Articles

Possible transmission of variant Creutzfeldt-Jakob disease by blood transfusion

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Summary

Background Variant Creutzfeldt-Jakob disease (vCJD) is a novel human prion disease caused by infection with the agent of bovine spongiform encephalopathy (BSE). Epidemiological evidence does not suggest that sporadic CJD is transmitted from person to person via blood transfusion, but this evidence may not apply to vCJD. We aimed to identify whether vCJD is transmissible through blood transfusion.

Methods The national CJD surveillance unit reported all cases of probable or definite vCJD to the UK blood services, which searched for donation records at blood centres and hospitals. Information on named recipients and donors was provided to the surveillance unit to establish if any matches existed between recipients or donors and the database of cases of vCJD. Recipients were also flagged at the UK Office of National Statistics to establish date and cause of death.

Findings 48 individuals were identified as having received a labile blood component from a total of 15 donors who later became vCJD cases and appeared on the surveillance unit's register. One of these recipients was identified as developing symptoms of vCJD 6·5 years after receiving a transfusion of red cells donated by an individual 3·5 years before the donor developed symptoms of vCJD.

Interpretation Our findings raise the possibility that this infection was transfusion transmitted. Infection in the recipient could have been due to past dietary exposure to the BSE agent. However, the age of the patient was well beyond that of most vCJD cases, and the chance of observing a case of vCJD in a recipient in the absence of transfusion transmitted infection is about 1 in 15 000 to 1 in 30 000.

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Introduction

Human prion diseases include sporadic Creutzfeldt-Jakob disease (CJD), which is of unknown cause; hereditary forms associated with mutations of the prion protein gene; variant CJD (vCJD), which has been causally linked to the bovine spongiform encephalopathy (BSE) agent; and iatrogenic cases transmitted via human pituitary hormones, human dura mater grafts, corneal grafts, and neurosurgical devices. All instances of iatrogenic transmission of CJD to date have been due to cross-contamination with high-titre tissues in or adjacent to the CNS,[1] and findings of epidemiological and observational studies have failed to provide evidence of transmission via blood transfusion or fractionated plasma products.[2,3] This evidence may not apply to vCJD, which is caused by a novel infectious agent for human beings and in which there is evidence of a peripheral pathogenesis different from other forms of human prion disease.[4] In vCJD, prion protein is readily detectable in lymphoreticular tissues such as appendix, spleen, tonsil, and lymph nodes, whereas these tissues are negative—by comparable methods—in other forms of human prion disease.[4]

The possibility that vCJD might be transmitted by blood transfusion led us to start a study with the aim to identify whether vCJD was transmissible by this mechanism.

Methods

Procedures

In 1997, a surveillance system was set up between the UK national CJD surveillance unit and the UK national blood services. Workers at the surveillance unit notified the relevant medical director of the blood services (National Blood Authority, Scottish National Blood Transfusion Service, Welsh Blood Service, Northern Ireland Blood Transfusion Service) of vCJD patients who were old enough to have donated blood (age >17 years). On receipt of this notification, workers at the blood services began an immediate search of donor records, irrespective of whether or not the case was reported by relatives to have been a blood donor. We searched current computer databases and archived records (computerised and paper-based records where appropriate) at individual blood centres, with name, date of birth, and a full set of previous addresses as identifiers. No search took place for donations or transfusions given before 1980, the presumed earliest possible exposure date to BSE. When donor records were found we identified all blood components made and issued to hospitals, and established their fate as recorded on blood transfusion laboratory records. We then checked recipient details against the national CJD surveillance unit register to establish if any individuals had developed vCJD.

This report does not include details of the current negative reverse study, in which donors of blood transfused to vCJD cases are traced, nor of a concurrent

study of sporadic CJD. The study has not, to date, entailed tracing of recipients of fractionated plasma products produced from pools containing a donation from an individual later diagnosed as a case of vCJD.

