

Position Statement

Creutzfeldt-Jakob Disease

12th March 2009

Prepared by: The vCJD Working Party of the Standing Advisory Committee on Transfusion Transmitted Infections.

This document will be reviewed whenever further information becomes available. Please continue to refer to the website for in-date versions.

Background

Creutzfeldt-Jakob Disease (CJD) is one of a group of diseases called Transmissible Spongiform Encephalopathies. These diseases in general, have long incubation periods and are characterized by severe and irreversible damage to the central nervous system resulting in death. So far no clinically effective treatments have been developed.

Sporadic, iatrogenic and familial Creutzfeldt Jakob disease

Sporadic CJD, which was first described in the early 1920s, occurs throughout the world and affects around one person per million per year with a median age of onset of 65 years. Patients experience a rapidly progressive dementia with death within around six months. Other forms of the disease have since been described, including Kuru which was endemic in the Fore people of Papua New Guinea in the 1950s and transmitted through cannibalistic funeral rites. There are also rare familial forms of CJD due to inherited genetic abnormalities. In addition, transmission of CJD has occurred during medical care through neurosurgical instruments, corneal and dura mater grafts and cadaveric-derived pituitary growth hormone and gonadotrophins. A series of epidemiological case control, look back and surveillance studies over the last twenty years have not revealed any confirmed cases of transmission of sporadic CJD by blood components, plasma products, or peripheral tissues (such as bone, skin and heart valves). However, as a precautionary measure, UK Blood Services apply agreed UK and European exclusion criteria (in line with WHO recommendations) to exclude anyone who could have an increased risk of sporadic, iatrogenic or familial CJD from donating blood, tissues or stem cells.

UK Blood Transfusion Services criteria for excluding blood and tissue donors who have, or who could have, an increased risk of prion-associated diseases:

Obligatory: Must not donate if:

Diagnosed with any form of CJD, or other prion associated disorder.

Identified at increased risk of developing a prion associated disorder.

This includes:

Individuals at familial risk of prion-associated diseases (have had two or more blood relatives develop a prion-associated disease or have been informed they are at risk following genetic counselling)

Individuals who have been told that they have been put at increased risk from surgery, transfusion or transplant of tissues or organs.

Individuals who have been told that they may be at increased risk because a recipient of blood or tissues that they have donated has developed a prion

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related disorder.

Recipients of dura mater grafts.

Recipients of corneal, scleral or other ocular tissue grafts.

Recipients of human pituitary derived extracts.

Exceptions: If the donor has had two or more blood relatives develop a prion-associated disease and, following genetic counselling, they have been informed that they are not at risk, accept.

This requires confirmation by a **Designated Medical Officer**.

Variant Creutzfeldt-Jakob Disease

A different form of Creutzfeldt-Jakob Disease (variant CJD) was first identified in 1996. Unlike sporadic CJD, the new disease affects younger people (a median age at death of 28, range 14-75 years old). Clinical presentation is also different. Variant CJD patients show signs of behavioural disorder, depression and anxiety followed by problems with sensation and co-ordination leading to progressive dementia and death over a period of on average six months to two years. The clinical, epidemiological, neuropathological and experimental data all point to variant CJD being caused by the same strain of prion as Bovine Spongiform Encephalopathy (BSE). This is a different strain of prion from those seen in sporadic CJD.

To date there have been 167 definite and probable cases of variant CJD in the UK, 23-cases in France, 5 cases in Spain, 4 in the Irish Republic, 3 in the USA and The Netherlands, 2 in Portugal and one case each in Italy, Canada, Saudi Arabia and Japan. Two of the Irish and the USA cases and the cases from Canada and Japan are thought to have been infected in the UK. The third USA case is believed to have been infected when a child in Saudi Arabia. The other patients are thought to have been infected in their country of origin. The eventual number of individuals within the UK population likely to develop variant CJD remains uncertain and it is similarly uncertain how many current or past blood or tissue donors could be incubating the disease. All cases of clinical vCJD, except three from the UK, are believed to be primary cases resulting from eating BSE contaminated meat products. In December 2003, the first probable transmission of variant CJD by blood transfusion was described. The transfusion occurred in 1996, the blood donor at the time was well but went on to develop symptoms of variant CJD in 1999. The recipient was diagnosed with variant CJD in 2003. A probable transmission of variant CJD prions, not leading to clinical disease, was reported in July 2004. On this occasion the patient received blood in 1999 from a donor who went on to develop symptoms of variant CJD 18 months later. The recipient died of unrelated causes 5 years after the transfusion with no evidence of neurological disease but was found to have evidence of prion accumulation in the spleen and a lymph node on post-mortem examination. The second transmission leading to clinical disease was reported in February 2006. The patient developed symptoms about 8 years after receiving a blood transfusion from a donor who developed symptoms of variant CJD about 20 months after

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donating blood. A third transmission leading to clinical disease was reported in January 2007 in a patient who developed symptoms just over 8 years after receiving a blood transfusion from a donor whose symptoms of variant CJD appeared about 17 months after donating this blood. This donor was also associated with one of the earlier transmissions.

