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別紙 3-3

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一般的名称			研究報告の公表状況	Clinical implications of emerging pathogens in haemophilia: the variant Creutzfeldt-Jakob disease experience Golan, G. Haemophilia 12. (Suppl. 1), 16 - 20 (2006)	公表国 英国	
販売名（企業名）						

研究報告の概要	使用上の注意記載状況・その他参考事項等
本文献は英国の血友病の実地臨床における変異型クロイツフェルト・ヤコブ病(vCJD)の影響を報告している。1980年代，血漿由来製剤による治療で，血友病患者団体がHIVとC型肝炎ウイルス感染の危険に直面するという厳しい教訓を得た。このため，1997年に英国血友病センターの医師団は，血友病患者に対する最適な治療法は遺伝子組換え凝固因子であると述べた。1996年の，英国で最初のvCJD症例報告の直後に，輸血を介してvCJD感染の恐れがあるという懸念が生じた。1997年，vCJDは英国においてのみ確認され，多くの血友病患者が英国由来の血漿因子濃縮製剤の投与を受けていたため，遺伝子組換え凝固因子による治療を受けられない患者には，非ヨーロッパ諸国，好ましくは米国で処理が行われた血漿因子濃縮製剤を用いるべきである，という追加勧告がなされた。後に，1996-97年に英国で供血された血漿因子濃縮製剤のいくつかのバッチが実際にvCJDを引き起こす病原因子で汚染されていたことが明らかになった。この結果，2005年4月現在，A型及びB型血友病患者全員に遺伝子組換え凝固因子が投与されている。輸血を介してvCJDに感染した最初の患者が2003年12月に死亡後，ヒト間での感染リスクが減少するよう計画された法案により，1980年から2001年の間に英国で供血されたヒト血漿由来の治療を受けた全血友病患者の取扱いが決定した。例えば，これらの患者が中枢神経系に関わる手術を受けた際，使用された手術器具は全て廃棄されなければならない。したがって，筆者は血友病患者にはリスクの最も低い治療法のみを適用することを推奨している。	BYL-2006-0220-3

報告企業の意見	今後の対応
弊社の第 VIII 因子製剤は遺伝子組換え製剤である。本剤の培養培地にはヒト血漿由来成分が使用されているが，弊社の血漿分画製剤の製造工程は，4log を上回るプリオンを除去することが確認されている。	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。

Haemophilia (2006), 12, (Suppl. 1), 16–20

Clinical implications of emerging pathogens in haemophilia: the variant Creutzfeldt–Jakob disease experience

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Summary. The impact of variant Creutzfeldt–Jakob disease (vCJD) on the clinical practice of haemophilia in the UK is coloured by the haemophilia community's experience of hepatitis C virus and human immunodeficiency virus (HIV) transmission via plasma-derived therapies in the 1980s, when the delay in recognizing and acting on the potential risks cost many patients their lives and left others to manage another chronic disease. This crisis prompted organisations such as the United Kingdom Haemophilia Centre Doctors' Organisation to advocate for the introduction of haemophilia therapies that would not be susceptible to contamination with blood-borne pathogens. After the identification of vCJD in 1996, a number of public health measures were taken in response to a government-sponsored vCJD risk assessment, and following reports of transfusion-transmission of vCJD, additional guidelines have been developed to prevent person-to-person transmission, some of which may impact the quality and availability of medical and surgical care. Variant CJD has had a significant negative effect on the UK haemophilia community, shaking patient confidence in the therapies they have received over the last 21 years, affecting the quality of care and creating the risk of stigmatizing the community as it was in the 1980s. As with HIV and vCJD, emerging blood-borne infectious agents will likely affect blood and blood-derived therapies well before we become aware of its presence. As a result, only therapies with the lowest level of risk should be used for care of patients with haemophilia.

Keywords: haemophilia, pathogen, variant Creutzfeldt–Jakob disease

Introduction

This article will review the impact of variant Creutzfeldt–Jakob disease (vCJD) on the clinical practice of haemophilia in the UK, with particular attention to how haemophilia treater and patient organizations have responded to this concern. The haemophilia community's response to vCJD is best understood in the context of the significant morbidity and mortality caused by the transfusion-transmitted hepatitis C virus (HCV) and human immunodeficiency virus (HIV) infections contracted in the 1980s. Given the delayed recognition of the risk that HIV and HCV posed to patients with haemophilia, the subsequent lack of rapid response and the many missed opportunities to protect patients from contaminated plasma-derived therapies, it is understandable that many patients with haemophilia and their caregivers are now very alert to the potential implications of emerging pathogens such as vCJD. This is especially true for those patients who still rely on plasma-derived therapies and transfusions.

