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| Keywords: | Prions, Transfusion medicine (in general), Epidemiology, Blood safety |
Creutzfeldt-Jakob disease and blood transfusion: updated results of the UK Transfusion Medicine Epidemiology Review Study

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ABSTRACT

Background and Objectives: This paper reports the results to 31st May 2015 of an ongoing UK study to look for additional cases of variant Creutzfeldt-Jakob disease (vCJD) transmission by blood transfusion, and to seek evidence whether other subtypes of Creutzfeldt-Jakob disease (CJD) may be transmissible via blood components.

Materials and Methods: All vCJD cases of appropriate age and any sporadic CJD (sCJD) or familial CJD (fCJD) cases with a history of blood donation or transfusion are notified to the UKBS. Donation records are sought and the usage of all donations is determined by look-back. Death certificates were obtained for all donors to CJD patients and recipients of transfused products from CJD patients who were deceased.

Results: The study identified 29 sCJD blood donors, of 370 reported, with subsequent transfusion to 211 recipients. Five cases were reported to have died with or of dementia, but these were not believed to be cases of CJD.

The vCJD arm found 18 vCJD blood donors who had donated blood which was issued for clinical usage, of 24 traced donors from 177 UK vCJD cases. To date, 3 cases of vCJD have been identified in this group, and one other recipient had post mortem confirmation of abnormal prion protein deposition in the spleen (all previously reported).

Conclusion: The results of the ongoing TMER study show no new cases of transfusion associated vCJD and no evidence of transfusion transmission of sCJD.
Introduction

Creutzfeldt-Jakob disease (CJD) is an untreatable and invariably fatal member of a group of neurodegenerative conditions known as prion diseases or Transmissible Spongiform Encephalopathies (TSEs). Prion diseases are recognised in both humans and other mammals and have a number of aetiologies including sporadic, acquired or familial forms. Despite this apparent heterogeneity, there is a unifying hypothesis linking all prion diseases: the “protein hypothesis” described by Prusiner [1] which proposes that a post-translational change occurs in the normal prion protein (PrP\textsuperscript{c} – cellular) forming the infective form of the prion protein (PrP\textsuperscript{Sc} – Scrapie). PrP\textsuperscript{Sc} essentially replicates by catalysing further transformation of PrP\textsuperscript{c} into PrP\textsuperscript{Sc}.

The variant form of Creutzfeldt-Jakob disease (vCJD) is the zoonotic form of bovine spongiform encephalopathy, a prion disease in cattle, which entered the human food chain in the UK between 1980 and 1996. vCJD has been transmitted by blood transfusion on three occasions [2], as well as one non-symptomatic transmission [3]. The most recent UK primary case of vCJD had symptom onset in 2012 and died in 2013, although surveillance to look for further cases continues. In contrast, sporadic Creutzfeldt-Jakob disease (sCJD), the most commonly occurring human subtype, is believed to be a spontaneous illness with no identified causative event or exposure. There has been one epidemiological study which has suggested blood transfusion may be a risk factor for the development of sCJD [4], but this has not been supported by a similar study in the UK [5] or through look-back studies [2,6,7].

The familial form of CJD (fCJD) is caused by a mutant copy of the PRNP gene, encoding a form of endogenous PrP\textsuperscript{c} prone to spontaneous conversion to PrP\textsuperscript{Sc}. fCJD is inherited in an autosomal dominant pattern, but family history may not be present in some cases due to loss of contact, non-paternity, variable penetrance, etc.

This paper updates the 2006 Transfusion Medicine Epidemiology Review (TMER) paper [2] and describes the results of the UK study on blood transfusion and the development of CJD, for all CJD subtypes.

Study Design and Methods

CJD Surveillance

The National Creutzfeldt-Jakob Disease Research & Surveillance Unit (NCJDRSU) was founded in Edinburgh, UK, in 1990 to identify all cases of CJD in the UK and to look for evidence of a link between BSE in cattle and CJD in humans. The methodology of the surveillance process has been described previously [8] and includes referral of suspected cases to the Unit from clinicians from a number of professional backgrounds, including neurologists, psychiatrists, other physicians and neuropathologists. The referred cases are seen, when possible, by a neurologist from the Unit, who carries out a detailed interview with the family of the patient and reviews the specialist investigations. The interview includes details about past medical history, blood transfusion and donation. Cases are
categorised according to WHO diagnostic criteria [9]. The Transfusion Medicine Epidemiology Review (TMER) was created in 1997 as a collaboration between the NCJDRSU and the UKBS to identify any evidence that CJD was transmissible via blood transfusion.

