the prion could become the ultimate transfusion-transmissible agent, while the risk connected to viruses, bacteria and parasites, known or emerging, would be controlled by pathogen inactivation.

If transfusion transmission of vCJD is a certainty from now on, benefits of transfusion obviously remain immeasurable compared to this risk. One must put in perspective the number of lives saved every day by transfusion and the number of cases of transfused vCJD counted on a worldwide scale. One also must compare this risk, which mainly concerns two European countries, with the infectious risks faced by transfused patients in parts of the globe where the means are so limited that safety is not always assured even for major blood-borne agents.

Never before have so many measures been taken in transfusion to counteract a risk that is numerically so low, some taken even before the first case of vCJD by blood transfusion had been reported. The precautionary principle has not just gone into the law: it has also penetrated the senses.

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bjh review

16

An update on the assessment and management of the risk of transmission of variant Creutzfeldt-Jakob disease by blood and plasma products

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Summary

There have been four highly probable instances of variant Creutzfeldt-Jakob disease (vCJD) transmission by non-leucocyte depleted red cell concentrates and it is now clear that the infectious agent is transmissible by blood components. To date there in no reported evidence that the infectious agent has been transmitted by fractionated plasma products, e.g. factor VIII concentrate. This review outlines current and potential risk management strategies including donor deferral criteria, the potential for donor screening, blood component processing and prion reduction filters, plasma product manufacture and the difficulties in identification and notification of those considered 'at risk of vCJD for public health purposes'.

Keywords: Creutzfeldt-Jakob disease, blood, plasma products.

This review offers an update on our recent assessment and management of the risk of transmission of variant Creutzfeldt-Jakob disease (vCJD) by blood components and plasma products (Ludlam & Turner, 2005). As that review surveyed perceptions on the nature of the prion agent, the spectrum of prion diseases in animals and man, and the range of animal studies relating to pathogenicity and infectivity (much of which still represents the current level of knowledge), these topics are not reviewed again here, other than where significant new relevant studies have been published. This current review focuses on the state of the art in relation to the safety of blood components and plasma products, which has also been reviewed elsewhere (Farrugia *et al*, 2005; Dolan, 2006; Ironside, 2006 and Clarke *et al*, 2007).

To date, a total of 203 probable, or definite, cases of vCJD have been reported worldwide, of which 166 have arisen in the UK, 23 in France, four in Eire and Spain, three in the USA, and one in each of Holland, Portugal, Italy, Saudi Arabia, Japan and Canada (http://www.cjd.ed.ac.uk/vcjdworld.htm). Of these, two of the Irish and US cases and those in Canada and Japan are thought to have been infected in the UK. The third US case is thought to have been infected in Saudi Arabia. The other cases are thought to have been infected in their countries of origin either through exported UK meat products or exported animals or animal foodstuffs. The UK outbreak of vCJD appears to have reached a peak around the year 2000 and has waned such that in 2007 there were only five new cases, though the frequency of new cases continues to increase in France and Spain. All clinically affected individuals thus far have been methionine homozygous at codon 129 of the prion protein gene (*PRNP*). Mathematical projections based on the current incidence of vCJD suggest a maximum likelihood estimate of 70 further cases (95% confidence interval 10–190) (Clarke & Ghani, 2005). This could prove to be an underestimate, however, if individuals of other codon 129 genotypes are also capable of being infected and/or secondary transmissions occur from asymptomatic individuals.

Two observations give pause for thought. The first is that the median age of onset of clinical disease (26 years) has not altered over the past 10 years as one might expect if a cohort of individuals were exposed to infection during a specific window of time. The best fit mathematical model suggests an age-related exposure/susceptibility during the teenage years. The second is the data from a retrospective study of tonsils and appendices (Hilton *et al*, 2004) in which 3/12 500 samples showed evidence of abnormal prion accumulation, giving a maximum likelihood estimate of 3000 future cases. The discrepancy between this estimate and that based on current clinical incidence is best explained by the proposition that around 93% of infected individuals may experience long-term pre- or sub-clinical infection (Clarke & Ghani, 2005). This is consistent with experimental animal studies and clinical studies in patients with iatrogenic CJD and kuru, which suggest that individuals who are heterozygous or valine homozygous at codon 129 have a longer incubation period and a lower incidence of development of clinical disease than those who are codon 129 methionine homozygous. These observations give rise to concern however that a significant cohort of individuals, maybe as many as 1/4000 of the general population in the UK, may have sub-clinical vCJD infection

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and be at risk of transmitting the disease through blood and tissue products or surgical and medical instrumentation, despite being asymptomatic themselves.

