Table 2: Relative probabilities of potential infection routes (including "non implicated plasma" products)

Prevalence, p	1 in 4,000		1 in 10,000	
Transmission probability, t1	0.5	1	0.5	1
Probability implicated plasma products	38%	38%	24%	24%
Probability of each of the 14 component donors	<0.03%	<0.03%	<0.02%	<0.02%
Probability primary	<0.03%	<0.03%	<0.02%	<0.02%
Probability non-implicated plasma products	61%	61%	76%	76%

Note: these are illustrative calculations only. All figures are rounded to the nearest %, or (for small probabilities) indicate an upper bound.

31. As can be seen, the previous conclusion about the low implied risk to each of the 14 component (red cell) donors still applies, with even greater force. However, these results also highlight something of a paradox. Combined with the infectivity scenario taken from the DNV assessment, the pool size / prevalence calculations suggest that many recipients of plasma products would have received very high infectious doses, *whether or not* they had received any "implicated" units with known linkage to an infected donor. This opens the question of why no clinical vCJD cases have been seen in the population of haemophilia / blood disorder patients designated as "at risk" because of their exposure to UK sourced blood products.[5] It might therefore be argued that the infectivity assumptions applied to plasma products are overly pessimistic.

32. Although this question is impossible to answer definitely, and in any case raises issues beyond the scope of this paper, it is appropriate to check that the conclusions we have already suggested about relative likelihoods would not be overturned were we to assume lower levels of infectivity in plasma derivatives. The DNV report itself suggests two possible methods for calculating the infectivity present in each plasma derivative, using different assumption about the effect of the various manufacturing steps. In line with the generally precautionary approach adopted by CJD Incidents Panel, the calculations so far use figures based on the more pessimistic of these. The less pessimistic alternative suggested by DNV (using the "highest single clearance factor" in the manufacturing process) leads to an infectivity estimate for Factor VIII that is lower by a factor of 4. However, it should also be noted that risk assessments carried out elsewhere take the clearance factors achieved at different stages to be at least partly additive, which would lead to much smaller infective loads.

33. In fact, reducing the assumed infectivity *increases* the relative chance of infection via "non-implicated" as compared to "implicated" plasma. For example, suppose

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5 *Possible* explanations include the following: that prevalence of infection amongst donors is much lower than in the scenarios considered here; that much more infectivity is removed during processing of plasma products than suggested by the DNV analysis; and/or there is a threshold dose-response effect and most recipients fall below this. Genotype effects may also be relevant (in providing resistance to infection or extending the time to clinical disease), but one would expect a substantial proportion of this group to be MM homozygotes – the most susceptible genotype.

the presumed infectivity in all the Factor VIII received was reduced by a factor of 100 (2 logs). Modifying the calculations in paragraph 27, this patient would then have received an expected:

- 0.006 ID_{50} from the two "implicated" pools (representing a transmission risk of 0.003)
- 0.24 ID_{50} from all the other "non-implicated" pools (representing an infection risk of 0.12).

34. Albeit with the same caveats as before about using the linear model to quantify the cumulative risks from successive doses, this suggests that the latter risk would outweigh the former by a factor of 40. Table 3 shows how the previous results for this patient would change, under this revised infectivity scenario. As can be seen, the previous conclusions still hold, in particular regarding the small implied risk to each of the 14 red cell donors.

Table 3: Relative probabilities of potential infection routes (including "non implicated plasma" products and using lower infectivity estimates for plasma products)

Prevalence, p	1 in 4,000		1 in 10,000	
Transmission probability, t1	0.5	1	0.5	1
Probability implicated plasma products	2%	2%	3%	3%
Probability of each of the 14 component donors	<0.05%	<0.09%	<0.05%	<0.09%
Probability primary	<0.09%	<0.09%	<0.09%	<0.09%
Probability non-implicated plasma products	97%	97%	97%	96%

Note: these are illustrative calculations only. All figures are rounded to the nearest %, or (for small probabilities) indicate an upper bound.

35. Finally, it should be stressed that although these conclusions appear reasonably robust on the assumptions given (taken from received scientific advice), many uncertainties remain. The most important are the prevalence of sub-clinical vCJD infection amongst donors and the levels of infectivity that would remain in plasma products after processing. Pending further evidence on these points, all conclusions must be regarded as provisional.

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Annex A: Application of DNV Risk Calculation to Factor VIII Units

(a) Implicated Donations

Key points: FHB4547

- There was one implicated (presumed infective) donation in a start pool of 26,303 donations (pool size supplied by Professor Frank Hill via email)
- Factor VIII is derived from cryoprecipitate, which has an estimated infectivity of 60 ID_{50}s / donation of infected whole blood according to the DNV model
- 70.45kg of cryoprecipitate was made from the start pool, of which 21.58kg was used in the FHB4547 batch
- This implies that (21.58kg / 70.45kg) of the 60 ID_{50}s made its way into the FHB4547 batch (18.38 ID_{50}s)
- 1,844 vials each of 500 units (iu) were made from the batch, which results in an estimate of 0.00997 ID_{50}s per vial or 1.99 x 10^{-5} ID50s per iu

Professor Frank Hill's report indicates that the index case received 8,025 units from this batch, giving an estimated 0.16 ID_{50} from the implicated donation.

Key points: FHC4237

- There was one implicated (presumed infective) donation in a pool of 21,330 donations (pool size again supplied by Professor Frank Hill)
- Factor VIII is derived from cryoprecipitate, which has an estimated infectivity of 60 ID_{50} / donation of whole blood
- 67.6kg of cryoprecipitate was made from the start pool, of which all was used in the FHC4237 batch
- This implies that the full dose of 60 ID_{50} made its way into the FHC4237 batch
- 5,074 vials each of 250 iu were made from the batch, resulting in an estimate of 0.0118 ID_{50} per vial or 4.73 x 10^{-5} ID_{50} per iu

Professor Frank Hill's report indicates that the index case received 1,000 units from this batch, giving an estimated dose of 0.05 ID_{50}.

