Questions on variant Creutzfeldt–Jakob disease and blood transfusion
March 2010, updated July 2011

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Executive summary

In 2009, two developments in the field of variant Creutzfeldt–Jakob disease (vCJD) occurred:

- A case report described a 30-year-old man who died in January 2009 with symptoms suggestive of vCJD. This individual had a genotype previously not associated with disease. This has created concern that there may be a second wave of vCJD cases in humans with a different genetic background.
- The identification of possible vCJD infection in the spleen of a patient with haemophilia A in the UK raised the possibility that vCJD infection can be transmitted from person to person through the use of plasma-derived products.

Based on these developments, a number of questions have been raised. Should current assumptions on the number of people that may develop vCJD in the future be reviewed? How does this impact the current assumptions regarding transmissibility through blood transfusion and tissue/cells transplantation? Does this change the number of individuals at risk of developing vCJD following a transfusion/transplantation? Are there measures to reduce any possible increased risk?

A rapid limited literature review was conducted; ECDC internal and external experts were consulted to prepare this risk assessment.

Mathematical analyses of likely future case numbers in the UK, taking account of the potential wider genetic susceptibility and secondary transmission via blood transfusion, have predicted an extended tail of the vCJD epidemic lasting for decades with an annual incidence of up to 10 cases. The heterozygote case described in December 2009 was classified as 'possible' vCJD, and because of the uncertainty of this diagnosis it is still unclear if this case indicates the start of a second wave of cases.

The identification of potential transmission of vCJD through plasma-derived products is a new finding calling for a review of current assumptions on the number of people that may develop vCJD in the future. Although no clinical cases of vCJD have yet been connected to plasma-derived products, there remains a theoretical risk that such products are able to transmit infection. However, the evidence for such transmission is currently limited.

The transmission of vCJD by plasma derivatives has been previously considered as a risk that could not be ruled out and preventive measures have been taken in regions with relatively high incidence of vCJD. The recent developments support the possibility of transmission, but do not justify major changes in intervention strategies.

Source, date and type of request

Based on the developments in the field of vCJD during 2009, the European Centre for Disease Prevention and Control (ECDC) was requested by the European Commission to perform an urgent assessment on the risk of vCJD transmission through blood and blood products. The request was put in on 14 January 2010 with a deadline for submission set to 4 February 2010. In July 2011 the report was updated for publication.

Background

Until recently, all persons dying from vCJD have had a methionine homozygous (MM) genotype at codon 129 of the prion protein gene. One individual with a methionine heterozygous (MV) genotype has been identified with evidence of infection with the abnormal prion protein associated with vCJD, but without clinical symptoms of the disease. In December 2009, the Lancet [1] published a case report on a 30-year-old man who died in January 2009 with symptoms suggestive of vCJD. This individual had an MV genotype. This has created concern that there may be a second wave of vCJD in humans in those carrying the MV genotype. The size of a possible second wave of vCJD cases is difficult to estimate, although it is unlikely that the bovine spongiform encephalopathy (BSE) infection attack rate in MV genotypes would be greater than that seen in MM genotypes. On this assumption, one estimate has suggested no more than about a hundred additional cases if there is wider genetic susceptibility to human BSE infection [2].

In February 2009, the United Kingdom reported that a person with haemophilia had been found to have post-mortem evidence of infection with the abnormal prion protein that causes vCJD. This patient had been treated in the 1990s with several batches of UK-sourced clotting factors, including one batch of factor VIII that was manufactured using plasma from a donor who went on to develop vCJD. However, in an attempt to identify the most probable infection route for the patient [3], the UK Department of Health came to the preliminary conclusion that although the prevalence of infection is low, there is a strong possibility that any given batch of plasma-derived medicines prepared from large pools sourced from UK donors in the period 1980–2001 could have contained at least one infected donation. Therefore, the UK concluded that the infected patient was more likely to have been infected by the receipt of large quantities of 'non-
implicated' factor VIII (i.e. not traceable to a donor who later went on to develop clinical vCJD) rather than by smaller quantities of 'implicated' factor VIII.

