseases, including HIV, have not identified any cases of sCJD that were missed or misdiagnosed, either in the UK or in the USA [22,23]. However, although epidemiological studies of sCJD have found no convincing evidence of its transmission by blood [24], the different pathogenesis of vCJD does not allow reassurance to be taken from these studies focusing on sCJD.

Genetic susceptibility to vCJD

Progress in the understanding of human prion diseases was accelerated following the identification of the PrP gene on the short arm of chromosome 20. The identification of pathogenic mutations and insertions in the PrP gene provided evidence to support the prion hypothesis, as familial prion disorders are both genetic and transmissible. Furthermore, it is now recognized that a polymorphism at codon 129 in the human PrP gene may influence susceptibility to prion disease.

Three genetic subgroups have been identified at codon 129 of the PrP gene: methionine homozygous (M/M), valine homozygous (V/V) and heterozygous (M/V). All clinical cases of vCJD have so far occurred in individuals with the methionine homozygous genotype [25,26]. This finding is important because only around 40% of the total human population are methionine homozygotes; approximately 10% are valine homozygotes and 50% are heterozygotes [27,28,29] (Table 2). However, among sCJD cases, only 65% are methionine homozygotes. Thus the methionine homozygous genotype is more susceptible to developing both sporadic and vCJD.

Diagnostic assays for vCJD

One of the largest issues that confront clinicians trying to manage this disease is the absence of a diagnostic screening test for vCJD. Confirmation of a clinical diagnosis of vCJD requires neuropathological examination of the brain following autopsy, with demonstration of the characteristic type 2B isoform of PrP^{Sc} in the brain and lymphoid tissues [25].

Table 2. PRNP codon 129 genotype frequencies [29].

	Genotype		
	M/M	M/V	V/V
Normal population	37%	51%	12%
Sporadic CJD	65%	17%	18%
Variant CJD	100%	–	–

CJD, Creutzfeldt–Jakob disease; M/M, methionine homozygous; M/V, valine heterozygous; V/V, valine homozygous.

Therefore, diagnostic assays are urgently needed for vCJD that are blood based and do not require an invasive brain or tonsil biopsy [30].

A major challenge to the development of such a test is that prions are devoid of nucleic acid, unlike bacteria or viruses, making rapid polymerase chain reaction-based diagnostics non-viable. In addition, as prions are modified cellular proteins and not foreign, there is an absence of a measurable host immune response; hence, an enzyme-linked immunoadsorbent assay (ELISA) diagnostic test is not feasible. The best diagnostic marker for prion diseases is the presence of the disease-associated isoform of the prion protein, PrP^{Sc} [30]. This is generally detected by western blot assay in the brain and in lymphoid tissues in vCJD [31], but attempts to detect PrP^{Sc} in blood from patients with vCJD have so far been unsuccessful, probably because of limitations in the sensitivity of this assay [32]. However, a conformation-dependent immunoassay was recently described that measures both the protease-resistant and protease-sensitive forms of PrP^{Sc} [33] and appears to be far more sensitive than western blot assays. Whether this method will be applicable to blood samples remains to be seen. Another technique that has recently been developed for enhanced detection of PrP^{Sc} is the cyclical amplification method [34]. This relies on a repeated series of incubation with normal PrP and subsequent cycles of sonication, and has recently detected PrP^{Sc} in blood from a rodent model of TSE [35].

Probable pattern of tissue infectivity in vCJD

In the UK, it is presumed that most of the adult population was exposed to the BSE agent through the ingestion of contaminated meat products in the late 1980s and early 1990s. However, because the incubation period of BSE in humans is unknown (incubation periods of 40 years or longer have been documented for other human TSE) [17], and because of the lack of a reliable screening test, it is currently unknown how many people may be in an asymptomatic phase of vCJD infection in UK.

In contrast to sCJD, vCJD infectivity is more widely distributed outside the CNS, and can readily be found in the peripheral nervous system and lymphoid tissues (tonsil, spleen, lymph node and gut) [31]. The levels of infectivity in these tissues are lower than in the CNS, but they still represent possible sources of person-to-person spread of infectivity (Fig. 2) [36]. As the asymptomatic phase of infection in vCJD may last for at least several years, infected individuals may represent a potential source

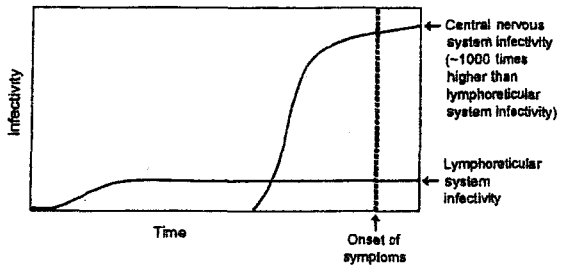

Fig. 2. Probable pattern of tissue infectivity in variant Creutzfeldt–Jakob disease [36].

of secondary spread of vCJD to others via contaminated surgical instruments (such as tonsillectomy instruments) or by blood transfusion.