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UKHCDO therapeutic guidelines

The United Kingdom Haemophilia Centre Doctors' Organisation (UKHCDO) was established in 1968 by doctors treating patients with bleeding disorders who sought to improve care, conduct research into the disorders and facilitate healthcare planning. The UKHCDO and the patient organization the Haemophilia Society had, for many years, argued for the introduction of recombinant therapies. This view was reflected in the UKHCDO haemophilia treatment guidelines, published in 1997, which stated that recombinant factor concentrates were the treatment of choice for patients with haemophilia [1]. The guidelines further stated that recombinant factor concentrates were the safest with respect to reducing the risk of transfusion-transmitted infection. At the

time the UKHCDO guidelines were released, the general consensus among haemophilia treaters was that the plasma therapies used in the UK had a relatively low risk for transmission of hepatitis or HIV, but because they could transmit other infectious agents, such as parvovirus B19 and hepatitis A, [2,3] they might in theory be the route of infection for new or altered agents.

The UKHCDO guidelines were accepted by most treaters but not by the majority of healthcare commissioners. In particular, the future risk of infection by emerging pathogens through plasma therapy was not accepted. Approximately 6 months later, the potential threat of vCJD to the haemophilia community emerged.

Shortly after vCJD was first described in the UK in 1996, concerns were raised that it could be transmitted through blood transfusion and blood therapies [4]. As a result, the UKHCDO convened a meeting with experts on prion diseases, including members of the National CJD Surveillance Unit and the Spongiform Encephalopathy Advisory Committee (SEAC), both of which were formed in 1990. The National CJD Surveillance Unit is sponsored by the Department of Health (DOH) and the Scottish Executive Health Department; SEAC is sponsored jointly by the Department for Environment, Food and Rural Affairs, the DOH and the Food Standards Agency (FSA). The purpose of the meeting was to determine, by means of a thorough review of all available evidence, if there were any measures available to effectively reduce the risk to patients with haemophilia of contracting vCJD and other prion-based diseases.

At the time, in 1997, vCJD had only been identified in Great Britain. Limited research indicated that this was a new disease with a long incubation period [5]. Relatively little epidemiological data were available, but evidence from some animal studies indicated that there existed the possibility of transfusion-transmitted vCJD infections. Further, it was surmised that many vCJD-infected, yet asymptomatic, individuals were continuing to donate blood that would be used in the processing of factor VIII and factor IX therapies. At that time, many patients with haemophilia in the UK were treated with UK-sourced plasma factor concentrates.

Based on the 1997 meeting of the UKHCDO, SEAC and the National CJD Surveillance Unit, several recommendations emerged [4]:

1 Healthcare providers should reduce the risk of vCJD transmission by using plasma factor concentrates sourced in other countries.

2 Recombinant factor concentrates should remain the treatment of choice for patients with haemophilia.

3 Plasma-derived concentrates processed with non-European plasma, preferably from the US, should be provided for those patients for whom recombinant factor concentrates were not made available.

As a consequence of these recommendations, the two main UK fractionators of plasma, Bio Products Laboratory and the Scottish National Blood Transfusion Service, were obligated to stop processing factor concentrate therapies. In the meantime, the UK imported plasma from the US for processing factor VIII and factor IX. This ban on utilization of UK-derived plasma resulted in long delays in resuming the processing of factors and interrupted the supply of other niche therapies such as factor VII and factor XI.

Patients and providers respond

Prior to 1997, many patients with haemophilia and their physicians held the view that UK-sourced plasma therapies were safer than any alternative and there had been a relatively slow uptake of recombinant therapies. With the introduction of these policies recommending the use of non-UK-sourced plasma, however, patient confidence was undermined and the pressure increased on government and healthcare commissioners to make recombinant therapies more widely available.

Against a background of increasing concern about the possible risk of vCJD, England's Department of Health agreed that recombinant therapies should be made available to all children with haemophilia [6]. In other health departments, in Scotland, Wales and Northern Ireland, they took the recommendations one step further and introduced recombinant therapies for all patients. But in England, the most populous country in the UK, adults continued to be prescribed and use plasma therapies, although derived from plasma imported from the USA.