We received ethical approval for the study, and it is noteworthy that hospitals were passed masked details with no mention of the diagnostic category. The UK Office of National Statistics flagged all identified donors and recipients to establish the date and cause of death. This component of the study also received ethical approval.

From the information provided by the Office of National Statistics, we calculated the length of time since receipt of the transfusion until death or Dec 18, 2003, for every recipient. Based on the total amount of follow-up time in the cohort of recipients, we calculated the number of vCJD cases we would have expected to record in the cohort in the absence of any vCJD transmission through blood transfusion, and hence the probability of noting one or more cases, assuming a Poisson distribution. We obtained the expected number of vCJD cases by assuming that the vCJD epidemic in the UK had been in progress for a period of 10 years (the first known case had onset at the beginning of 1994), calculating average annual crude and age-specific incidence rates in the UK population over this period, and applying these to the cohort of transfusion recipients, assuming that all recipients were susceptible (not just those methionine homozygous at codon 129 of the PrP gene, *PRNP*).

Role of the funding source

The sponsor of this study had no role in study design; in collection, analysis, and interpretation of data; in writing of the report; or in the decision to submit the paper for publication.

Results

Case report

In 1996, a patient aged 62 years was transfused with 5 units of red cells at time of surgery. One of the units had been donated by a 24-year-old individual who developed symptoms of vCJD 3 years 4 months later, and who died in 2000 of pathologically confirmed vCJD.

In late 2002, 6·5 years after the blood transfusion, the recipient became withdrawn and irritable, and within 3 months, treatment with antidepressants was started—without benefit. The depression deteriorated and was associated with a shuffling gait and repeated falls. Blurred vision, shooting pains in the face and abdomen, fidgety movements, and difficulty with motor tasks such as dressing developed over subsequent months. Admission took place 6 months after onset of symptoms, and cognitive impairment, dyspraxia, a shuffling unsteady gait, and extensor plantar responses were seen. Routine investigations were normal. Cerebrospinal fluid (CSF) was acellular with normal constituents apart from a modest rise of CSF protein of 0·67 g/L. CSF 14-3-3 immunoassay was not done. MRI brain scan was reported as normal and was not judged to show the pulvinar sign after review. The patient deteriorated rapidly, showed myoclonic jerks of the limbs, and died 13 months after onset of illness.

As a result of flagging, the death certificate, which listed dementia as a cause of death, was forwarded from the Office of National Statistics to the national CJD surveillance unit, and the link through blood transfusion to the donor case was established. Independently of this process, the post mortem had been provisionally reported as showing changes suggestive of CJD, and the case was referred to the surveillance unit after death and tissues were sent for review. Subsequent investigation showed that the patient was a methionine homozygote at codon 129 of the prion protein gene (*PRNP*), and sequencing did not show any mutation. Prion-protein typing confirmed deposition in the brain of type 2B prion protein, which is pathognomic of vCJD. The neuropathological changes were typical of those seen in vCJD, with extensive florid plaque deposition.

Year of transfusion	Blood component transfused	Number of recipients (n=48)
1980–1984	Whole blood	1
	Red blood cells	1
1985–1989	Red blood cells	1
1990–1994	Red blood cells	8
1995–1999	Whole blood	1
	Red blood cells	16
	Red blood cells, buffy coat depleted	2
	Red blood cells, leucodepleted	1
	Fresh frozen plasma	3
	Cryodepleted plasma	1
	Cryoprecipitate	1
	Platelets	1
2000–2003	Red blood cells, leucodepleted	10
	Fresh frozen plasma, leucodepleted	1