Conclusion

In total, these calculations suggest that index case would have received an estimated 0.21 ID_{50} from the "implicated" donor. Using a linear dose-response model (where 1 ID_{50} translates into a transmission probability of 0.5 and 2 ID_{50} or more translates into transmission probability of 1) this represents a transmission probability of 0.104 or 10.4%.

(b) Non-implicated Donations

In addition to the implicated donations, we have also to consider the possibility of other donors contributing to a pool being infective. With pool sizes of the order of 20,000 donations, each pool will be likely to contain contributions from one or more infected donors by chance, unless p is very small. For implicated pools, these will be *in addition to* the "known" implicated donor.

With a prevalence of 1 in 10,000, one might therefore expect the two implicated pools to contain two *further* infected donations, taking the total from 1 to 3 per pool.

This would make the infective dose received via the implicated units three times that calculated above, i.e. a total of roughly 0.6 ID_{50}, yielding a transmission probability of 0.3.

This patient also received approximately 391,000 iu of UK-sourced Factor VIII plasma treatment *not* known to be associated with any infected donor. In round figures, this can be visualised in terms of 20 exposures to pools of 20,000 donors, each typically containing 2 donations from infected donors. The exact infective dose passed on to the patient will vary from batch to batch. However, the two examples given in part (a) suggest an eventual dose of 2-5 x 10^{-5} ID_{50} per unit, per infected donor. For illustration, therefore, suppose that each unit exposed the recipient to 6 x 10^{-5} ID_{50}, 400,000 such units would therefore have exposed the recipient to 24 ID_{50}.

Haemophilia 資料2

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ORIGINAL ARTICLE

Variant CJD infection in the spleen of a neurologically asymptomatic UK adult patient with haemophilia

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Summary. All UK patients with bleeding disorders treated with any UK-sourced pooled factor concentrates between 1980 and 2001 have been informed that they may be at an increased risk of infection with variant Creutzfeldt–Jakob disease (vCJD). We describe a study to detect disease-associated, protease-resistant prion protein (PrP^{res}) in 17 neurologically aysmptomatic patients with haemophilia considered to be at increased risk of vCJD. Materials from 11 autopsy and seven biopsy cases were analysed for PrP^{res}. The tissues available from each case were variable, ranging from a single biopsy sample to a wide range of autopsy tissues. A single specimen from the spleen of one autopsy case gave a strong positive result on repeated testing for PrP^{res} by Western blot analysis. This tissue came from a 73-year-old male patient with no history of neurological disease, who was heterozygous (methionine/valine) at codon 129 in the prion protein gene. He had received over 9000 units of factor VIII concentrate prepared from plasma pools known to include donations from a vCJD-infected donor, and some 400 000 units not known to include donations from vCJD-infected donors. He had also received 14 units of red blood cells and had undergone several surgical and invasive endoscopic procedures. Estimates of the relative risks of exposure through diet, surgery, endoscopy, blood transfusion and receipt of UK-sourced plasma products suggest that by far the most likely route of infection in this patient was receipt of UK plasma products.

Keywords: haemophilia, plasma, prion protein, spleen, vCJD

Introduction

Variant Creutzfeldt–Jakob disease (vCJD) was identified in the UK in 1996 [1] and subsequently shown to be caused by a transmissible agent with identical properties to the bovine spongiform encephalopathy (BSE) agent [2,3], most likely as a consequence of consumption of BSE-contaminated meat products [4]. Variant CJD represents the only known example of a human prion disease caused by exposure to an infectious prion agent from a non-human source. It is also unique in that the transmissible agent is detectable in a much wider tissue distribution than is the case for other forms of human prion disease. Both infectivity and the protease-resistant form of disease-associated prion protein (PrP^{res}) are readily detectable in a range of tissues apart from that of the central nervous system in vCJD, particularly in lymphoid tissues and the peripheral nervous system, albeit at lower levels than in the central nervous system [5,6].

Since 2004, four instances of vCJD infection (three clinical cases, one asymptomatic) in the UK have been associated with the transfusion of non-leucodepleted packed red cells from asymptomatic donors who subsequently died from vCJD [7–10]. The National Blood Authorities in the UK have taken a

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number of steps to reduce the likelihood of secondary transmission of vCJD by blood components [11]. It is known that plasma donations from asymptomatic individuals infected with vCJD have also contributed to some batches of pooled clotting factor concentrate (termed 'vCJD-implicated batches'). The potential vCJD infectivity of these batches has been estimated by the UK CJD Incidents Panel (CJDIP) based on findings from a risk assessment commissioned by the Department of Health (DH) [12], together with batch-specific manufacturing data. Variant CJD-implicated batches of clotting factor concentrates factor VIII (FVIII) and IX were assessed to be likely to carry sufficient levels of vCJD infectivity to warrant the implementation of public health measures in recipients to minimize the possible risk of onward transmission [12]. A public health notification exercise of patients with bleeding disorders was conducted in 2004 by the Health Protection Agency and Scottish Centre for Infection and Environmental Health on behalf of the UK Departments of Health, at which time it was considered likely that further batches of UK-sourced plasma products would become implicated as future cases of vCJD arose [13]. Therefore, on the advice of the UK Haemophilia Centre Doctors' Organisation (UKHCDO), all patients with bleeding disorders who had been treated with any UK-sourced pooled factor concentrates between 1980 and 2001 were informed that they may be at an increased risk of infection with vCJD and were required to take measures to prevent the possibility of secondary spread of infection. This inclusive 'population' approach was endorsed by the CJDIP, DH and the Haemophilia Society.