Variant CJD prevalence study in UK

To estimate the number of individuals in the UK who are asymptomatic for vCJD and who could potentially contribute to the iatrogenic spread of the disease, a retrospective study of lymphoid tissues was recently performed using immunohistochemistry for prion protein in surgically removed tonsillectomy and appendectomy specimens. Researchers reported three positive samples out of 12 674 tested, or an estimated prevalence of 237 vCJD cases per million in the UK (CI 95%) [37,38].

These findings indicate a far higher prevalence than clinical cases would predict, suggesting that additional cases of vCJD are likely to emerge in the UK. Furthermore, they emphasize the importance of preventive measures already instituted by the UK Department of Health to reduce the potential spread of vCJD through blood therapies. These findings also point to the urgent need for large-scale screening of lymphoreticular tissue samples to determine with greater precision the incidence of vCJD infection in the asymptomatic UK population [38].

However, there remains a distinct possibility that some infected patients may never develop clinical symptoms but will remain asymptomatic carriers who can potentially transmit the disease to other individuals. Therefore, screening of infectious individuals will be a critical component for individuals who rely on blood transfusions and/or blood therapies.

Transmission of vCJD infectivity via blood transfusion in humans

Two cases of probable iatrogenic vCJD transmission through blood transfusion have been reported. The first case was a 69-year-old male who presented with

clinical symptoms typical of vCJD in 2002, 6.5 years after receiving one unit of non-leucodepleted packed red blood cells [39]. This patient died 1 year later. Sequencing of the prion protein gene revealed that he was methionine homozygous at codon 129 of the prion protein gene. The asymptomatic donor developed symptoms 3.5 years after donation and subsequently died.

The second case was an elderly female patient who was a known recipient of a blood transfusion from an asymptomatic donor who later developed vCJD [40]. The female patient died of an unrelated illness and without any vCJD clinical symptoms. Because of her known exposure, a medicolegal autopsy was performed. Abnormal prion protein was detected in the spleen and lymph nodes; however, PrP^{Sc} was not detected in the CNS and there were no other significant abnormalities in the CNS. Interestingly, this patient was heterozygous (M/V) at codon 129 in the prion protein gene.

Because that was the first identified case of vCJD infection occurring in the heterozygous subgroup [40], this case raises many important issues regarding the disease, including whether this genotype may have influenced either its incubation period or distribution of infectivity in this patient. These findings underscore the importance of developing effective screening tools and techniques to identify blood donors who may be asymptomatic. In addition, they highlight the need to ascertain whether all vCJD/BSE infections result in clinical disease or whether a subclinical carrier state may occur.

Epidemiological considerations

In the absence of a transfusion-transmitted infection, one statistical analysis has estimated that the probability of acquiring vCJD is approximately 1 in 15,000 to 1 in 30,000 [39]. Therefore, while dietary exposure can never entirely be ruled out, in the aforementioned cases, the infections were far more likely associated with vCJD-contaminated blood transfusions.

To examine a probable link between transfusion and vCJD infection, a review of blood transfusion policies in the UK and a risk assessment on the implications for plasma therapy recipients was commissioned by the Department of Health [41]. The commissioned research concluded that the infectivity concentrations in blood were likely to be highest in the buffy coat fraction, followed by those in plasma and whole blood (Table 3). Moreover, the report stated that levels of the infectious agent present in a full unit of blood would probably be sufficient to cause infection in recipients [41]. The Department of Health's Health Protection Agency also evaluated the risk of different plasma products in an attempt to determine which were most likely to carry the greatest degree of vCJD infectivity. Recipients of factor VIII, factor IX and antithrombin were estimated to have the highest risks: administration of even a single one-vial dose of these products was determined to be sufficient to cause transmission of the disease [42]. Intravenous immunoglobulin (IVIG) and large doses of albumin were concluded to be of medium risk, and anti-D and IVIG were determined to be of low-risk of infectivity.

Table 3. Selected infectivity of blood components [41].