Table 1: **Number of recipients transfused, by year and blood component given**

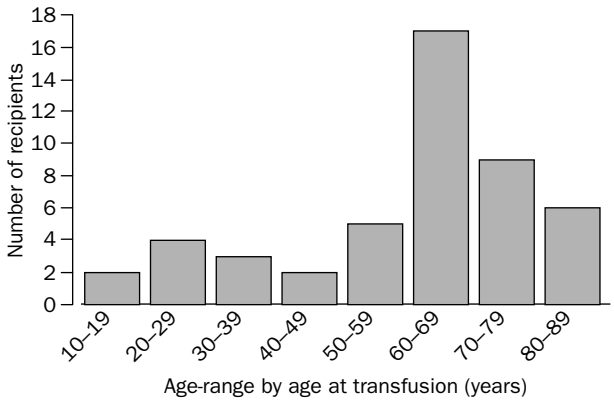
Statistical analysis, taking account of reported vCJD mortality to date and details of the recipients of vCJD donations (see below), indicated that the probability of recording a case of vCJD in this population in the absence of transfusion transmitted infection ranges between about 1 in 15 000 and 1 in 30 000. The first figure is based on crude analysis of the data, whereas the latter figure takes account of the ages of the transfusion recipients.

Review of records established that the affected donor had donated another unit of blood, the red cells of which were transfused to a patient who died of cancer 5 months after the transfusion. The platelets from this donation were included in a platelet pool, which has not been traced to a recipient. Plasma from both the donations was included in two different plasma pools for the production of fractionated plasma products.

vCJD cases with history of blood donation

As of Dec 18, 2003, 135 vCJD cases (of a total of 145 on the national CJD surveillance unit register) who were old enough to have been potential blood donors were notified to the UK blood services. 15 individuals were confirmed to have donated blood, with the number of components made and issued for use by the blood services ranging from one to eight per donor.

55 labile components originating from 15 donors were issued to UK hospitals over the period 1982–2002, most being issued between 1996 and 2000. Of these, 48 were



Age-range of recipients at transfusion

Interval from transfusion to death (years)	Number of recipients (age [years] at death)	Cause of death	Blood component transfused (single units)	Interval between blood donation and onset of clinical symptoms in donor (months)
<1	7 (68, 68, 65, 87, 88, 53, 69)	Cancer	FFP, RBC-BCD, RBC-LD, RBC-LD, RBC, RBC, WB	17, 15, 2, 18, 59, 31, 9
	1 (64)	Myocardial infarction	Cryoprecipitate	7
	2 (76, 66)	Myelodysplasia	RBC, RBC	58, 7
	1 (81)	Myelofibrosis	RBC-LD	13
	1 (70)	Peritonitis	RBC-LD	10
	1 (68)	Postoperative pneumonia	RBC-LD	16
	2 (53, 17)	Septicaemia	FFP, RBC	–6, 93
	2 (49, 72)	Not yet available	RBC, RBC	139, 116
1 to <2	1 (52)	Acute myeloid leukaemia	RBC	34
	1 (27)	Heart disease and chronic renal failure	FFP	13
	1 (62)	Spinal haemangioblastoma	RBC	55
	1 (85)	Not yet available	RBC	127
2 to <3	1 (76)	Chronic obstructive airways disease	RBC	32
	1 (68)	Acute myeloid leukaemia	Platelets	58
3 to <4	1 (29)	Disseminated sepsis	RBC-LD	21
	1 (36)	Ischaemic heart disease	FFP	0
4 to <5	1 (80)	Ischaemic heart disease	RBC-BCD	6
6 to <7	1 (23)	Acute lymphoblastic leukaemia	RBC	93
7 to <8	1 (69)	Dementia*	RBC	40
	1 (70)	Ischaemic heart disease	RBC	112
>10	1 (99)	Bronchopneumonia	WB	141
	1 (69)	Ischaemic heart disease	RBC	191

*vCJD case. RBC=red blood cells. RBC-BCD=red blood cells, buffy coat depleted. RBC-LD=red cells, leucodepleted. FFP=fresh frozen plasma. WB=whole blood.

Table 2: **Dead recipients (n=31) of labile components from vCJD donors**

transfused to recipients. Seven components (issued between 1982 and 1996) were sent to hospitals that were unable to trace their fate. 20 units of plasma were included in pools for the production of fractionated products.