To date, no validated test for CJD/vCJD is available for the general population or for blood donations.

On 27 October 2009, the SaBTO (Advisory Committee on the Safety of Blood, Tissues, and Organs – a UK government advisory body) recommended that prion-filtered red cells should be used for transfusions in children under the age of 13 [4]. The UK Department of Health is considering the committee’s advice, but a report from Ireland has suggested that the filters may not be cost effective [5].

As regard to blood transfusions and transplantations of substances of human origin, the Blood Directive 2002/98/EC [6] and the Tissue and Cells Directive 2004/23/EC [7] permanently exclude from donation any individual who could be a potential vector of transmission of transmissible spongiform encephalopathies (TSEs), including vCJD. More precisely, the deferral criteria are the following:

- persons diagnosed with CJD/vCJD;
- persons having a family history of non-iatrogenic (genetic) TSE placing them at risk of developing a TSE;
- persons who have received a corneal, dura mater or scleral graft;
- persons who have been treated in the past with medicines made from human pituitary glands (such as hormones).

Specifically for tissues and cells, are excluded:

- persons with a history of rapid progressive dementia or degenerative neurological diseases, including those of unknown origin;
- persons who have undergone undocumented neurosurgery (where dura mater may have been used).

Both the directives on blood and tissues and cells provide that for vCJD ‘further precautionary measures may be recommended’. On these grounds, in addition to the fact that these directives only set minimum standards, several Member States have introduced permanent deferral from donation of persons who have received a blood transfusion since 1980, and others exclude persons who lived in the UK for at least six months between 1980 and 1996, the period of the BSE epizootic [8]. In a recent review of policies aimed to prevent CJD transmission in medical settings obtained from 17 countries representing 87% of the EU population and Norway, all respondent countries stated that they had official TSE documents that included measures to protect blood supplies from variant Creutzfeldt–Jakob disease (vCJD). However, detailed recommendations varied widely among the respective countries [8].

Specific questions and problems

1. Based on the recent findings mentioned above, should the current assumptions on the number of people that may develop vCJD in the future be reviewed? A synthesis of the current epidemiological situation regarding vCJD in the Member States, including an update on the latest developments of the European Creutzfeldt–Jakob Disease Surveillance Network (EUROCJD) and ECDC projects, would be a useful complement.

2. Should the answer to question 1 be positive, would this have an impact on the current assumptions regarding: (1) transmissibility of vCJD through blood transfusion and tissue/cells transplantation; and (2) the number of individuals at risk of developing vCJD following a transfusion/transplantation?

3. Should the answer to question 2 be positive, what steps would effectively reduce the risk of transmission through transfusion/transplantation in light of recent findings?

Consulted experts

**ECDC experts:** Johanna Takkinen, Carmen Varela Santos, Howard Needham, Daniel Palm

**External experts:** Jesús de Pedro Cuesta (Centro Nacional de Epidemiología, Instituto de Salud Carlos III, Madrid, Spain) and Robert Will (National CJD Surveillance Unit, Department of Clinical Neuroscience, Western General Hospital, Edinburgh, UK).

Evidence accessed

This analysis is based on recent literature in the field, expert opinions and ongoing systematic literature reviews from the ECDC project 1250 ‘Prevention of Creutzfeldt–Jakob Disease transmission in healthcare settings’.
Risk assessment

Data sources

See Evidence Assessment and References.

Formulation

Q1. Based on the recent findings mentioned in the background section, should the current assumptions on the number of people that may develop vCJD in the future be reviewed? A synthesis of the current epidemiological situation regarding vCJD in the Member States, including an update on the latest developments of the EUROCJD and ECDC projects, would be a useful complement.

ECDC funds the EUROCJD system for the surveillance of variant CJD in Member States. This system provides real-time data on the number of cases of variant CJD in Europe (and internationally) together with residential history and risk factor analysis, including history of blood transfusion, in all incident cases.