A further transmission of variant CJD prions was described in February 2009. The patient suffered from haemophilia and had received batches of FVIII to which a donor who subsequently developed variant CJD had contributed plasma. The patient died of other causes but was found to have evidence of prion accumulation in his spleen. Further details are awaited.

The UK blood services have taken a number of measures to try to reduce the risk of transmission of variant CJD by blood, plasma and tissue products:

- Withdrawal and recall of any blood components, plasma derivatives, cells or tissues obtained from any individual who later develops variant CJD (announced December 1997).
- Importation of plasma from countries other than the UK for fractionation to manufacture plasma derivatives (announced May 1998, fully implemented October 1999).
- Leucodepletion of all blood components (decision announced July 1998, fully implemented autumn 1999).
- Importation of clinical FFP for patients born after January 1996, announced on 16 August 2003 and implemented by the end of June 2004. Extended to all patients under the age of 16 by July 2005.
- Exclusion of whole blood donors who state that they have received a blood component transfusion in the U.K. since 1 January 1980, (April 2004). Extended to whole blood and apheresis donors who may have received a blood component transfusion in the UK since 1st January 1980, (August 2004) and to any donors who have been treated with UK plasma derived, intravenous immunoglobulin or have undergone plasma exchange. This was further extended in November 2005 to transfusions anywhere in the world.
- Exclusion of live bone donors who have been transfused since 1st January 1980 (July 2005).
- Exclusion of blood donors whose blood has been transfused to recipients who later developed vCJD, where blood transfusion cannot be excluded as a source of the vCJD infection and where no infected donor has been identified (July 2005).
- Importation of skin for treatment of patients born after January 1996 (February 2008).
- Promotion of appropriate use of blood and tissues products and alternatives throughout the NHS.

Questions and Answers

- *How many people are currently incubating variant CJD in the UK?*

Estimates of the number of people likely to develop variant CJD (and therefore currently

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incubating the disease) continue to vary. It is also possible that some people could be "infected" with this agent but never progress to clinical disease. Recent reports from the CJD surveillance unit suggest that the increasing trend in variant CJD mortality peaked in 2000 and has since fallen. The observation is encouraging, however some caution should be exercised. There is a discrepancy between the likely incidence of cases projected from the current clinical evidence of variant CJD and the number of infected people projected from the retrospective study of tonsil and appendix samples which suggests that around 1 /4,000 (range 1 /1,500 to 1 /20,000) healthy people in the general population could be sub-clinically infected (www.seac.gov.uk). Up to now all cases of probable and confirmed clinical variant CJD, where testing has been carried out, have been in people who are methionine homozygous at codon 129 of the prion protein gene. The second of the transfusion recipients referred to above, who had evidence of subclinical disease, was however heterozygous at this locus and 2 of the patients positive for abnormal prion accumulation in the retrospective study of tonsils and appendices have recently been shown to be valine homozygous. These observations suggest that other genotypes may also be susceptible to infection with variant CJD prions, possibly with a lower frequency of disease and/or longer incubation periods (as has been seen in Kuru and peripherally transmitted iatrogenic CJD). In addition, further cases may arise due to secondary human to human transmission via medical or surgical instruments or blood, plasma, cell or tissue products.

- *How many patients have been exposed to blood components or plasma products from donors who went on to develop variant CJD and will they be informed?*

Eighteen people who later developed vCJD have been traced as blood donors and gave blood donations that were transfused to recipients. Sixty-six recipients of blood components from these donors have been identified of whom 23 are still alive, 21 of whom have survived for at least 5 years since the blood transfusion. Their doctors have been informed of their exposure to these products. (www.cjd.ed.ac.uk/tmer/tmer.htm)

Eleven blood donors have contributed to 25 plasma pools from which 191 plasma product batches have been manufactured. The CJD Incidents Panel has developed a model to allow an assessment of the level of risk of exposure of recipients to variant CJD through the implicated plasma products. They have calculated a dose of each product beyond which it is likely that an infection-control threshold will be surpassed. Patients recognized to fall into this category have, where possible, been informed of their exposure to these products and precautionary steps taken to minimize the risk of any further transmission through, blood, tissue or organ donation, or by medical or surgical instrumentation. Further information can be obtained from the Health Protection Agency website (www.hpa.org.uk/infections/topics_az/cjd/menu.htm).