48 people were identified who received blood from 15 donors who went on to develop vCJD. Table 1 shows the number of recipients transfused by year and the type of blood component transfused. 41 (85%) received red-cell components (39 red blood cells, two whole blood), six (13%) were transfused with plasma components (four fresh frozen plasma, one cryoprecipitate, one cryodepleted plasma), and one (2%) received platelets. A third of the red-cell recipients received cells that had been leucocyte-depleted by prestorage filtration to less than 5×10^6 leucocytes per unit after introduction of universal leucocyte depletion of the UK blood supply in 1999 as a precautionary measure against vCJD transmission.

The figure shows the age-range of the 48 recipients. 32 (67%) were aged older than 60 years at the time of transfusion and thus would not have been eligible to enrol as blood donors subsequently. At Dec 18, 2003, none of the remaining recipients had themselves donated blood, although five were still young enough to be eligible as donors.

31 recipients (65%) were known to have died, with mean age at death 63 years (SD 20; range 17–99). 17 (55%) died less than 12 months after receiving their transfusion. Table 2 shows the cause of death as stated on death certificates for 28 recipients; the other three were confirmed dead, but cause of death was not available from the Office of National Statistics. No further information on clinical or neuropathological features was available for these cases.

At Dec 18, 2003, 17 (35%) recipients were alive. The mean age of these recipients was 65 years (SD 19, range 29–88). Ten patients survived for longer than 5 years after being transfused. Table 3 shows the number of living recipients according to time elapsed since transfusion, component transfused, and the interval between donation and onset of clinical symptoms of vCJD in the donor, as estimated by the national CJD surveillance unit to the nearest month after reviewing the case notes. None of these recipients have appeared on the surveillance register as vCJD cases. Most donations were made before onset of clinical illness (table 3) although two cases donated shortly after the first signs of clinical illness. These individuals would have seemed healthy when attending donor sessions and passed the normal medical checks as being fit to donate.

Time elapsed since transfusion (years)*	Number of recipients (current age in years*)	Blood component transfused (single units)	Interval between blood donation and onset of clinical symptoms in donor (months)
1 to <2	1 (88)	RBC-LD	–5
2 to <3	2 (50, 65)	RBC-LD	9, –3
3 to <4	2 (69, 73)	RBC-LD	5, 4
4 to <5	2 (40, 82)	RBC	5, 18
5 to <6	3 (71, 80, 85)	RBC	17, 13, 55
6 to <7	2 (29, 74)	RBC	20, 49
7 to <8	1 (72)	RBC	70
8 to <9	1 (31)	Plasma†	7
	2 (47, 85)	RBC	15, 82
>9	1 (65)	RBC	46

*To Dec 18, 2003. †Cryoprecipitate-depleted plasma. RBC=red blood cells. RBC-LD=red blood cells, leucodepleted.

Table 3: **Living recipients (n=17) of labile blood components donated by vCJD cases**

Discussion

The identification of a case of vCJD who received a blood transfusion from a donor who later died of vCJD raises the possibility that this infection was transfusion transmitted. Although statistical analysis suggests that coincidence is an unlikely explanation for this case, it is important to stress that this is a single case and there is a possibility that infection was due to dietary exposure to the BSE agent, the presumed route of zoonotic transmission of BSE.

The hypothesis of transfusion transmitted infection implies an incubation period of 6·5 years and that there was infectivity in the blood of the donor more than 3 years before development of clinical symptoms. The shortest incubation period in iatrogenic CJD due to human growth hormone treatment is 4·5 years,[1] which accords with the incubation period in this case. The route of administration, intramuscular rather than intravenous, and the probable amounts of infectivity in the implicated tissue—brain versus blood—suggest that a direct comparison between these iatrogenic mechanisms of prion transmission might not be valid. However, findings in experimental models show that blood may contain infective agents of prion diseases,[5,6] that no barrier to transmission exists with intraspecies transmission, and that the intravenous route of exposure to prions is fairly efficient.[7] The seminal experiments by Houston and Hunter[8,9] have shown transmission of BSE by blood transfusion in sheep, and it is noteworthy that the blood for transfusion in these experiments was obtained from sheep midway through the incubation period. Infectivity has also been noted in the incubation period and symptomatic phase in a rodent model of vCJD.[10] This evidence accords with the possibility of transfusion transmitted infection in the case reported here.