As there is no currently accepted blood test that reliably identify vCJD infected individuals (see below), further studies have been carried out to try to refine the estimate of the prevalence of sub-clinical disease. The National Anonymised Tonsil Archive aims to test 100 000 tonsil samples. Currently, there have been no confirmed positive samples out of 45 000 tested (http://www.hpa.org.uk/infections/topics_az/cjd/tonsil_archive.htm). However there are reservations around the interpretation of these data, given that the sensitivity of the assays in detecting subclinical vCJD is uncertain, the frequency of involvement of the tonsil as a site of preclinical infection is unknown, and a large proportion of the study population are too young to have been exposed to dietary bovine spongiform encephalopathy (BSE). The Spongiform Encephalopathy Advisory Committee (SEAC) has therefore not felt it appropriate to amend the current prevalence estimates within the UK at present (http://www.seac.gov.uk).

Infectivity in the peripheral blood

Infectivity remains undetectable in the peripheral blood of patients with vCJD despite the fact that clinical transmission has clearly occurred. This apparent contradiction is probably explained by the presence of a species barrier between man and mouse and the limited volumes of blood that can be inoculated into test animals.

Studies in hamsters infected with the 263K strain of scrapie showed similar results to those in the Fukuoka-1 GSS strain in mice (Brown *et al*, 1998; Ludlam & Turner, 2005), with a point estimate of 1–10 infectious doses (ID)/ml of whole blood of which around 40% was associated with the leucocytes and most of the remainder in the plasma (Gregori *et al*, 2004). Further studies in this model suggest that the majority of cell-associated infectivity is only loosely bound and can be washed off and therefore that the plasma form of infectivity probably predominates. Further studies in mice suggest that the level of infectivity is similar in vCJD-infected animals (Cervenakova *et al*, 2003a). Studies in sheep naturally infected with scrapie, or experimentally infected with BSE, suggest a transmission frequency of up to 50% from blood taken during the preclinical or clinical phase of disease and transfused into recipients from a scrapie-free flock (Hunter *et al*, 2002). BSE has also been transmitted through buffy coat to the primate *Microcebus* (Bons *et al*, 2002).

Variant CJD transmission by blood transfusion

Within the UK, the Transfusion Medicine Epidemiology Review (TMER) has proved an effective system for collating evidence of possible transmission of vCJD by blood components (Hewitt *et al*, 2006). The UK CJD Surveillance Unit in Edinburgh shares information about new cases of vCJD with the Blood Transfusion Services, which search their databases to ascertain whether these patients have been blood donors in the past. In this event attempts are made to identify the fate of the blood components (http://www.cjd.ed.ac.uk/TMER) and trace, notify and monitor living recipients. The 'reverse' arm of the TMER study attempts to identify which individuals who develop vCJD have received blood transfusions and to identify the donors.

Eighteen patients with vCJD have, or had previously, been blood donors, from whom a total of 66 recipients have been identified, 26 of whom are still alive. Of those who have died, four cases of transmission of vCJD prions have been identified (see below). Many of these patients however will have died of their underlying conditions within 5 years of the implicated transfusion and will not have had time to show clinical evidence of vCJD if infected.

The first symptomatic case of vCJD disease associated with blood transfusion was identified in December 2003. This individual developed vCJD 6·5 years after transfusion of red cells donated by an individual who developed symptoms of vCJD 3·5 years after donation (Llewelyn *et al*, 2004).

A second case of transmission was identified a few months later in a recipient of red cells from a donor who developed symptoms of vCJD 18 months after donation. This patient died from causes unrelated to vCJD 5 years after transfusion. Postmortem investigations found abnormal prion protein accumulation in the spleen and a cervical lymph node, but not in the brain, and no pathological features of vCJD were found (Peden *et al*, 2004).

A third patient developed symptoms of vCJD 6 years and died 8·7 years after receiving a transfusion of red blood cells from a donor who developed vCJD about 20 months after this blood was donated (Health Protection Agency 2006).

The fourth case of transmission developed symptoms of vCJD 8·5 years after receiving a transfusion of red blood cells from a donor who developed vCJD about 17 months after this blood was donated. The donor to this patient also donated the vCJD-implicated blood transfused to the third patient (Editorial Team, 2007).

All four patients received transfusions of non-leucodepleted red blood cells between 1996 and 1999. Since October 1999, leucocytes have been removed from all blood used for transfusion in the UK.

These data therefore demonstrate clearly that non-leucodepleted red cells from asymptomatic individuals incubating vCJD can transmit the infection by blood transfusion to other individuals and that the risk of them doing so is relatively high.

Donor deferral criteria

There has been little substantive change in blood donor criteria since our previous review (Ludlam & Turner, 2005). Whilst other countries continue to defer those who have spent more than a specified cumulative period of time in the UK, within