Variant CJD: a potential new threat to factor concentrate safety

In 2000, Bio Products Laboratory notified the UKHCDO about the identification of batches of factor concentrates that had been prepared in 1996 and 1997 and used before 1998. It was determined that these concentrates were prepared from plasma pools that included plasma from a donor who had

subsequently developed vCJD. Since then there have been further notifications of batches of factor concentrates prepared from plasma from donors who were later diagnosed with vCJD. Table 1 enumerates all the batches of therapies distributed and subsequently identified as being potentially infected with vCJD, as of September 2004 [7]. These therapies were produced by either Bio Products Laboratory or Protein Fractionation Centre and, in most circumstances, many patients were treated with these therapies before notification had been given.

At the time there was no clear evidence that vCJD could be transmitted by blood products. There was no test to identify potentially asymptomatic but infected donors, and there was no treatment to offer patients for reassurance or for further assessment. Because vCJD has a long incubation period, clinical examination was of little or no use. With these facts in mind, healthcare providers and policy makers were faced with the decision of what, or even if, to tell their patients.

Response to possible risk of transfusion-transmitted vCJD

In 2004, the decision was made to inform all patients about the possible risk of transfusion transmitted vCJD, irrespective of whether they had received concentrates or not from the implicated batches. Patients were given three choices: they could come into their healthcare providers' offices and discuss the information in person; they could choose to be fully informed by letter; or they could refuse to be informed in any way. Many patients chose the third option. Patients who chose to be educated about the potential risks were given information disclosing that they might be infected with vCJD. Given that the majority of patients were not able to have access to recombinant therapies, this situation caused considerable concern.

For the UKHCDO, responding to the potential infection of haemophilia patients created a huge administrative burden. There was an urgent need to review all records, to contact all patients possibly infected and to give each of them the option to review all information then known about vCJD. Added to the administrative burden were government-mandated timelines as to when the patients needed to be informed.

Table 1. Batches of 'implicated' UK plasma therapies [7].

Factor VIII	16*
Factor IX	8*
Antithrombin	1
Immunoglobulin G	11
Albumin 4.5%	28
Albumin 20%	21
Factor VIII with albumin excipient	76
Intramuscular immunoglobulin	12

*Indicates widely distributed throughout the UK.

The threat of vCJD among members of the haemophilia community increased the political pressure for more widespread use of recombinant coagulation factor concentrates in the UK. And as a result, as of April 2005, all patients with haemophilia A and B have been offered recombinant factor concentrates.

Risk of vCJD from implicated plasma-derived concentrates

One of the questions that remain unanswered today is what risk do the recipients of plasma concentrates exposed to vCJD pose to others? This issue came to the forefront in December 2003 when the Health Secretary informed the UK Parliament of the first death probably related to transfusion-transmitted vCJD. This case was later confirmed as being related to vCJD [8,9].

The Department of Health established the CJD Incidents Panel, an expert committee sub group of the Advisory Committee on Dangerous Pathogens Working Group on Transmissible Spongiform Encephalopathies, in 2000 in order to help the medical community handle cases such as this. The mandate of this committee is to review the available literature, establish a formal risk assessment of infectivity of blood and blood therapies and formulate guidelines for response by the medical community. The CJD Incidents Panel advises hospitals, trusts and public health teams throughout the UK on how to manage incidents involving possible transmission of CJD between patients.

Based on a risk assessment commissioned by the DOH in 2003, the CJD Incidents Panel attempted to identify patients who had received at least one dose of a plasma therapy, which the committee judged to increase the risk of vCJD exposure by more than 1% over background. Therapies that were considered the highest risk were factor VIII, factor IX and antithrombin. The administration of just one vial, or 500 units, was considered enough to put patients in a high-risk category. Medium risk therapies included intravenous immunoglobulin G and albumin 4.5% administered in large doses. Low-risk therapies were defined as albumin 20%, intramuscular immunoglobulin and factor VIII with excipient albumin administered in extremely large doses [10].

In refining the risk assessment, the question emerged: which of the 'at risk' patients need be treated with precaution: those with known exposure to contaminated or potentially contaminated batches of plasma concentrates, or any patient treated with plasma-derived concentrate in the period from 1980 to 2001? Because the possibility existed that, over time, additional donors might be identified as having vCJD, it was decided to treat all haemophilia patients who had used therapies from UK-derived plasma in this 21-year-period with measures designed to reduce the risk of human-to-human transmission [11].

Measures to prevent human-to-human vCJD transmission

Following the 2001 release of a DOH-sponsored summary of the risks of vCJD transmission via surgical implements [12], the Advisory Committee on Dangerous Pathogens and the Spongiform Encephalopathy Advisory Committee published a set of guidelines in 2003 for the precautionary management of potentially-infected patients, both healthy and deceased, in order to minimise the risks of transmission to other patients and healthcare staff [13]. These guidelines were a significantly expanded version of recommendations that were released in 1998 but kept under review until a number of uncertainties were better understood, including the routes of infection, threshold infectious dose, potential for inactivating the agent and the quantity of people who might be incubating the disease.