To date, 170 cases of vCJD have been identified in the UK, including the three clinical cases in which infection is likely to have been transmitted by non-leucodepleted packed red cells transfused from asymptomatic donors who subsequently died from vCJD [7,9,10]. The annual incidence and death rate for vCJD have both declined in UK over the past few years, but the prevalence of vCJD infection in the UK remains uncertain. A retrospective study to detect disease-associated prion protein in paraffin-embedded sections of tonsil and appendix tissue indicated that the prevalence of vCJD infection might be higher than the current number of clinical cases recorded would suggest, with three positive cases being found in 12 674 tissue samples studied, giving an estimated prevalence rate of 237 vCJD infections per million in the UK population (although with wide confidence intervals) [14,15]. Further investigations on a large series of tonsil samples found a prevalence of disease-associated prion protein in tonsils from a 1961–1995 combined birth cohort of 0/32 661 with a 95% confidence interval of 0–113 per million [16]. In the 1961–1985 cohort, the prevalence of zero with a 95% confidence interval of 0–289 per million was lower than, but still consistent with, the results of the previous survey of tonsil and appendix tissues by Hilton *et al.* [14]. The prevalence of vCJD infection in the general UK population could therefore be around 1 in 10 000, based on an approximate average value between the results of these studies [14,16,17].

To date, no case of vCJD has been identified in any recipient of UK-sourced plasma products. In 2001 DH commissioned and funded a project to undertake active surveillance of UK patients with haemophilia for the possibility of vCJD infection. This study included the prospective and retrospective analysis of lymphoid tissues and brain tissue in biopsy material and/or autopsy material for the presence of the PrP^{res} isoform characteristic of vCJD.

We report the laboratory findings in this study, demonstrating for the first time the presence of PrP^{res} in the spleen of a UK adult haemophilic patient who at the time of death had no neurological signs or symptoms attributable to vCJD.

Materials and methods

Collection of tissue samples

Ethical approval was obtained for the project entitled 'Surveillance of new variant CJD-UKHCDO' (MREC/01/2/11) and the study was administered through the UKHCDO. All haemophilic patients undergoing surgical procedures involving the central nervous system and lymphoid tissue (including tonsil, lymph nodes and spleen) were encouraged to participate in the study. This applied only to patients who were to undergo surgical biopsy or resection of relevant tissues for medical reasons and was therefore opportunistic. Consent was obtained from patients for the analysis of biopsy samples and from relatives of the patient for autopsy tissues following the death of a patient undergoing either a hospital or Coroner's autopsy.

Cases and tissue specimens

Material from 11 autopsy cases and seven biopsy cases from 17 patients had tissue samples submitted to the National CJD Surveillance Unit for investigation. One patient had biopsy samples submitted on two occasions, and another patient had both biopsy and autopsy materials examined. The number of tissues

available from each case was variable, ranging from single lymphoid tissue samples from living patients to a wide range of autopsy tissues (brain, tonsil, spleen, lymph node, appendix) in others. The samples were analysed in this study by a combination of Western blotting, paraffin-embedded tissue (PET) blotting and immunohistochemistry for disease-associated, protease-resistant prion protein (PrP^{res}). Cases of clinically suspected CJD that were given an alternative final pathological diagnosis were used as negative controls, as they lack PrP^{res} in the brain and peripheral tissues. Ethical approval for the acquisition and use of this autopsy material for research on transmissible spongiform encephalopathies in the National CJD Surveillance Unit brain bank is covered by LREC 2000/4/157 (JWI). The polymorphic status of codon 129 of the prion protein gene (*PRNP*) of each case was determined by restriction fragment length polymorphism as described previously [18].

NaPTA precipitation/Western blot analysis for PrP^{res}

Frozen central nervous system (cerebral frontal cortex, cerebellum, spinal cord) and lymphoreticular (spleen, tonsil, appendix) tissues (when available) from cases in this study and from vCJD and non-CJD control patients were homogenized to 10% (w/v) in 2% sarkosyl/PBS using the FastPrep™ instrument (Anachem, Cambridge, UK) and 500 μL samples of this homogenate were analysed by sodium phosphotungstic acid precipitation followed by high-sensitivity Western blotting (NaPTA/WB), as described previously [8,19,20]. At least four samples of spleen and other lymphoid tissues (when available) were studied.

Criteria for assigning positives

Samples of frozen brain (frontal cortex) and spleen from non-CJD neurological control patients were available for use as negative controls in the Western blots in this study. As a positive control in the NaPTA/WB analyses of either central nervous system tissue or lymphoreticular tissue, 10% (w/v) vCJD brain homogenate (3 μL) was diluted into 500 μL of a 10% (w/v) homogenate of either brain or spleen tissue from a non-CJD control patient. These spiked homogenates were then diluted with a further 500 μL of 2% sarkosyl/PBS as described in the standard protocol used for all the test samples [8]. Samples of tissue from haemophilic patients in this study were assessed by comparison with positive and negative control samples run on the same gel. The following criteria were established before interpreting the results: a positive result was assigned if at least two bands were observed to co-migrate with the corresponding PrP^{res} bands in the positive control and no bands were seen in the lane containing non-CJD control sample, after maximum exposure to HyperFilm ECL (GE Healthcare Life Sciences, Buckinghamshire, UK).

Centrifugal concentration/Western blotting

A number of samples of tissue homogenate prepared in 2% sarkosyl/PBS as described above were re-analysed using the centrifugal concentration/Western blot method described by us previously [6].

Densitometric analysis of PrP^{res} levels and glycoform ratios

For densitometric analysis, immunoblot images were scanned using a Bio-Rad GS-800 Densitometer and images were analysed and processed with QUANTITY ONE™ software (Bio-Rad, Hertfordshire, UK). Immunoblot images were included in the densitometric analysis if all three bands (di-, mono- and unglycosylated) were in the linear range.

Immunohistochemistry and PET blotting

Paraffin-embedded tissue blot analysis was carried out as described by us previously [21], using a modified version of the method of Schulz-Shaeffer *et al.* [22]. Immunohistochemistry for disease-associated prion protein was performed using a panel of four different anti-prion protein antibodies as previously described [21].