Application of a similar approach of tracing and notification of recipients of tissues, should a tissue donor develop vCJD, has been approved by the CJD Incidents Panel and a pilot study will commence.

- *Are additional donor selection criteria being applied?*

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Countries outwith the UK including the USA, Canada, New Zealand, Australia, Hong Kong and several European countries including Germany, Switzerland, Austria and Eire have taken the precautionary step of excluding blood donors who have spent more than a defined period in the UK between 1980 and 1996. From 5th April 2004, whole blood donors who know that they have received blood component transfusions in the UK since 1 January 1980 have been excluded from blood donation. This measure generally resulted in the deferral of 3-5% of blood donors. As of August 2004 this deferral criterion has been extended to blood donors who are unsure whether they have received a transfusion and to platelet apheresis donors. Live bone donors are now also included in this deferral criterion as of July 2005. The potential impact, on the supply of tissues, of extending this deferral criterion to deceased tissue donors is currently being assessed. Anyone who has received UK derived coagulation factors, IV normal immunoglobulin or has undergone plasma exchange between 1980 and 2001 is also deferred from blood donation.

- *Will you continue to use non- transfused UK donors?*

At present, the majority of blood components (i.e. red cells, platelet and clinical plasma) and peripheral tissue (bone, skin, tendon, heart valves and cells) are derived from UK donors. It is unlikely that large quantities of blood or tissues could be sourced from non-remunerated donors outwith the UK. Even if this were possible, it could increase the risk of exposure to other infectious agents, would be very difficult to implement for components with short shelf lives and could precipitate critical shortages. The issue is therefore one of balance of risks. The UK Blood Services import FFP, which is then methylene blue treated in the UK, from United States volunteer donors for neonates and children born after 1st January, 1996. The rationale for this cut off date is that children born since 1996 are considered to have received minimal exposure to the BSE agent because of the effectiveness of the animal feed ban which was fully implemented from 1996 and the exclusion of animals above 30 months entering the food chain. Consideration is being given to the importation of red cells for this group of patients. The importation of FFP has now been extended for the treatment of all patients under 16 years of age and consideration is being given to extending this to all patients.

The option of importation of some tissues for children born after January 1996 has been considered, and importation of skin for treatment of this group commenced in early 2008.

- *Is there a blood test available for variant CJD?*

Not at present. The types of tests that are used to screen blood and tissue donations for viruses cannot be applied to variant CJD because it is a different type of disease. Several international groups of research workers are working to develop a blood test. One test is now well advanced in the independent assessment of sensitivity and specificity but it remains unclear when a test suitable for blood donor screening will become available.

- *Can donors contract variant CJD from giving blood or tissues?*

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No. Blood donations are taken through sterile, non-reusable, disposable needles and equipment so it is not possible for anyone to contract variant CJD by blood donation. The UK Blood Services have a duty to supply hospitals with the blood components needed for patient care. This can only be achieved with the help of blood donors and their continued support is vital.

In the context of cadaveric tissue donations this risk is not applicable. For live tissue donation, no excess risk is involved in the operation, that would not otherwise be incurred as part of the operation itself, to treat the patient's underlying condition.

- *Will universal leucodepletion reduce the risk of transmission of variant CJD?*

Universal leucodepletion was announced by the UK government in July 1998 and implementation was completed by the autumn of 1999. In patients with sporadic CJD and in animal models where infectivity has been found in the peripheral blood, a large proportion has been associated with the white blood cells. Recently published animal data show that leucodepletion removes a proportion (about 40%) of prion infectivity, but is unlikely, by itself, to remove all infectivity.

- *Are there any other components processing steps which could reduce the risk of transmission of variant CJD by blood or tissues?*

The UK Blood Services are engaged in a programme to increase the sourcing of all platelet components from individual donors using a process known as apheresis, in order to reduce the number of donors to whom an individual patient is exposed. A number of commercial companies are working on the development of filters to selectively remove infectious prions from blood components and the UK Blood Services are evaluating these technologies.

An extensive validation has been carried out by the Blood Services to remove as much marrow (containing a large proportion of white blood cells) from bone as possible. Investigations are now taking place on refining the process, to make it operationally possible.