	Volume (mL unit^{-1})	Infectivity (ID_{50}/unit)	Infectivity concentration (ID_{50}/unit)
Whole blood	450	900	2.0
Plasma	225	480	2.1
Filtered plasma	225	480	2.1
Red cells	212	219	1.0
Buffy coat	14	201	14.9

The risk of contracting vCJD from plasma therapies

As recipients of plasma therapies appear to possess the highest risk of contracting vCJD, it is theoretically possible that many patients with bleeding disorders in the UK have already been exposed to the agent responsible for vCJD. Patient groups and the UK Haemophilia Centre Doctors' Organisation believed that the Health Protection Agency's CJD Incidents Panel should recommend that all patients with bleeding disorders in the UK who were treated with UK-source pooled factor concentrates between 1980 and 2001 be considered at potential additional risk for public health purposes [42].

The risk of contracting vCJD has implications for the overall safety of the worldwide blood supply. To address this concern, various measures have been taken to protect the blood supply in the UK, including the sourcing of plasma from the United States (Table 4). Future efforts to minimize the risk of prion contamination of the blood supply might include improved filtration steps to more effectively remove this pathogen.

Variant CJD worldwide as of October 2005

As of October of 2005, 184 confirmed cases of vCJD have been reported worldwide. Individual countries include: UK (158), France (15), Ireland (3), Italy (1),

Table 4. Measures taken to reduce the risk of variant Creutzfeldt–Jakob disease (vCJD) transmission via blood and blood therapies in the UK.

Date	Measure
1997	Withdrawal and recall of any blood components, plasma therapies or tissues obtained from any individual who develops vCJD
1998	Importation of plasma from the USA for fractionation
1998–1999	Leucodepletion of all blood used for transfusion
2002	Importation of fresh plasma from the USA for patients born on or after 1, January 1996
2004	Blood donation is not accepted from people who have received a blood transfusion in the UK since 1980, or who are unsure of this
2005	Donors of blood to patients who have subsequently developed vCJD are advised that they may be at 'increased risk' of vCJD and should not continue to donate blood
Today	Promotion of appropriate use of blood and alternatives in NHS
The future?	Use of 'prion filters'?

USA (1), Canada (1), Saudi Arabia (1), Japan (1), the Netherlands (1), Spain (1) and Portugal (1). The individuals in the USA, Canada and Japan who contracted vCJD and one person in Ireland had all lived in the UK; therefore, these four cases are considered as UK infections.

Japan confirmed its first case of vCJD in 2005. This patient had briefly visited the UK in the late 1980s, fell ill in 2001 and died in 2004. While BSE has been identified in 15 Japanese cattle, officials contend that the patient most likely contracted the disease while in the UK [43]. Because the patient is believed to have visited the UK for less than a month, the Japanese government has changed its blood donation policy to ban donations from anyone who visited UK for a day or more between 1980 and 1996. Previously its policy had been to accept blood donors who had visited the UK for up to 1 month [44].

The fact that cases of vCJD have been reported in many different countries suggest that the disease has spread from the UK to other continents. Although the number of deaths per annum of vCJD in the UK has steadily declined from 28 in the year 2000 to only two by the middle of 2005, the onset of new cases has gradually risen to nine in 2004 from five in 2003 [45]. These data suggest that the disease may become endemic at a low level in the UK population.

Research priorities for vCJD

There are four immediate research priorities. First, to reduce the potential spread of vCJD, there is an urgent need for development of a new screening assay that is applicable to blood and is both highly specific and sensitive. Second, enhanced epidemiological surveillance of potentially infected donors should be broadened to encompass all age groups in the UK. Third, improved methods of decontamination of surgical and laboratory instruments must be developed and implemented across the country to reduce further iatrogenic infections. Finally, progress in the treatment and prophylaxis of vCJD is desperately needed.

Conclusions

In the last decade, a variant of CJD has emerged in many countries that has been causally linked to dietary exposure to BSE during the 1980s and early 1990s. Preliminary studies in animal models suggest that prions, including the BSE agent, can be transmitted by blood. Based on two recent reports of iatrogenic vCJD transmission by blood transfusion in humans, a UK DOH-sponsored risk assessment warned that recipients of plasma therapies are now at risk of contracting vCJD from potentially infected donors. In the absence of screening tests or effective therapies to treat this disease, a formidable worldwide public health challenge lies ahead to prevent new infections, accurately assess infection rates and treat infected patients.