Results

Biochemical analysis

The high-sensitivity Western blot (NaPTA/WB) analyses were conducted on receipt of tissue and were subject to the availability of frozen tissue specimens, which varied between patients (Table 1). One sample of spleen out of the initial four tested from one of these patients gave a very strongly positive signal for PrP^{res} producing a poorly resolved smear, but with the highest densities in the region of the immunoblot typical for authentic PrP^{res}. A smaller volume of the positive homogenate (50 μL rather than 500 μL) was re-analysed by NaPTA/WB in order to obtain better resolution of the immunoreactive bands, and a positive signal was confirmed according to our criteria (Fig. 1). The glycoform ratio of this positive sample was consistent with vCJD, showing a predominance of the diglycosylated form of PrP^{res}.

Table 1. Summary of frozen tissue samples analysed by NaPTA/WB for PrP^{res}.

Case number (*PRNP* codon 129)	Tonsil	Spleen	Lymph node	Appendix	Brain	Bone marrow	Gut
1 (MV)	–	–	–	–	0/9	–	–
2 (MV)	–	0/4	0/3	0/4	0/8	–	–
3 (MV)	0/4	0/12	0/4	–	0/12	–	–
4 (MM)	–	–	0/4	–	0/8	–	–
5 (MM)	–	–	–	–	0/8	–	–
6 (VV)	–	0/3	–	0/4	0/14	0/4	0/8
7 (MM)	0/3	0/3	–	0/3	0/3	–	–
8 (MM)	–	–	–	–	0/16	–	–
9 (MV)	–	1/26	0/2	–	0/11	–	–
10 (MM)	–	0/4	0/4	–	0/8	–	–

Depending on availability a minimum of four samples were tested from the tissue listed above. The results are given as the number of PrP^{res} positive samples as a proportion of the total number of independent samples tested for each tissue specimen.
A dash (–) indicates that no samples were available for analysis; M, methionine; V, valine; PrP^{res}, protease resistant prion protein; NaPTA/WB, sodium phosphotungstic acid precipitation/Western blotting.

The remaining 100 μL aliquot of this homogenate was analysed by the centrifugal concentration/Western blotting protocol and was again strongly positive (data not shown). Densitometry was used to compare the total signal (of all three PrP^{res} bands) with a dilution series of PrP^{res} samples from vCJD brain run in parallel with this and the previous sample. This analysis indicated that the level of PrP^{res} in this spleen sample was 3–5% of that found in vCJD brain.

NaPTA/WB analysis of a further 22 samples taken from the available spleen tissue from this case failed to show any evidence of PrP^{res} (Table 1). Exhaustive immunohistochemical and PET blot analysis of this tissue was similarly negative and NaPTA/WB, immunohistochemistry and PET blotting all failed to detect the presence of PrP^{res} in lymph node, frontal cortex or cerebellum in this case (Table 1). All other tissues from the remaining cases were negative by each of the methods used.

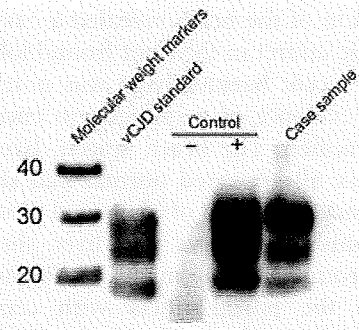

Fig. 1. Sodium phosphotungstic acid (NaPTA) precipitation/Western blotting analysis of spleen tissue samples for the presence of protease-resistant prion protein (PrP^{res}). A sample of spleen homogenate from case 9 (case sample) corresponding to 5 mg of tissue was analysed alongside spleen samples from a control case with non-CJD neurological disease (control) corresponding to 50 mg of tissue. One of the latter control samples (+) had been spiked with an amount of variant Creutzfeldt–Jakob disease (vCJD) brain homogenate, corresponding to 300 μg of tissue, prior to NaPTA precipitation. Standard vCJD brain PrP^{res}, corresponding to 100 μg of brain tissue, analysed without prior NaPTA precipitation, was run in the lane marked 'vCJD standard'. The molecular weight markers (in kDa) are shown in the leftmost lane.

To make a more quantitative assessment of the glycoform ratio in the positive specimen, we again used densitometry. The glycoform ratio of the specimen positive by NaPTA/WB mapped close to, but at the extreme diglycosylated side of the area defined by Western blot analysis of vCJD brain tissue, including vCJD brain tissue 'spiked' into negative control spleen and analysed by NaPTA/WB (Fig. 2). The glycoform ratio of this positive specimen was also more predominantly diglycosylated than the samples of vCJD spleen PrP^{res} used as positive controls in this study.

Genetic analysis

The results of the *PRNP* codon 129 analysis on each of the eight cases studied are included in Table 1. The case containing PrP^{res} in the spleen was heterozygous (methionine/valine) at this codon.

Immunohistochemistry and PET blotting

Immunohistochemistry and PET blot analysis on all the PET blocks in this study were negative in all cases, including the case in which PrP^{res} was detected biochemically in the spleen.