Notification of CJD cases with a history of donation

sCJD and fCJD cases with a reported history of blood donation, including cases where a family may be uncertain, are notified to UKBS retrospectively, following the visit by the NCJDRSU clinician. All vCJD cases old enough to be a blood donor are notified to UKBS at diagnosis irrespective of whether they have a reported history of blood donation. Following this notification, all computer and any archived paper records are searched at blood centres for evidence of the documented donation – using name, date of birth and address at time of donation as identifiers. If available, information about dates and places of donation is used to target the search. If donor records are identified, a list is generated of all components issued for clinical usage. The outcome for each component is determined from hospital transfusion laboratory records, with the names of recipients of these components cross-checked against the NCJDRSU database of known CJD cases and flagged with the Health and Social Care Information Centre (HSCIC, formerly Office of National Statistics) to collect data from death certificates regarding cause and date of death.

Notification of CJD cases with a history of transfusion

Where relatives have indicated any fCJD, sCJD or vCJD patient is suspected to have received blood or blood components, the information collected is passed to the relevant blood service, which contacts the hospital transfusion laboratories to confirm, if possible, details of the transfusion. The transfused components are identified from records, and details passed back to the blood centre for attempted identification of the donors. As above, the donor details are checked against the NCJDRSU database and flagged with the HSCIC.

Further information

UKBS and hospital transfusion records prior to 1980 are extremely limited, making such historical searches frequently unrewarding. For cases where HSCIC data lists potentially relevant diagnoses on the death certificate (e.g. dementia, Alzheimer's disease) but the individual concerned has not been seen by the NCJDRSU clinician, we have sought further information where possible regarding the nature of this illness, from either general practitioner or hospital notes.
Results

sCJD donors

A total of 370 sCJD cases were reported to be blood donors, with 204 of these believed to have donated after 1980. In only 29 of 204 cases were these individuals traced as blood donors; blood components from these donors were transfused to 211 recipients.

Fate of recipients from sCJD donors

To date, 143 individuals (67.8%) of the 211 recipients identified in this study have died, 44 (20.9%) were alive and 24 individuals (11.4%) were of unknown status due to insufficient information to identify the individual, or relocation of that individual abroad. Of the 143 who had died, death certificates are available. The underlying causes of death for all cases are listed in Table 1. Five of 143 had dementia (including Alzheimer’s disease) listed on their death certificates but are not thought to represent cases of CJD. These 5 cases had mean age at death of 88 years, and in each case dementia was not listed as the primary cause of death. In one of these 5 cases, dementia was considered a relevant comorbidity, rather than the underlying cause of death on the certificate, hence only 4 dementia deaths are listed in Table 1. The first case received whole blood donation about 21 years before becoming symptomatic of dementia; and had a 6 year, slowly progressive illness, dying 26 years after receiving the transfusion. The donor became symptomatic of CJD nearly 21 years after the donation. The second case received red cells (non leucocyte depleted) 10 months prior to death, while the donor became symptomatic of sCJD almost 4 years after donation (more than 3 years after the recipient died). The third case received red cells (non leucocyte depleted) 8 years before death; the donation occurred 4 ½ years before the donor became symptomatic of sCJD. The fourth case received fresh frozen plasma 28 months before death; the donor became symptomatic 5 ½ years after donation. The fifth case received red cells (non leucocyte depleted) 18 years before death; the donor became symptomatic 15 ¾ years after donation.

Eighty-eight of 143 (61.5%) sCJD recipients died less than one year after transfusion, 25 (17.5%) between one and 5 years after transfusion and 28 (19.6%) more than 5 years after transfusion (range in this group 5.77-26.10 years, median 8.97); for 2 recipients the transfusion date was unknown.