The detailed guidelines recommend measures for laboratory containment and control, infection control of CJD and related disorders in a healthcare setting, decontamination and waste disposal and quarantining of surgical instruments, among others. For example, when patients who used UK-sourced plasma-based therapies in the years 1980–2001 undergo any surgery involving high-risk tissues, such as the central nervous system or the lymphatic system, the surgical instruments used must be subsequently destroyed [14].

Some general precautions included using single-use instruments wherever possible; performing all procedures in a controlled environment, such as an operating theatre; performing the procedure after all others; involving the minimum number of healthcare personnel; and using liquid-repellent operating gowns over plastic aprons, as well as goggles or full-face visors [15].

More controversially, the guidelines stipulated that if these patients have an endoscopic procedure of the gastrointestinal tract or the olfactory mucosa, the instruments used in those procedures also must be quarantined, i.e. not used again or destroyed [15]. The quarantine or destruction of surgical instruments has, of course, financial consequences: the quarantine of an endoscope is estimated to cost approximately £30 000 per instrument per year. Endoscopy services are in high demand, and quarantining an endoscope, or destroying it after every use, is not a reasonable or cost-effective policy for any healthcare institution. In the risk-assessment guidelines, it was suggested that capsule wireless endoscopes be used instead, but expertise in capsule endoscopy is limited, so the issue has yet to be fully resolved.

Potential stigmatization

One of the negative outcomes of the distribution of the guidelines of the CJD Incidents Panel was that persons with haemophilia became identified as presenting a risk of infection to others. In some medical centres, reluctance to performing invasive procedures became an issue in all but serious cases.

Despite assertions that these precautions should not compromise care for patients with haemophilia, the potential exists that these patients will be stigmatized again, as they were early in the HIV crisis, and that their normal medical and surgical care may be interrupted.

Scope of the problem

Cases of vCJD have also been reported outside the UK. In France, for example, 14 cases of vCJD have been reported, with three identified in persons who donated blood over a 10-year-period. Again, most of the donations have been used to make factor VIII, von Willebrand factor, and other plasma therapies. In response, the French have recalled all plasma-derived therapies, where possible, and all patients have been informed.

To further complicate matters, it is known that the French fractionators have exported concentrates to other countries, such as Belgium. And in the UK, Bio Products Laboratory also exported factor concentrate to other countries. At this point in time, there are no clear guidelines on how to manage potential risk in these situations.

Another concern involves haemophilia patients who visited the UK: unknown numbers of visitors were treated with UK-sourced factor concentrates during the crucial 21-year-period. Because records on the treatment of visitors to the UK are not readily

available, it is very difficult to identify or advise those patients.

Conclusion

The phenomenon of emerging vCJD is yet another warning against the complacent assumption that plasma-derived therapies can be made completely safe. Variant CJD has had a significant negative effect on the haemophilia community in the UK, shaking patient confidence in the therapies they have received over the last 21 years, affecting the quality of current and future medical and surgical care and creating the risk of stigmatizing the community as it was in the 1980s, at the beginning of the HIV crisis.

Our awareness of vCJD is not even a decade old. Much about the disease is still unknown, including the best means for preclinical detection and effective inactivation. But given its long incubation period, it's possible that the impact of vCJD on patients with haemophilia may be significant.

As described elsewhere in this supplement, the barriers to the emergence of pathogenic agents, both air- and blood-borne, continue to diminish. And as with HIV and vCJD, the next emerging blood-borne infectious agent will likely affect blood and blood-derived therapies well before we become aware of its presence. It is because of these reasons that only the therapies with the lowest level of risk should be used for care of patients with haemophilia.