Acknowledgements

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一般的名称	①②人血清アルブミン ③④乾燥濃縮人アンチトロンビンⅢ ⑤人ハプトグロビン ⑥乾燥濃縮人血液凝固第Ⅷ因子	研究報告の公表状況	J Neurol. Neurosurg. Psychiatry online/ doi:10:1136/jnnp:073395	公表国 イギリス
販売名（企業名）	①献血アルブミン-Wf ②献血アルブミン(5%)-Wf ③ノイアート ④ノイアート静注用1500単位 ⑤ハプトグロビン注-ヨシトミ ⑥コンコエイト-HT			

研究報告の概要

CJDは、孤発型、遺伝型、医原型及び変異型の4つの臨床形態をとる。世界中で最もありふれた形態である孤発型CJDの原因は不明であり、2つの研究が以前に処置された外科的治療によるものと示唆しているものの、症例対照研究は何ら一貫性のある危険要因を確認することができていない。遺伝型CJDは、プリオン蛋白に内在する変異と関係し、これが一般的に直接的な原因と考えられている。しかし変異は多分、現在はまだ認められていないものの、感染源に対しての責任を増している。残り2つのCJDの型は、後天的なものである。変異型CJDは、BSEが原因と考えられ、これは汚染食品によるとされている。医原型CJDは、医療又は外科治療の行為によってCJDの不注意な感染に由来する。医原型CJDの内、2つの最も重要な事例は、死体からのヒトの成長ホルモン治療及び外科手術の際の硬膜移植片の使用によるものである。角膜移植、深部電極及び脳神経外科もまた、まれに関与していた。
硬膜関連CJDの最初の報告は1987年であり、より詳細な報告が翌年に公表された。硬膜関連CJDは現在までに、世界中で164の症例があることが認められている。本報告では、英国におけるサーベイランスで確認された硬膜移植関連CJDの7症例、及び最初のブタ硬膜レシピエントのCJD症例について報告及び記述する。
レシピエントは1988年に右の前頭部髄膜腫の切除術を受けた、そして、豚皮質移植片が硬膜を修復するのに用いられた。レシピエントは、134ヵ月後に頭痛、失調と認識減退を呈した。調査により明らかにされた特徴は、一貫して孤発型CJDであり、典型的な脳波によっても確認され、病理学的診断が下された。検死の結果、前頭および側頭の皮質に海綿状変化を示し、同様の特徴は大脳基底核、視床及び小脳にも認められた。免疫細胞化学検査はPrPの広範囲にわたる蓄積を示し、そして、ウエスタンブロット試験は1型アイソフォームを示した。
我々は、症例VIII（硬膜補修にブタの真皮を使用）がヒト以外の移植片に曝露されたヒトでの最初のCJD感染症例であると考える。発症年齢、潜伏期間、臨床並びに調査の特徴は孤発型CJDの典型例に似ていた。さらに、病理学的特徴もまた、孤発型CJDに特有なものと考えられ、1型PrP^{res}と確認された。いずれも、未確認の病原体感染の可能性を完全には排除することができない。しかし、ブタにおけるTSEは、動物モデルでの感染実験による感染でも現在認められていないことから、偶然によるとするのが、最も妥当な説明である。

使用上の注意記載状況・その他参考事項等

代表としてノイアート（献血）の記載を示す。
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	今後の対応
英国におけるサーベイランスにおいてブタの真皮を硬膜補修に用いた患者がCJDを発症したとするヒト以外の移植片に暴露されたヒトでの最初のCJD感染症例である。 ブタのTSEは動物実験においても認められていない。また、これまで血漿分画製剤によってスクレイピーを含むプリオン病が伝播したとの報告はない。しかしながら、万一TSE感染動物由来原材料が本剤の原料に混入した場合には、製造工程においてプリオンを低減し得るとの報告があるものの、製剤から伝播する可能性を完全には否定し得ない。そのため、弊社の血漿分画製剤の製造工程におけるTSE感染性低減に関する検証実験を加速し、自社データを早期に取得し、工程評価を行い、必要に応じて工程改善を実施する予定である。	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。

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SHORT REPORT

Dura mater-associated Creutzfeldt–Jakob disease: experience from surveillance in the UK

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Between 1970 and 2003, seven cases of human dura mater-associated Creutzfeldt–Jakob disease (CJD) were identified in the UK. Furthermore, we identified a case of CJD in a porcine dura graft recipient. The mean incubation period of the human dura mater cases was 93 (range 45–177) months. The clinico-pathological features of the cases are described and compared with cases previously reported in the world literature.