Of the 44 recipients still alive as of May 2015, all have survived more than 9 years from the date of transfusion. Twenty-two (50%) of these recipients received donations from 8 donors who donated less than 5 years before they became symptomatic of sCJD (range 0.23-4.92 years, median 2.21). None of these living recipients have developed sCJD and been referred to the NCJDRSU.

vCJD donors

Of the 177 UK cases of vCJD, 167 were old enough to have been blood donors. In thirty-two of the 167 cases, family reported to the NCJDRSU clinician a possible history of blood
donation. A further 4 cases not reported by the families as donors appeared on UK databases, but only one of these 4 had donated. In total, 24 had records with the UKBS, but only 18 of these 24 had donations which were subsequently used clinically. Sixty-seven blood components from these 18 donors were traced to identified recipients; a further 6 components known to have been issued could not be traced.

**Fate of recipients from vCJD donors**

Thirty-four (50.7%) of the 67 successfully traced recipients died within 5 years of their transfusion – none were thought to have died from CJD, but none of these cases had post mortem examination to look for PrP<sup>Sc</sup> deposition. Three cases (4.5%) of vCJD have already been reported from this cohort of 67 [2]; these 3 developed vCJD between 6 ½ and 8 years 4 months after their transfusion. Five (7.5%) of the 67 died more than 5 years after transfusion and had post mortem examination including examination for PrP<sup>Sc</sup> - only the single case already reported tested positive [3], with PrP<sup>Sc</sup> deposition in the spleen. A further 11 recipients who died more than 5 years after transfusion did not have post mortem examination to look for PrP<sup>Sc</sup> deposition. To date, 14 of the 67 recipients remain alive. One recipient has moved abroad and their fate is currently unknown while the remaining 13 have now survived more than 10 years after receiving transfusion from vCJD donors. There have been no new cases of vCJD identified by the NCJDRSU among the recipients of blood from vCJD donors.

**fCJD donors**

Of the 17 familial/genetic cases reported to have been donors, four were traced by the UKBS, one with a D178N mutation, one with an E200k mutation and two with octapeptide repeat insertion mutations. Fifteen recipients were traced and of these 8 have died, all of a non-neurological disorder, other than one with a history of stroke. Four are alive and 3 could not be identified. Blood transfusions took place between 1977 and 2002 and 4 recipients are alive more than 13 years after the transfusion. None of the recipients appear on the NCJDRSU database as CJD cases.

**sCJD recipients**

199 sCJD cases were reported to have received blood or blood component transfusion, 111 of these after 1980. The records were traced in 23 (20.7%) of these 111 cases, with 214 donors identified. These 23 cases received their first blood or blood components between 0.3-14.2 years before becoming symptomatic of sCJD (mean 3.89, median 2.61).

**Fate of donors to sCJD recipients**

To date, 205 (95.8%) of the 214 donors are still alive, 4 (1.9%) have died and 5 (2.3%) were of unknown status due to insufficient data (4) or relocation abroad (1). The surviving donors
ranged from 25 to 82 years of age (median 56). Three of the four deceased donors died of causes other than dementia (intracerebral tumour, liver disease and suicide), but for one individual, dementia was listed on the death certificate; this donor died almost 12 years after the donation, aged 76, and was thought likely to have vascular dementia, rather than CJD. The other three donors died aged 54, 59 and 63 years, respectively 4, 10 and 12 ½ years after their donations.

vCJD recipients

Fifteen of the 177 UK vCJD cases were reported to have received blood or blood components. Transfusion laboratory records were traced in 10 of these 15 cases, which include the 3 cases of transfusion-associated vCJD previously published and listed earlier in this paper [2]. One of the 10 recipients had onset of symptoms less than one year after transfusion and is unlikely to represent possible transfusion associated vCJD given the timings of the 3 known cases. Four of the 10 received blood components from 112 donors; the remaining two recipients received a total of 6 blood components, but it was not possible to identify the donors in these cases.

Fate of donors to vCJD recipients

Six of these donors have died of causes unrelated to CJD (Table 2), 104 are currently alive and the fate of 2 is not known (one having moved abroad).

fCJD recipients

None of the familial/genetic human prion disease cases had a history of having received a blood transfusion.