Case history

The clinical history of the haemophilic patient in whom PrP^{res} was detected in the spleen was reviewed in detail as follows:

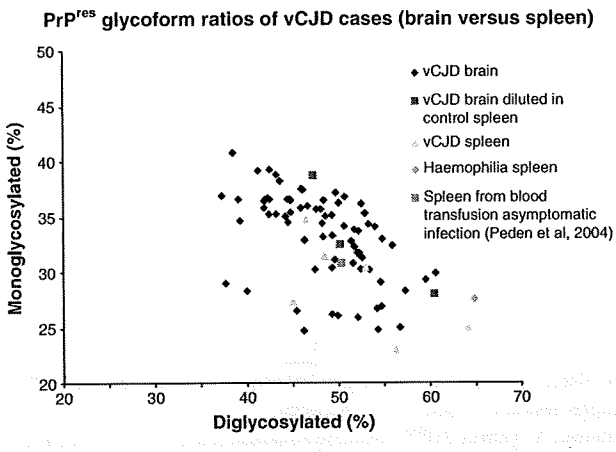

Fig. 2. Scattergram analysis of percentage diglycosylated and percentage monoglycosylated isoforms found in individual cases of variant Creutzfeldt–Jakob disease (vCJD). The glycoform ratio of protease-resistant prion protein (PrP^{res}) following sodium phosphotungstic acid (NaPTA) precipitation in the positive spleen sample from the Haem UK study case 9 (light blue diamond) is compared with vCJD brain PrP^{res} without NaPTA precipitation (dark blue diamonds), vCJD brain PrP^{res} diluted in non-CJD neurological control spleen homogenate with NaPTA precipitation (red squares), endogenous vCJD spleen PrP^{res} with NaPTA precipitation (yellow triangles). The glycoform ratio of spleen from a single case of preclinical vCJD infection following blood transfusion in an asymptomatic *PRNP* codon 129 MV individual (green square) is also shown.

The patient had severe haemophilia A (FVIII <1%). He was one of 10 children and all six of his affected brothers had died at an early age. He never developed antibodies to FVIII. He suffered from severe haemophilic arthropathy and despite multiple orthopaedic surgical procedures was wheelchair-bound by the age of 36 years. He also suffered from recurrent gastrointestinal (GI) bleeding and at the age of 39 sustained an intracerebral haemorrhage. He had multiple exposures to UK-sourced plasma-derived FVIII receiving 754 '500-unit' vials between 1980 and 2001 (approximately 400 000 units as the vials were overfilled). When tests became available, he was found have both antibodies to hepatitis C and to have the virus detectable in his blood. However, his liver function tests remained normal and he did not develop any clinical signs of liver disease. He was treated with two vCJD-implicated FVIII 8Y batches in 1994 (Batch FHC 4237, 1000 units) and 1996 (Batch FHB 4547, 8025 units), the latter given over a 3-day period for a bleed into the right hip joint. Both batches included a donation from a single donor who subsequently died from vCJD in 1997.

It is also recorded that the patient had been transfused with red blood cells in 1998 (3 units), in 1999 (5 units), in 2003 (3 units) and in 2007 (3 units). The red cell transfusion in 1998 was unlikely to have been leucodepleted, but the remaining transfusions were likely to have been leucodepleted. Apart from the earlier orthopaedic procedures, the patient had undergone multiple lower GI endoscopic procedures from 1980 to 2007, with polyp resections on five occasions between 2003 and 2007; an upper GI endoscopy without biopsy was performed in 1999.

At the age of 73, he was admitted to hospital in 2008 with chest pain, having fallen out of bed 2 days previously. On examination, he was noted to be in pain with a blood pressure of 135/80 mmHg with a heart rate of 95/min. He was fully conscious (Glasgow coma scale score 15/15) and showed no evidence of cognitive impairment or any other neurological abnormalities. A 5- to 6-cm haematoma was noted over the posterior aspect of the left side of his chest. Two days later, he deteriorated suddenly with a loss of consciousness and development of hypotension. He was suspected to have sustained an intracranial haemorrhage and died the following morning. An autopsy was performed under HM Coroner's instructions, which found a thrombosed fusiform aneurysm of the left iliac artery with extension of thrombus into the lower aorta. The elbow and knee joints were swollen with evidence of previous surgery to the left knee and multiple cutaneous bruises were present over the left upper limb and left side of the trunk.

Examination of the brain revealed a cavitated old haemorrhagic infarct in the right frontal lobe, but no evidence of recent haemorrhage was noted and no histological evidence of a spongiform encephalopathy was identified. The heart, spleen, lymph nodes and appendix all appeared normal and showed no evidence of accumulation of abnormal prion protein on immunohistochemistry. The liver showed evidence of a prominent mononuclear inflammatory cell infiltrate in the portal tracts with centrilobular microvacuolation and steatosis, in keeping with the history of hepatitis C infection. Sections of the iliac artery aneurysm showed the features of a longstanding aneurysm with a patchy infiltrate of chronic inflammatory cells in part of the wall. There was also evidence of both previous and fresh haemorrhage into the thrombus within the aneurysm, with foci of acute haemorrhage that were contiguous with foci of haemorrhage into the adjacent vessel wall. The most likely interpretation of these findings is that the patient's fall caused bleeding into the wall of the large left iliac artery aneurysm and accumulation of this haemorrhage resulted in occlusion of the vessel

with rapid propagation of blood clot upwards into the aorta resulting in hypotension, loss of consciousness and death.

Following the autopsy and with appropriate consent, frozen tissue samples from the brain, spleen and lymph node were submitted to the National CJD Surveillance Unit, along with fixed samples from the heart, liver, spleen, lymph node and appendix and iliac artery aneurysm.

Discussion

We describe the pathological analysis of tissues from a group of 17 UK patients with haemophilia considered to be at increased risk of vCJD through exposure to UK-sourced plasma products during the period between 1980 and 2001. Eleven out of 17 patients had died, of whom six patients had previously recorded treatment with vCJD-implicated batches, including one patient who had received treatment with an implicated batch made from the same plasma pool as batch FHB 4547 (received by the index case). Another patient (not included in this study), who is still alive, has received treatment with two vCJD-implicated batches, one of which contained plasma from the donor of implicated batches FHC 4237 and FHB 4547. None of the patients in this study showed any evidence of a neurological disease consistent with vCJD. Immunohistochemistry and PET blot analysis for the abnormal form of the prion protein was consistently negative in all central and peripheral tissues examined. A single specimen from the spleen of one of these patients did, however, give a strong positive result on repeated testing for PrP^{res} by Western blot analysis. The positive result had all of the expected characteristics of a true positive result in terms of the electrophoretic mobility, abundance and glycoform ratio of vCJD PrP^{res}, and more specifically that of vCJD lymphoreticular tissue [6,8]; however, exhaustive re-sampling of other regions of the residual spleen tissue failed to identify any similar findings. Immunohistochemistry and PET blotting of the spleen from this case were also negative for abnormal PrP.