No evidence of transmission of sporadic CJD by blood transfusion exists, despite the identification of individuals who were exposed to blood donated by people who later developed this disease.[3] These data may not, however, be relevant to vCJD because this disease is due to a novel infectious agent in human beings and because the amount of disease-associated prion protein in peripheral lymphoreticular tissues is higher than in sporadic CJD,[4] indicating a different pattern of peripheral pathogenesis. In one study, infectivity in plasma and buffy coat in vCJD has not been detected,[11] but this fact, as in many previous studies of prion diseases, might be because of the severe restrictions in volumes of blood components that can be inoculated intracerebrally into experimental animals, leading to sampling errors in a tissue with low levels of infectivity and species-barrier effects.

The clinical presentation of the individual in this report is typical of vCJD,[12] and preliminary examination confirmed that the neuropathological features were identical to previous experience of this disease.[13] The MRI scan did not show the pulvinar sign, which is present in most cases of vCJD, but fluid attenuated inversion recovery sequences were not obtained, and these have the highest sensitivity.[14] The fact that the clinical and pathological phenotype was largely consistent with vCJD does not preclude the possibility that this case is caused by secondary transmission. The effects of serial transmission on phenotype are unpredictable in experimental models,[15] but it is noteworthy that the neuropathological features are stable in serial transmission of BSE and vCJD in macaque monkeys.[16] It is also of note that this case is the second oldest one of vCJD identified to date.

The red blood cells transfused in this case were not leucodepleted, although this measure was introduced during 1998 as a precaution to keep the chance of transmitting vCJD through blood transfusion to a minimum. However, uncertainty exists about the probable efficiency of leucodepletion in reducing infectivity,[6] and we cannot assume that the risk of transmitting vCJD will have been abolished by this measure.

The surviving recipients of blood transfusions donated by individuals who later developed vCJD may be at increased risk of developing vCJD and, after consideration by the Department of Health CJD incidents panel, are being informed of this risk and the need not to act as blood or organ donors. Additional measures might be considered, including exclusion of transfusion recipients from donating blood and extension of the policy of sourcing of fresh frozen plasma from outside the UK, but the most direct action to reduce risk is a careful case-by-case evaluation of the need for blood transfusion. Although the epidemic of vCJD presently seems to be in decline,[17] a proportion of the UK population could be incubating vCJD[18] and acting as blood donors.

20 units of plasma from individuals who later developed vCJD were included in pools for the production of fractionated products before 1998, at which time a policy was introduced to source plasma for fractionation from outside the UK. Before this date, many thousands of individuals may have been exposed to fractionated products derived from pools containing a donation from an individual incubating vCJD. To date, no case of vCJD has been identified with a history of exposure to fractionated blood products, and findings of experimental studies show that significant clearance of infectivity happens in several of the component steps in the plasma fractionation process.[19] The risks from fractionated plasma products to a recipient are probably less than from blood transfusion, not least because the volume of material to which an individual is exposed could be an important determinant of the level of risk.

Our report suggests that human prion diseases may be transmissible through blood transfusion and underlines the importance of epidemiological surveillance systems. Although experimental studies are important, only through the study of natural disease can evidence of an actual iatrogenic risk be identified. The risk of vCJD is not restricted to the UK, and the identification of cases of vCJD and examination of history of blood donation may be important in other European countries and elsewhere.

Contributors

C A Llewelyn, P E Hewitt, J Mackenzie, and R G Will were responsible for design, data collection, and management of this study. S Cousens did statistical analyses. R S G Knight and K Amar were responsible for the clinical data in the case report. All authors contributed to writing and amendment of the paper.

Conflict of interest statement

None declared.

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