Creutzfeldt–Jakob disease (CJD) exists in four clinical forms: sporadic, genetic, iatrogenic and variant. The cause of sporadic CJD, the most common form worldwide, is unknown and case–control studies have failed to identify any consistent risk factor, although two studies have implicated previous surgical interventions.[1 2] Genetic forms of the disease are associated with underlying mutations of the prion protein gene (*PRNP*), which are generally considered to be directly causative. Mutations, however, possibly increase liability to some, as of yet unrecognised, source of infection. The two remaining forms of CJD are acquired. Variant CJD is considered to be caused by bovine spongiform encephalopathy,[3–5] through contaminated food products; iatrogenic CJD results from the inadvertent transmission of CJD during the course of medical or surgical treatment. The two most numerically significant instances of iatrogenic CJD resulted from treatment with cadaveric human growth hormone and the use of dura mater grafts in surgery. Corneal grafts, depth electrodes and neurosurgical instruments have also rarely been implicated.[6 7]

The first report of dura mater-associated CJD was published in 1987,[8] with a more detailed report appearing the following year;[9] to date, 164 cases have been recognised worldwide (P Brown, personal communication). This paper reports and describes the seven cases of human dura mater graft-associated CJD identified during surveillance in the UK and also, for the first time, reports a case of CJD in a porcine dura graft recipient.

METHODS

CJD surveillance in the UK has been undertaken in four phases.

- A retrospective review was carried out in England and Wales from 1970 to 1979.
- A prospective study was carried out in England and Wales from 1980 to 1984.
- A retrospective review was conducted in UK to cover the period from 1985 to 1990.
- A prospective surveillance was instituted in the UK in 1990 and continues.

The methodology of the National CJD Surveillance Unit has been described in previous publications.[10 11]

RESULTS

Human dura mater

During the period between 1970 and 2003, seven cases of human dura mater-associated CJD were identified in the UK. Table 1 shows the basic demographic features. The latent period between surgery and the onset of CJD ranged from 45 to 177 (mean: 93) months. The mean age at surgery was 33 years, with a mean age at onset of 41 years.

Lyodura (B Braun Melsungen, Germany), a particular brand of human dura mater, was implicated in six of the seven cases (the manufacturer of the dura graft implicated in case I is unknown).

The six cases associated with Lyodura were exposed to the presumed source of "infection" between 1983 and 1987, with the first recognised case in the UK exposed to human dura mater in 1969.

A detailed account of both clinical and investigative features is available online. In four cases, the clinical phenotype at onset appears to correlate with the site of graft placement or underlying parenchymal damage (cases II, III, V and VI). For example—in case II, the initial illness presentation included a right visual field defect; a left hemisphere tumour was also diagnosed. The subsequent CJD began with a right visual field disturbance and progressed with signs indicating the involvement of the left hemisphere. Some of the cases were investigated before the widespread availability of MRI, and therefore MRI was only available in only four of the seven cases. None of the cases showed the characteristic radiological features of human prion disease[14] with post-surgical change being the most commonly recognised abnormality. Despite all seven cases having at least one electroencephalogram during the course of investigation, only three of the seven cases showed the "typical" features.

Autopsy was carried out in five of our seven cases. In general, the neuropathology was characterised by widespread spongiform change accompanied by variable neuronal loss and gliosis. Western blot analysis for PrP^{res} was carried out in three cases (cases II, VI and VII). The mobility and glycoform ratio of the PrP^{res} is indistinguishable from those of the type 1 PrP^{res}, identified in cases of sporadic CJD, and is distinct from type 2B, PrP^{res} identified in variant CJD.

Porcine dura mater

We believe the identification of CJD in a porcine graft recipient to be the first such report worldwide (table 1,case VIII). The recipient underwent excision of a right fronto-

Abbreviations: CJD, Creytzfeldt–Jakob disease

Case V received two dura grafts, is assumed that the first graft was responsible for transmission.