We therefore investigated the possibility that the positive results derived from an unexplained misidentification or contamination of samples in the laboratory. Meticulous review of the audit trail for specimen receipt, storage, sampling and analysis of this case found no opportunity for specimen misidentification, substitution or cross-contamination. Additionally, the glycoform ratio in the positive spleen sample clearly rules out sample contamination with vCJD brain, as both the abundance and glycoform ratio are consistent with those expected from a vCJD lymphoreticular tissue [6,8]. We therefore conclude that the spleen of this case had a highly discrete positive region with readily detectable levels of PrP^{res}, having a glycoform pattern typical of vCJD. In a previous report, we described the detection of PrP^{res} in the spleen of another asymptomatic UK patient (who did not have haemophilia), who 5 years prior to death had received a transfusion of packed red cells from a donor who subsequently died from vCJD [8]. In this case, the levels of PrP^{res} in the spleen were highly variable, with only one of the eight regions tested giving a similar result to the index case described above. Another five regions sampled gave a weak PrP^{res} signal, while the remaining two regions sampled were negative. The earlier patient was also a heterozygote (methionine/valine) at codon 129 in the *PRNP* gene. However, immunohistochemistry in that case showed positive staining for abnormal prion protein in occasional follicles in the spleen, unlike the current case.

These observations together suggest that the distribution of PrP^{res} in the spleen of asymptomatic patients is highly variable and that multiple samples need to be analysed to ensure (as in our current case) that false negative results are avoided. Immunoblotting for PrP^{res} is more sensitive than immunohistochemistry and PET blot analysis, so it is not surprising that the immunohistochemical and PET blot findings in the current case were negative, although it should be noted that the amount of fixed tissue available for immunohistochemistry and PET blot analysis was smaller in quantity than the frozen spleen tissue for biochemical analysis. It is also conceivable that the distribution of PrP^{res} in the spleen may be influenced by the *PRNP* codon 129 polymorphism, as the distribution of PrP^{res} in lymphoid tissue of scrapie-affected sheep is variable between different *PRNP* genotypes [23].

The detection of PrP^{res} in the spleen of this patient with haemophilia, who had no evidence of any neurological disease (including vCJD) in life, requires careful interpretation. There are four known possible routes of exposure to vCJD infection that may have resulted in this finding, namely via the food chain, transfusion with donor red cells, surgical and invasive endoscopic procedures, and finally via treatment with UK-produced FVIII, including two vCJD-implicated batches.

Dietary acquisition of vCJD infection is considered unlikely in this individual, who was aged 73 when he died, based on the observed incidence of vCJD in this age group. None of the 14 blood donors to this patient has developed vCJD, but there remains the

possibility that this group of donors could include asymptomatic carriers of vCJD infection. The investigation of patients who have also undergone endoscopy with the endoscope used on this patient has found no clinical cases of vCJD to date.

This patient's only proven link to a vCJD source is the receipt of two separate batches of FVIII, which contained plasma from a donor who subsequently developed vCJD 4.5 years after the first donation. As part of the 2004 notification exercise, the recipients of 98% of these batches have been identified and to date there have been no reports of neurological diseases (including vCJD) in this haemophilia cohort. FVIII made from another vCJD-implicated batch from the same donor was received by one of the other haemophilic patients included as an autopsy case in this study, in whom no evidence of PrP^{res} was identified in the brain, spleen, tonsil or lymph node. The interval between treatment and death in that patient was 3 years shorter than that in the patient with PrP^{res} detected in the spleen in this study. The vCJD donor had also made earlier blood donations; the Transfusion Medicine Epidemiology Review records one surviving recipient of non-leucodepleted red cells who is well [24]. Furthermore, there have been no reports of neurological events in patients with bleeding disorders who have received other batches of clotting factor concentrates linked to this donor.

Estimates of the relative levels of risk to which this individual was exposed, through diet, surgery/endoscopy, blood transfusion and receipt of plasma products, suggest that by far the most likely route through which this individual was infected is through receipt of UK-sourced plasma products [25] (Table 2). It is known that the individual concerned was exposed to some 9000 units of FVIII prepared from plasma pools that included donations from a donor who went on to develop vCJD and was presumed to have been infected at the time of donation. There is no chromatographic step in the production of FVIII 8Y, which may reduce the clearance of any potential prion contamination. However, as the plasma products concerned were produced from very large pools of donors (c. 20 000), and because this individual received many units from batches not known to be implicated (c. 400 000), it is highly likely that this individual was also exposed to infectivity in presently unimplicated batches.

While there is clear evidence of the transmission of vCJD infectivity by non-leucodepleted packed red cell transfusion in humans [7–10], and transmission of scrapie and BSE by whole blood and buffy coat transfusion in sheep [26], uncertainty remains about the risk of transmission of vCJD by UK-sourced plasma. Because of this uncertainty, precautionary public health measures to prevent onward transmission of vCJD were introduced in 2004 for patients with bleeding disorders who had been treated with UK plasma-sourced products between 1980 and 2001. The current situation, with its accompanying uncertainties for the future, causes ongoing concern for these patients and their families.

Conclusion

We believe that the findings in this case indicate vCJD infection in the spleen of this UK haemophilic patient, albeit in a very restricted distribution that may relate to the small dose of infectivity likely to

Table 2. Summary of haemophilia risk calculations assuming a population prevalence of one in 10 000.

