

Transmission of vCJD by blood and tissues: managing the risk

Although the number of clinical cases of variant Creutzfeldt-Jakob disease in the UK is falling, there is continuing concern about effective risk management measures to stop the future spread of the disease. Here, Marc Turner looks at the risk of transmission of the agent responsible via donated blood and tissues.

Variant Creutzfeldt-Jakob disease (vCJD) was first described in 1996. It differs from the sporadic form of the disease in a number of important respects, including a younger age at onset (median 28 years, range 14–74 years), an unusual clinical presentation consisting of behavioural disturbance, dysaesthesia and cerebellar ataxia followed by more generalised neurological deterioration, and a prolonged clinical phase (median 14 months, range six to 48 months). The epidemiological, clinical, neuropathological and experimental data all point to vCJD being the same strain of prion disease as bovine spongiform encephalopathy (BSE).

INCIDENCE AND PREVALENCE

To date there have been 165 definite and probable cases of vCJD in the UK, four in the Irish Republic, three in the USA, two in The Netherlands and one each in Canada, Italy, Japan, Portugal, Saudi Arabia and Spain. Two of the Irish and US cases, along with those from Canada and Japan, are thought to have been infected in the UK, while the third US case is believed to have been infected in Saudi Arabia. The other cases are thought to have been infected in their countries of origin.

Although the number of clinical cases in the UK is falling, there is an increase in geographical spread and an important discrepancy between the number of clinical cases is now projected (maximum likelihood

estimate 70, 95% confidence interval [CI] 10–190) and the apparent prevalence of abnormal prion protein accumulation in a retrospective study of tonsils and appendices of three per 12,674.

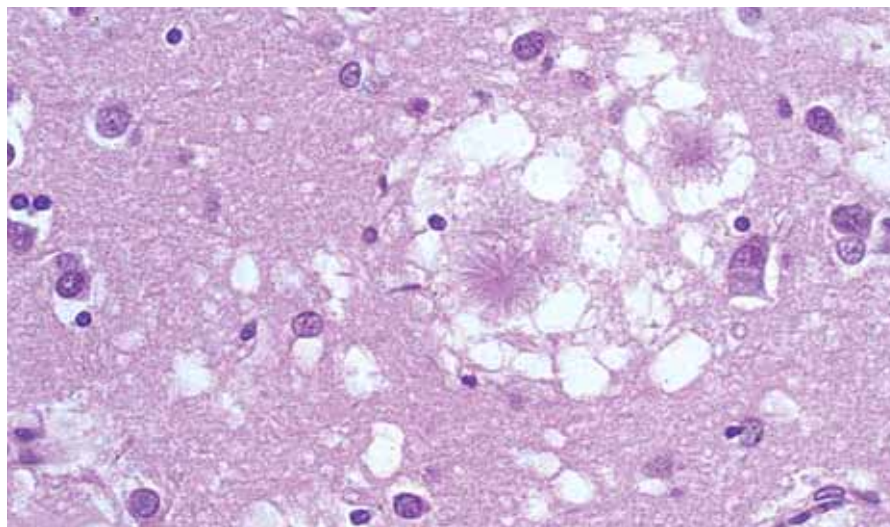
On the basis of these data, current mathematical models project a maximum likelihood estimate of 3000 infected people (95% CI 520–6810), suggesting a possibility of subclinical infection of 0.93 (95% [CI] 0.7–0.97). This would equate to a prevalence of subclinical disease in the UK donor

population in the order of one in 4000 to one in 20,000. It should be remembered, however, that these estimates are based on small amounts of data and that further large-scale prospective epidemiological studies are in progress.

INFECTIVITY AND TRANSMISSIBILITY

Extrapolation from animal studies suggests that there are around 10 infectious prion doses/mL of whole blood, of which approximately half is associated with leucocytes and half with plasma. It is now apparent that, despite our inability to detect the abnormal conformer of prion protein (Pr^{PTSE}) or infectivity by bioassay in the peripheral blood of patients with vCJD, the disease is transmissible from blood donated during the preclinical stages of disease.

The first probable transmission occurred in 1996; the blood donor was well at the time but went on to die of vCJD in 1999. The recipient was diagnosed with vCJD in 2003. The second



Prominent 'florid' plaques typical of variant CJD are visible in this section of brain tissue.

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probable transmission was described in July 2004; the patient received blood in 1999 from a donor who developed symptoms of vCJD 18 months later. The recipient died from unrelated causes five years after the transfusion, with no evidence of neurological disease, but at post-mortem examination was found to have evidence of prion accumulation in the spleen and in one cervical lymph node.

A third transmission was reported in February 2006. The patient developed symptoms eight years after receiving a transfusion from a donor who developed evidence of vCJD around 20 months after donating blood. The most recent (fourth) transmission was reported in January 2007. Again, the patient developed symptoms just over eight years after receiving a blood transfusion from a donor whose symptoms of vCJD appeared 17 months after donating blood. This donor was also the source of one of earlier transmissions.