Table 1 UK case details—human dura mater

Case	Surgical procedure	Dura	Year of surgery	Year of death	Incubation period (Months)	Duration of illness (Months)
I, Esmonde *et al*[12]	Suboccipital craniotomy and C1/2 laminectomy for cerebellar ectopia and syringomyelia	?	1969	1979	104*	6
II, Esmonde *et al*[12]	Excision of a left temporal cortex meningioma	L	1983	1991	93*	5*
III	Repair surgical leak after acoustic neuroma excision	L	1985	1989	51	2
IV, Willison *et al*[13]	Posterior fossa decompression and cervical laminectomy for cerebellar ectopia or syringomyelia	L	1985	1989	45*	4
V	Excision of a left parietal cortex meningioma	1) L	1985	1993	1) 86	11
		2) L	1986		2) 79	
VI	Excision of a cerebellar astrocytoma	L	1986	1997	103	33
VII	Excision of a eosinophilic granuloma right frontal region skull	L	1987	2003	177	5
Porcine Dura Graft:						
VIII	Excision of a right frontoparietal meningioma	P	1988	2000	134	3

*Revised from previously published figures.
L, Lyodura; P, Porcine dura.

parietal meningioma in 1988 and a zenoderm graft was used to repair the dura. The recipient presented with headaches, ataxia and cognitive decline after 134 months. Investigative features were consistent sporadic CJD, with a typical electroencephalogram was identified, and pathological confirmation was obtained. Autopsy showed spongiform change in the frontal and temporal cortex, with similar features identified in the basal ganglia, thalamus and cerebellum. Immunocytochemistry for PrP showed widespread accumulation and western blot analysis showed the type 1 isoform.

DISCUSSION

Human dura mater is a rare, but important source of transmission of human prion disease, with only seven cases recognised in a 33-year period. Surveillance systems worldwide have identified 164 cases of CJD in people previously exposed to human dura mater. Prevalence is particularly high in Japan and probably reflects neurosurgical practice, with an estimated 20 000 grafts used each year.[15] The overall risk of CJD associated with human dura grafts in the UK is unknown because an accurate estimation of human dura graft use and thus a denominator for calculation of risk is not available. The estimated risk after exposure in Japan has been estimated to be approximately 1 per 2000 patients treated between 1979 and 2000 and approximately 1 per 1000 between 1983 and 1987.[16] Neurosurgical practice in Japan, with widespread use of dura mater, may be different from other countries throughout the industrialised world and therefore it would seem unreasonable to extrapolate any estimated risk from these data. If neurosurgical practices in the UK were more akin to those in Australia, then a subsequent study by Brooke and co-workers would help provide additional information pertaining to estimated risk. By using information from the Australian CJD Surveillance system, Brooke and co-workers estimated the risk associated with exposure to human dura mater to be approximately 1 per 500 patients treated between 1978 and 2003.[17] Clearly, the risk of developing CJD in this patient population is considerably higher than we would expect by chance.

The human dura mater implicated in the transmission of CJD was processed, almost exclusively, by B Braun Melsungen in Germany and traded under the name Lyodura. Over 100 Japanese cases, and all but one of the UK cases (the source of the first case identified in the UK is unknown), have been associated with this particular product and only rarely has dura processed by other manufacturers been associated with transmission.[18 19] Although the first case in the UK was exposed to potentially infectious dura in 1969, a disproportionately large number of cases were exposed between 1983 and 1987 (80% of those identified worldwide and six of the seven cases in the UK). Interestingly, the apparent reduction in the number of cases post-1987 coincided with the introduction of stringent donor selection criteria and also the introduction of sodium hydroxide immersion techniques in the manufacturing process.

We found no temporal or geographical association between any of the dura-associated cases, or any other case of CJD identified in the UK, despite potential contamination of neurosurgical instruments.

It has been proposed that clinical features at onset are dependent on the site of graft placement or underlying parenchymal damage[20–22] and our findings may support such a proposition. The explanation for this observation is unclear. We, could, however, speculate that the pathological process starts within a region adjacent to the graft and that this is reflected in the early clinical features. This proposition may also be supported by findings obtained at autopsy, with severe pathological changes identified adjacent to graft placement in three cases. Overall, the pathology is consistent for that previously described in dura mater-associated CJD.[9 18] We did not identify either "kuru-type" or florid PrP plaques. The florid PrP plaques were previously noted in limited distribution in a small number of dural graft-associated iatrogenic CJD cases in Japan.[21 23 24]

We believe case VIII represents the first reported case of CJD in a person previously exposed to a graft from a non-human source. The age at onset, duration of illness, clinical and investigative features were similar to a typical case of sporadic CJD. Furthermore, the pathological features were also considered characteristic of sporadic CJD, with type 1 PrP^{res} identified. Neither finding can definitively exclude the possibility of transmission of a yet unidentified pathogen. As natural transmissible spongiform encephalopathies are, however, as yet unrecognised in pigs, despite experimental transmission in animal models,[25] a chance association seems the most plausible explanation.

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