Route	Estimated risk	Assumptions
Diet	1 in 10 000*	Background risk
Blood [12,28]	7–14 in 10 000	Assuming transmission probability is between 0.5 and 1
Endoscopy with biopsy [25,29]	1–6 in 10 000	Reduced risk based on a general surgical model (set of 20 instruments) by a factor of 10 (1 small biopsy head)
Implicated plasma products [12,25]	0.2–0.6 ID50s implies risk of 1000–3000 in 10 000	Linear dose response; the possibility of unidentified vCJD-infected donors to the plasma pools is also taken into account
Non-implicated plasma products [12,25]	>2 ID50s implies infection very likely	c. 400 000 units of factor VIII, to which unidentified vCJD-infected donors may have contributed

vCJD, variant Creutzfeldt–Jakob disease.
*The assumed prevalence of vCJD infection in the general UK population is one in 10 000, based on an approximate average value between the results of the study by Hilton *et al.* [14] and the more recent National Tonsil Archive Study [16,17].

have been present in the UK plasma products used in treatment, and perhaps also to the heterozygous *PRNP* codon 129 genotype in this patient. Continuing surveillance for vCJD infection, both symptomatic (passive) and asymptomatic (active), is required to help clarify the degree of overall risk in this group of patients from treatment with UK-sourced plasma products. The findings also have implications for laboratory methodology in the proposed autopsy-based prevalence study of vCJD infection in the UK [27].

Acknowledgements

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Disclosures

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資料３

変異型クロイツフェルト・ヤコブ病の発生件数（累計）

	発生数	備考
世　　界	２１７例	
イギリス	１７０例	うち４例生存 中国（香港）例を含む
フランス	２５例	１例は英国滞在歴あり
アイルランド	４例	２例は英国滞在歴あり
アメリカ	３例	２例は在米英国人 １例は在米サウジアラビア人
オランダ	３例	
イタリア	２例	
カナダ	１例	英国滞在歴あり
スペイン	５例	
ポルトガル	２例	
サウジアラビア	１例	うち１例生存
日本	１例	英国滞在歴あり

世界の状況に関する出典：UKCJDSU（英国保健省報告）　[2010.01.05]

InVS（仏　国立衛生監視研究所）[2010.01.10]　他

厚生労働科学研究費補助金（難治性疾患克服研究事業）
プリオン病２次感染に対する現実的滅菌法の開発研究
平成２１年度　分担研究報告書

プリオン滅菌の現実的方法論の検討

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研究協力者：高田　　恵　（東京医療保健大学大学院医療保健学研究科）

研究要旨

手術器械を対象としたプリオンの滅菌法については、アルカリ洗浄剤を使用したウォッシャ・ディスインフェクターによる洗浄後にプリバキューム式高圧蒸気滅菌器による 134～135℃ 8～10 分間の処理法がある。しかし、臨床現場においては内視鏡手術の増加に伴い、非耐熱性の手術器材を滅菌する機会が多くなっている。非耐熱性の器材に対するプリオン対策としては、文献的検索において過酸化水素低温ガスプラズマ滅菌法がクローズアップされている。今回の報告では、全国の医療現場において現実的な処理方法について、中央材料部での対応を中心に 300 床以上の病院に対してアンケートを実施し、現場で採用しうる処理方法にいついて検討した。

その結果、CJD プリオン汚染の可能性のありハイリスク症例に試用した手術器械については、アルカリ洗浄剤を使用したウォッシャ・ディスインフェクターによる洗浄後に、プリバキューム式高圧蒸気滅菌 8～10 分間行う方法が、医療現場で最も活用されている方法であることが明らかとなった。一方 3%SDS による処理法は、現場では採用しにくい方法であることが明らかとなった。

A．研究目的

厚生労働省は、2008 年 5 月 28 日付け事務連絡にて“ハイリスク手技に用いた手術器具を介する CJD 二次感染予防について”を発出している。同年 9 月 12 日付けでの各都道府県衛生主管部（局）長宛通知“「プリオン病感染予防ガイドライン（2008 年版）要約」について”が出されている。それらの中で、4 つの処理方法が示されている。

病院の中央材料部における CJD プリオン汚染の可能性のある器材の洗浄・滅菌処理に対して、いかなる対応がなされているかを中心に 300 床以上の病院に対してアンケートを実施し、現場で採用しうる処理方法にいついて検討した。

B．研究方法

事務連絡および通知では、4 つの方法を示している。1)適切な洗浄＋3%ドデシル硫酸ナトリウム（SDS）による煮沸 3～5 分間、2)アルカリ洗浄剤使用ウォッシャ・ディスインフェクター処理＋プリバキューム式高圧蒸気滅菌 134℃、8～10 分間、3)適切な洗浄＋プリバキューム式高圧蒸気滅菌 134℃、18 分間、4)アルカリ洗浄剤洗浄＋過酸化水素低温ガスプラズマ滅菌 2 サイクルである。(表 1)

これらの方法に対して、医療現場で採用しやすい順位と、まず現場では採用しないであろうという処理方法について質問した。質問用紙の発送先は、300 床以上の 1,125 病院である。

（倫理面への配慮）
本研究は、ヒトを対象としたものではなく、プリオン汚染の可能性のある器材の処理法について調査したものである。したがって特段の倫理面への配慮はおこなっていない。

C．研究結果

これまでに、1,125 施設中 443 施設（39.4%）より有効回答を得た。有効回答の中で、脳神経外科手術を実施している施設は 143 施設であった。

集計結果では、医療現場においては、高圧蒸気滅菌が、最も日常的な滅菌方法であり、ウォッシャ・ディスインフェクター処理＋プリバキューム式高圧蒸気滅菌 134℃、8～10 分間の処理が第一選択として 68.0%の施設で採用されている。過酸化水素低温ガスプラズマ滅菌器は、保有していない施設も少なくない。

脳神経外科手術を実施している施設では、第一選択としている処理法はウォッシャ・ディスインフェクター処理＋プリバキューム式高圧蒸気滅菌 134℃、8～10 分間の処理であり、59.4%である。