- *Are plasma derivatives likely to be infectious?*

As of October 1999, all plasma products including Factor VIII and Factor IX, immunoglobulins and albumin have been derived from donors outwith the UK. Therefore, there should be minimal risk to patients receiving plasma products provided donors are from countries with a known low risk for BSE. The risk to patients who received plasma products before October 1999 is uncertain, but it does now appear that a case of transmission of infection to a patient with haemophilia has occurred, though the patient himself did not develop clinical disease. The UK Blood Services have engaged in research on the ability of the plasma fractionation processes to remove prions. These experimental spiking studies have shown that there are steps during each manufacturing process which remove prions, though it remains unclear how closely these reflect the way in which the natural infective agent behaves. Similar studies have been performed by other organisations with similar results. The starting level of infection in plasma from UK donors also remains unknown. The risk from most UK derived plasma products is likely therefore to have been low, but it cannot be assumed that the risk

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was zero.

- *Are cell or tissue products likely to be infectious?*

The UK Blood Services Tissue Services are undertaking a formal review together with the Department of Health's Economic and Operational Research Department (EOR) to consider the risks of transmission of variant CJD by cells and tissues including new safety issues raised through *in vitro* propagation of cells.

Some specific initiatives have also been considered and / or implemented for improvement in the safety of tissues within the UK Blood Services to try to reduce the risk of transmission of variant CJD by bone and tissue transplantation. These include:

- Improved washing and blood removal techniques for processed sterilized bone grafts.
- The use of disposable instruments for some types of tissue retrieval and processing.
- Improvement in decontamination procedures prior to sterilization of instruments.
- Batching of retrieval and processing of instruments to allow for the tracking of their use.
- Dura mater grafts are not provided

Further processing measures are under evaluation

- *Should UK patients continue to accept blood and tissue products?*

Blood, plasma, cell and tissue products should only be given when they are essential to the quality of life, health or survival of the patient. In these circumstances the benefits are carefully weighed against other transmission risks including variant CJD. In some circumstances alternatives are available which could reduce the exposure to blood or tissue products. UK Blood Services' clinicians are continuing to work with colleagues throughout the National Health Service in establishing and implementing guidelines for the appropriate use of blood and tissues. It is a priority for the UK Chief Medical Officers and the medical community in the UK to ensure that patients are treated with blood or tissue products only when there is real clinical need.

- *Is any treatment available for CJD?*

There is no treatment currently available for CJD. Ongoing research suggests that there are a number of drugs which could be of value in prevention of transmission or treatment of disease during the early pre-clinical phase of the disease or with the onset of clinical problems. Several approaches are looking particularly promising. Peripheral infusions of monoclonal antibodies have recently been demonstrated to prolong life in scrapie infected mice when given after intraperitoneal challenge. Pentosan sulphate has similarly been shown to delay or in some cases prevent onset of clinical disease following peripheral TSE challenge in animal models. These approaches suggest that it may be possible to reduce the risk of infection or prolong the incubation phase of the disease if a patient is known to have been at risk of infection for example by exposure to blood transfusion from an infected donor or following a positive result on a variant CJD screening assay. However much work still needs to be done in translating these laboratory findings into clinically approved

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therapeutic approaches. The Medical Research Council has been carrying out a clinical trial for potential treatments for CJD (Prion-1 Trial).

- *What is being done to ensure that blood and tissues are used only when there is a good clinical indication?*

On the advice of the UK Chief Medical Officers, national programmes for good transfusion practice have been established, supporting the work of local Hospital Transfusion Committees. Transfusion practitioners have been or are being appointed to many hospitals. Their roles include training staff in safe blood administration (including detailed documentation), assisting with clinical audit, the development and implementation of evidence based clinical guidelines for the use of blood, and assisting with the investigation and reporting of adverse events to the Serious Hazards of Transfusion reporting scheme (SHOT). There is increasing use in the NHS of techniques that can, for some patients, reduce the need for transfusion of blood donor or avoid it all together. Among these are: the use of regional and hypotensive anaesthetic techniques, good temperature control in the perioperative period, salvage and reinfusion of red blood cells lost during surgery and the use of antifibrinolytic agents. However, transfusion may be unavoidable and life saving for patients who suffer massive blood loss, and for those undergoing chemotherapy for leukaemia or being treated for cancer there may be no alternative to the use of donor blood components during periods when the bone marrow is not functioning normally.

Tissue usage is much more restricted than that of blood and in many instances tissues are used when there is no better alternative. Notwithstanding, there are initiatives on auditing usage of particular tissues in specific circumstances to encourage and facilitate best practice.

(1) **Joint United Kingdom Blood Transfusion Services and National Institute for Biological Standards and Control Professional Advisory Committee**