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医薬部外品　研究報告　調査報告書
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別紙 3-4

識別番号・報告回数		回	報告日 年　月　日	第一報入手日 2006 年 2 月 28 日	新医薬品等の区分 該当なし	総合機構処理欄
一般的名称			研究報告の公表状況	Implications of emerging pathogens in the management of haemophilia Haemophilia 12, (Suppl. 1), 26 -28 (2006)	公表国 米国	
販売名（企業名）						

研究報告の概要

英国保健当局と医療関係者間の以下2点に関する議論の要旨である。
i) 現在の血友病患者が直面している新規の，血液媒介病原体による潜在的感染の危険性
ii) 過去25年間にこの分野で判明した教訓
2番目の議論に関して，英国の血友病患者にとってエイズまたは変異型クロイツフェルトヤコブ病(vCJD)の危険性が大きな脅威であった。これまで，血液凝固第VIII因子，又は第IX因子療法を受けている患者のvCJD症例報告はなかった。しかし，正式にこの可能性を否定するには，恐らく以前より時間がかかるであろう。また，白血球除去や血漿分画といった技術改善は感染症のリスクを減少させる際に僅かに効力を示すのみであった。
最近では，遺伝子組換え製剤による治療は完全にウイルス感染リスクをなくすわけではない，ということが明らかになっている。特に，現在の不活性化法に耐性のあるパルボウイルスB19のような非エンベロープウイルスとなるとなおさらである。西ナイルウイルスのような血液を介して感染する新規病原体は予想以上に早く出現する，と医師はみている。そのため彼らは最高水準の安全管理を推奨し，新規病原体のスクリーニングテストが可能となれば即時，血友病患者に対して積極的に行い，適切な手段と規制を実施することを提案している。

使用上の注意記載状況・その他参考事項等

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報告企業の意見	今後の対応
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(26)

Haemophilia (2006), 12, (Suppl. 1), 26–28

DISCUSSION SESSION

Implications of Emerging Pathogens in the Management of Haemophilia

Discussion Session

1. Is there any evidence that haemophilia patients in the UK have been infected with variant Creutzfeldt–Jakob disease (vCJD) via therapies made from contaminated blood donations? Phrased differently, are there good data to support the decision in the UK to phase out the use of recombinant factor VIII (rFVIII) therapies processed with plasma additives, and are the surgical precautions in treating haemophilia patients necessary?

DOLAN: Initial discussions surrounding these issues were definitely controversial, and we in the medical community were not sure how far we needed to go in trying to protect patients. But the recommendations and surgical measures were devised after very detailed consultation with experts who knew far more about prion disease than we did.

Certain decisions, such as ceasing use of UK plasma-derived therapies, were difficult for both patients and their providers. But the subsequent events, in particular the later evidence that there have been at least two probable cases of transfusion-transmitted variant CJD, seem to justify that early stance by not just the UK but other countries as well.

2. Do you think that the fact that vCJD has not been identified in any patient receiving plasma derivatives worldwide since 1980 suggests that the risk of vCJD is minimal or non-existent from these therapies?

IRONSIDE: First of all, let's be quite clear about why 1980 has become a benchmark. The date 1980 was chosen simply because that was thought to be the earliest date at which human exposure to bovine spongiform encephalopathy (BSE) in the UK was likely to have occurred. Overall, human exposure to BSE probably would be very low in the early 1980s and highest in the late 1980s and early 1990s. It is also important to remember that we are dealing with a primary disease transmission with an incubation period of approximately 15 years on average. So, we may have to wait a few more years before we can be certain about the absolute risk of contracting vCJD.

I would be very cautious about relaxing policies and guidelines at present because, as we all understand, there are other emerging infectious agents – identified and unidentified – that are cause for concern in addition to the vCJD-causing prion.

3. Do you know of any vCJD transmissions by plasma-derived FVIII/FIX therapies?

IRONSIDE: At present, no. There is no evidence that vCJD has occurred or infection has been transmitted by these therapies. Although, as I stated earlier, this may be due to the fact that we are dealing with an agent that has a long incubation period. The level of infectivity in plasma therapies may be lower or variable. But it is too soon to exclude that possibility.

The United Kingdom Haemophilia Centre Doctors' Organisation, along with several patient groups, is engaged in enhanced surveillance of the haemophilia population. We are looking for evidence of vCJD – even of subclinical infection – in patients who died or who have a lymphoid tissue biopsy for whatever reason.

4. What is the likely impact of the UK experience with vCJD in the United States and what might those treatment implications be?

DOLAN: Reported cases of BSE in the United States are very few. And if the number of cases remains at this low level, or even disappears altogether, then perhaps US practitioners and policy makers won't be obligated to take the more sweeping measures that we did in the UK. However, as a general concept, we must all remember that emerging pathogens can affect transfusion therapy. So, based on the UK experience, if healthcare providers have an opportunity to minimize risk to patients, then it is a prudent course of direction that should be considered seriously and likely taken.

5. Are there data that leukodepletion of blood will decrease the risk of transmitting vCJD? If not, what is the rationale?

IRONSIDE: This is a very interesting question because the UK has been using leukodepletion as one of its main strategies for risk reduction in terms of blood transfusion. The data from experimental