一方、通常の手術器械において現場では実施できない処理法としては、3%SDS 煮沸処理に対して、362/396 施設（91.4%）で、まず現場では採用しない処理方法であると回答している。（図 1～3）

D．考察

最近の新たな幾つかの報告では、高圧蒸気滅菌、および、過酸化水素低温ガスプラズマ滅菌の CJD プリオン不活性化に関する効果が明白になってきた。今回のアンケート結果においても、医療現場では、高圧蒸気滅菌が、最も日常的な滅菌方法であり、アルカリ洗浄剤を使用したウォッシャ・ディスインフェクター処理＋プリバキューム式高圧蒸気滅菌 134℃、8～10 分間の処理が第一選択されていた。

これらの処理法は、多くの医療施設において日常的に行われている方法であり、現状の処理がおこなわれていれば、CJD プリオンの二次感染は概ね防止できるものと思われる。

E．結論

厚生労働省の研究班がガイドラインとして示す 4 つの処理方法の中で、作業者の安全性はもちろん、医療現場の混乱を招来しない処理方法の選択が求められている。

F．健康危険情報

特になし

G．研究発表

1．論文発表

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H．知的財産権の出願・登録状況

（予定も含む。）

1．特許取得
なし

2．実用新案登録
なし

3．その他
なし

表1

プリオン病感染予防ガイドライン（2008年版）要約

2008年9月12日　厚生労働省　通知

A：適切な洗浄＋3%SDS煮沸 3～5分間

B：アルカリ洗浄剤使用WD洗浄＋
真空脱気高圧蒸気滅菌134℃ 8～10分間

C：適切な洗浄剤による十分な洗浄＋
真空脱気高圧蒸気滅菌134℃ 18分間

D：アルカリ洗浄剤洗浄＋
過酸化水素低温ガスプラズマ滅菌 2サイクル

図1

第一選択となる処理方法

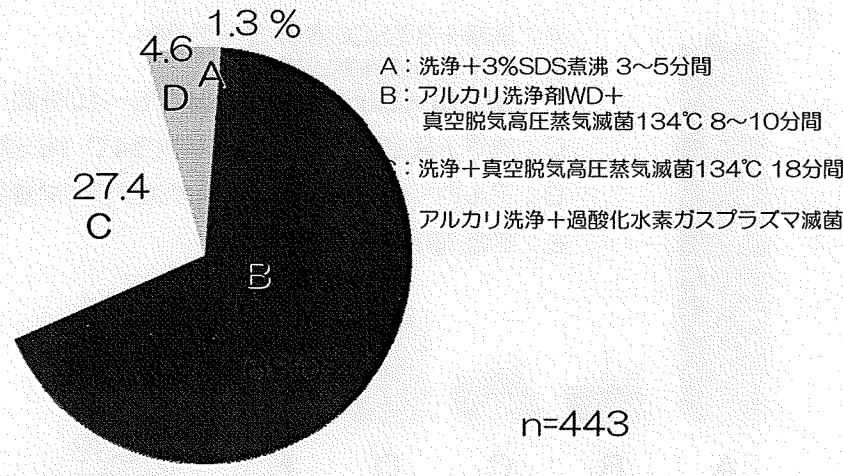


図2 脳神経外科手術を行っている施設が第一選択とする処理方法

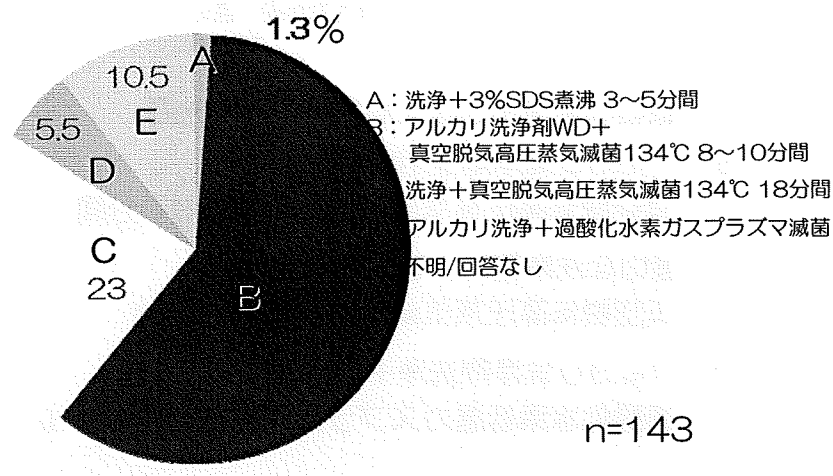
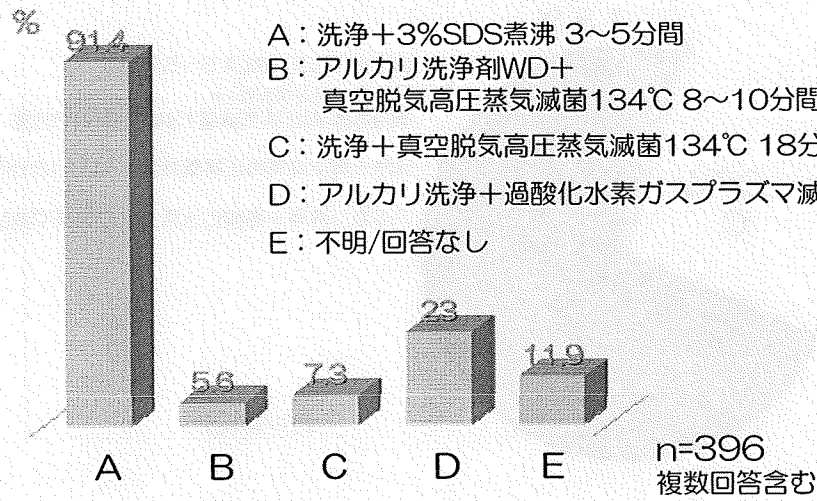


図3 通常の手術器械において現場では実施できない処理方法



研究成果の刊行に関する一覧表