It appears that vCJD can be transmitted up to three years before the development of clinical vCJD and that it might take six to eight years thereafter for the recipient to develop vCJD, although clearly longer incubation periods may not yet have come to light. All four transmissions were via non-leucodepleted red cell units. Therefore, the combination of a cohort of subclinically infected individuals in the donor population with evidence of the transmissibility by blood transfusion gives rise to continuing concern about the likely efficacy of current risk management measures.

DONOR SELECTION

In the UK it is not possible to identify subgroups of the population at significantly higher risk of vCJD, apart from those considered 'at risk for public health purposes' by the CJD Incidents Panel. In addition, UK blood services exclude donors who themselves have received blood or tissue, in order to reduce the risk of prolonging the vCJD outbreak through tertiary and higher-order transmissions.

Other countries have taken steps to exclude blood donors who have spent a specified cumulative period of time in the UK and in some other western European countries over the period of highest risk of dietary exposure (1980–1996). Such policies are likely to have some mitigating effect on the risk of vCJD transmission, but in some cases have led to significant damage to the donor base.

Although plasma from non-UK donors is used for product manufacture and also for clinical plasma for patients under the age of 16 years or for those exposed to large volumes of plasma (eg through undergoing plasma exchange for thrombotic thrombocytopenic purpura), it is not practical to import most other blood components and tissue products in sufficiently large amounts from non-remunerated donors outside the UK due to availability and to concerns about the quality, safety and shelf-life of the products.

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BLOOD COMPONENT PROCESSING

The estimated concentration and distribution of infectivity noted above suggests that while plasma reduction is likely to be beneficial in terms of reducing the overall level of infectivity, sufficient infectivity would remain in individual components to effect transmission.

Universal leucodepletion was implemented as a precautionary measure in the UK in 1999. Overall, the experimental data suggest that leucodepletion removes 40–70% of infectivity in whole blood but has little or no impact on plasma infectivity. These data again suggest that while leucodepletion is likely to reduce infectivity, it is unlikely to be sufficient to impact on overall transmissibility.

A number of companies are now developing prion reduction devices that offer the potential of a further three to four log reduction in infectivity, which, if achievable, would be more likely to impact on transmissibility. There is the need, however, for independent evaluation of the efficacy of these devices and the concerns about ensuring the quality and safety of the blood components that have been processed in this way. Prion reduction devices would also be likely to represent a further significant increase in the unit cost of blood components.

DONOR SCREENING

Some 10 to 12 peripheral blood assays are now under development worldwide, most of which rely on detection of PrPTSE through a variety of approaches that includes monoclonal antibodies, affinity ligands and proteinase digestion. Evaluation of such assays is problematic given the small number of patients with clinical vCJD and the difficulty in extrapolating from studies using human brain homogenates and animal blood.

Sensitivity has proved a significant challenge, but perhaps of more concern is the likelihood that first-generation assays will have relatively poor specificity, leading to large numbers of false-positive results. In the absence of confirmatory assays, such individuals will need to be informed and excluded from the donor base, despite the absence of clarity on the importance of a positive assay.

The detrimental psychological and social

impact on the donor, the direct negative impact on the donor base of excluding false positives, and the indirect impact represented by the unwillingness of people to continue to donate are all areas of serious concern.

PLASMA PRODUCT MANUFACTURE

Since 1999, plasma products manufactured in the UK have used non-UK-sourced plasma. In addition, much of the experimental data suggest that the plasma fractionation process is likely to reduce infectivity in therapeutic products. Nevertheless, it has been felt prudent to identify and notify individuals who have been exposed to implicated plasma product batches in order that appropriate public health measures can be taken.

CELLULAR AND TISSUE PRODUCTS AND ORGAN TRANSPLANTATION

Given the mass of tissue involved in transplantation of cellular therapies (eg haematopoietic stem cells), tissues (eg cornea, bone and heart valves) and solid organs, it is thought likely that transmission would occur should the donor be infected. With the possible exception of skin, importation of such products has proved problematic. Studies are ongoing to explore the possibility of reducing the infectivity through tissue processing, and a feasibility study of cadaveric tonsil testing is ongoing.

CONTINUING CONCERN

The uncertain prevalence of subclinical vCJD among donor populations, coupled with the clear demonstration of transmission by red cell components, gives rise to continuing concern about the risk of secondary transmission by blood and tissue products. Several precautionary donor selection and component processing policies have been put in place, but it seems unlikely that these obviate this risk entirely.

Several new technologies, including prion reduction filters and prion assays, are in development; however, these bring important issues of evaluation, cost and potential negative impact on the donors or on the quality and safety of products. It is likely that managing the risk of vCJD transmission will continue to be highly problematic for the foreseeable future. ■

FURTHER INFORMATION

- National CJD Surveillance Unit. www.cjd.ed.ac.uk
- Transfusion Medicine Epidemiological Review. www.cjd.ed.ac.uk/TMER/TMER.htm
- UK Blood Transfusion and Tissue Transplantation Services Professional Guidelines. www.transfusionguidelines.org

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