Discussion

This study has not identified any new cases of transmission of vCJD by blood transfusion, with only 4 documented infections to date, as described in an earlier TMER publication in 2006 [2]. The possibility that there are significant numbers of missed transfusion cases is judged to be unlikely, not least because the great majority of vCJD cases have no history of blood transfusion [2,10]. It is surprising that there have been no further transfusion transmitted cases in view of the estimated prevalence of abnormal PrP positivity of 1/2000 in the general UK population, derived from an anonymised survey of routine appendix tissue [11]. All clinical cases of vCJD with data on genotype have been methionine homozygotes at codon 129 of the PRNP gene. Analysis of the codon 129 distribution in the UK population indicates that 44% are MM homozygotes, with 45% MV heterozygotes and 11% VV (valine homozygotes) [12]. It is possible that individuals who are either heterozygotes or valine homozygotes may experience a longer pre-symptomatic phase before developing clinically evident vCJD and all codon 129 genotypes were represented in the positive appendix samples in the recent prevalence study. However, it is 20 years since the onset of symptoms in the first case of vCJD and no definite or probable case of vCJD
with a non-MM homozygous genotype has yet been identified in the UK or internationally.

The codon 129 genotype is known in 19 of the 67 recipients, including the 3 vCJD cases (MM homozygotes) and the pre-clinical infection (MV heterozygote). Four deceased recipients with no evidence of abnormal PrP in brain or peripheral tissues have been genotyped. These 4 individuals had survived for 6.3-15.9 years post transfusion and the interval from the donation to the onset of clinical symptoms in the donor was between 2 months and 6.8 years. Two were MV heterozygotes and two were MM homozygotes. Two further cases without post mortem examination were MM homozygotes. Nine recipients who are currently alive have been genotyped. Five are MV heterozygotes and 4 are MM homozygotes. One of the MV heterozygote recipients had a tonsil biopsy which showed no evidence of abnormal PrP deposition. This recipient received a transfusion from an individual from whom an earlier donation was implicated in two of the three known transfusion-transmitted cases, who were, as previously stated, MM homozygotes. It is of interest that in 3 surviving asymptomatic MM homozygotes, red cells had been leucodepleted, a policy introduced in the UK as a v-CJD risk-reduction measure in 1999. In addition, the fourth surviving asymptomatic MM homozygote had received cryo-depleted plasma.

The high proportion (50.7%) of blood transfusion recipients who died within 5 years of transfusion reflects the comorbidities which led to blood transfusion. Extrapolating from other acquired prion diseases, kuru and iatrogenic CJD, the minimum incubation periods are at least 4.5 years [13,14], and it is unlikely that this group would have manifest symptoms of vCJD prior to death, even if infected. The observed interval from transfusion to symptom onset in the identified transfusion cases was 6 ½ to 8 years, 4 months. It is also likely that there may be variable levels of infectivity in blood from vCJD donors relating to the proximity of the time of the donation to symptom onset in that individual and early donations might have a lower level of infectivity, which could be associated with a longer pre-symptomatic phase in recipients.

Recipients of any blood transfusion are now deferred from themselves donating blood, which prevents the potential propagation of a transfusion vCJD epidemic, which is important if some donors have a subclinical infection. It is of note that laboratory transmission studies using splenic tissue from the sub-clinically infected vCJD case have confirmed the presence of infectivity and this case was a codon 129 heterozygote [15].

In contrast to the vCJD group, as yet there have been no cases of sCJD with definite epidemiological evidence to support a transfusion link. Evidence of an increased risk through blood transfusion in sCJD with a lag period of more than 10 years in an Italian study [4] was not replicated by a similar analysis of UK data [5]. In our study of sCJD there has been a total of 1194 patient-years survival following transfusion from a sCJD donor with no evidence of transmission via blood transfusion. The absence of any observed cases supports the hypothesis that blood infectivity, should it be present at all, is lower in sCJD than vCJD. This would be compatible with the extensive PrPSc deposition in lymphoreticular tissues in vCJD, which contrasts with sCJD where there is comparatively much less
peripheral PrP<sup>c</sup>. Nevertheless, animal studies using transgenic mice overexpressing human PrP<sup>c</sup> have suggested there can be infectivity in sCJD blood [16] and work is ongoing to attempt to use amplification techniques, such as real-time quaking induced conversion (RT-QuIC), to identify a positive signal in blood in sCJD. The identification of positive findings in sCJD blood using highly sensitive techniques may be difficult to interpret in relation to actual risk and epidemiological data remains important in assessing risks for public health.

As in the recipients of blood from the vCJD donor group, early mortality among recipients of blood transfusion is high in the sCJD study and it is possible that some of these recipients could be in the presymptomatic phase of sCJD infection at time of death. Post mortem uptake is low in the UK population, and, unless explicitly looked for, changes of early sCJD may be missed. The combination of these factors raises the possibility of as yet undetected transmission of sCJD by blood transfusion, although this is unlikely given the negative data in this study and similar findings from other studies [2,6,7]. The cumulative data from look-back studies in sCJD suggests that transfusion transmission of sCJD is a rare event, should it occur at all.

The data on fCJD show no evidence of transfusion transmission and, although the data is very limited, there is some evidence of restricted peripheral pathogenesis in hereditary forms of human prion disease similar to sCJD.

The study has some limitations. Both the sCJD and fCJD arms depend on relatives reporting blood transfusion or donation at the time of the NCJDRSU clinician interview; if the relative was uncertain, or believed a patient may have possibly donated blood or received a transfusion (e.g. intraoperatively), this was still flagged to the UKBS. Despite this it is likely that some sCJD and fCJD patients who had either donated blood or received transfusion were not identified by the current methodology. By comparison, all vCJD cases of donation age are flagged to UKBS, reducing potential under reporting. Investigation of all sCJD and fCJD cases, whether or not they have been reported to be blood donors or recipients, has been considered, but follow-up of cases is labour intensive and investigating these cases regardless of the transfusion history is unlikely to provide much additional information.

A further limitation is that no transfusion or donation records have been identified for some cases. In some instances, this may be because the possible donors or recipients as reported by the family had never donated or received blood, but these cases are in the minority. The lack of centralised computer records, particularly prior to 1980, and the tendency of many hospital trusts to destroy old, unused, medical records means a large pool of potentially useful data has been lost. This problem is compounded in the non-vCJD group, as these patients tend to be older and are therefore more likely to have had their contact with the UKBS prior to the improvement in record keeping.

The reliance on data derived from death certificates is also a limitation as the final diagnostic classification of identified cases relies on the conditions listed on the death certificate. There have been widely variable estimates of inaccuracy on death certificates. An Office for National Statistics survey suggested inaccuracy in 22% of certificates, with under-reporting
of common underlying conditions including heart disease and cancer [17]. It is likely that dementia of any cause is also under-reported, and CJD may not be diagnosed in life, with symptoms attributed to an alternative cause of dementia. Review of death certificate data on CJD since 1990 at the NCJDRSU suggests that the sensitivity and specificity of a correct diagnosis on death certificates is about 80%. It is also likely that not all UK cases of CJD are referred in life or identified through death certificates or post mortem findings.

Despite these caveats the data presented in this paper has provided no evidence that cases of sCJD have developed the condition as a result of prior blood transfusion. The unexplained mismatch between the observed data in vCJD and prevalence estimates in the general population and the recent experimental evidence of infectivity in sCJD blood underline the importance of continuing the epidemiological studies of blood transfusion in all forms of human prion disease.

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RGW, PEH, CAL and JMM all contributed to the research design, acquisition and analysis of data, PU contributed to data acquisition and data analysis and wrote the first draft of the paper. All authors contributed to drafting the paper and all approved the final version.

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References


Table 1: Underlying causes of death in recipients from sCJD donor

Table 2: Cause of death in 6 donors
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<td>Leukaemia, myeloma, myelodysplasia, myelofibrosis, sideroblastic anaemia</td>
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<tr>
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<td>Pneumonia</td>
<td>10*</td>
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<tr>
<td>Stroke</td>
<td>7</td>
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<tr>
<td>Liver disease</td>
<td>5</td>
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<tr>
<td>Dementia (including Alzheimer's)</td>
<td>4</td>
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<tr>
<td>Abdominal aortic aneurysm</td>
<td>3</td>
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<tr>
<td>Chronic obstructive pulmonary disease</td>
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<td>Septicaemia</td>
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<td>Small bowel obstruction</td>
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*in one case, Alzheimer's disease was recorded as a co-morbidity
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<td>2</td>
<td>Hypertensive heart disease</td>
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<td>3</td>
<td>Pulmonary Embolus/Deep Vein Thrombosis/Ischaemic Heart Disease</td>
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<td>4</td>
<td>Bronchopneumonia/disseminated sigmoid colon carcinoma</td>
</tr>
<tr>
<td>5</td>
<td>Complication of heart valve surgery</td>
</tr>
<tr>
<td>6</td>
<td>Bronchopneumonia/Stroke/Atrial Fibrillation/Ischaemic Heart Disease</td>
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