Currently, ECDC has one other CJD-oriented project running: the review of existing guidelines and drafting EU-wide guidelines for the prevention of Creutzfeldt–Jakob disease transmission in healthcare settings, outsourced to Dr Jesús de Pedro Cuesta at Instituto de Salud Carlos III/CIBERNED (Spain). The project purpose is to develop guidelines for the prevention of CJD (including vCJD) transmission in medical settings in the EU. The guidance produced will be based on literature reviews on the best public health practices, accompanied by a report summarising the guidelines currently in existence. The final report will include the following aspects: blood safety, public health policies for confirmed or suspected CJD cases, specific precautionary measures in healthcare settings (e.g. surgery, dentistry), and decontamination methods.

As of July 2011, a total of 221 cases of probable or definite cases of primary vCJD have been reported worldwide. Of these, 172 have arisen in the UK, 25 in France, 5 in Spain, 4 in Ireland, 3 in the Netherlands, 2 in Portugal and 2 in Italy [9]. The incidence rate in this epidemic peaked in the UK in the year 2000, with 28 deaths. Ever since, the trend has been declining and is currently down to around two new cases per year. There has also been a decline in cases in France while the trend in Spain is uncertain.

All tested definite or probable clinical cases of vCJD have been characterised as methionine homozygote (MM) at codon 129 of the human prion protein, a genetic background shared by approximately one third of the UK population. Observations made in human-acquired TSE cases and TSEs in animal models have shown that different genotypes at this locus (MV or VV) are linked to variations in susceptibility to infection and prolonged incubation times. Therefore, the possibility of an outbreak of vCJD cases in the non-MM population has been recognised for many years. A previous mathematical modelling exercise of the likely impact of this occurrence indicated that there could be an additional 54–363 cases of clinical vCJD in the UK if there was wider genetic susceptibility. This analysis depends on a range of assumptions, including the prediction that MV and VV individuals are no more susceptible to BSE infection than MM individuals [10]. A more recent estimate is 1–246 such cases [2].

Surveillance information supports the theory that people with non-MM genetic backgrounds may be susceptible to infection. First, the presence of abnormal prion protein (PrPsc) in peripheral tissues was identified in an individual with an MV genotype, who died of an illness unrelated to prion disease five years after receiving an infected blood transfusion [11]. Second, in a retrospective tonsil and appendix investigation, two asymptomatic VV-patients were detected [12].

In December 2009, a case report was published describing the first symptomatic vCJD case in a heterozygote (MV) patient [1]. However, the diagnosis was made on the basis of the clinical features and exclusion of other diagnoses. The MRI brain scan was not considered vCJD positive by all involved neuroradiologists and no other laboratory or autopsy data was available to confirm the diagnosis. The case was classified as a ‘possible’ vCJD case.

For risk assessment, it is unfortunate that the index case indicating a possible second wave of CJD was not better characterised. If clinical disease is confirmed in future cases with a non-MM genotype, there will be a need for a prompt risk assessment and detailed analysis of potential implications for public health. Mathematical analyses of possible future case numbers in the UK and France, taking account of the potential MV case, have been carried out and suggest a relatively small number of additional clinical cases if there is wider genetic susceptibility [2,13].

The vast majority of cases in the primary vCJD epidemic, including those outside Europe, are thought to have been infected through dietary exposure in the UK or through exported UK food products, exported animals or animal foodstuffs [14]. Secondary transfer of disease from patients in the subclinical phase by non-leucodepleted red cell concentrates have been documented [11,15] and donor deferral criteria has been set up in the UK for persons ‘at risk of vCJD for public health purposes’ [14].

The identification of possible vCJD infection in the spleen of a patient with haemophilia A in the UK raised the possibility that vCJD infection has been transmitted from person to person through the use of plasma derived products [16]. This individual had been treated with a large amount of factor VIII over an extended period and had received a relatively
limited purity form of factor VIII, 8Y. Some years ago, a risk assessment in the UK suggested that certain plasma product recipients in the UK might be at increased risk of developing vCJD and this population were informed that they had been designated as ‘at risk for public health purposes’ [17].

It is of note that plasma for production of these therapeutic agents has been imported to the UK, mainly from the USA, since 1999 and that evidence does not suggest that any of the clinical cases of vCJD to date have been caused by exposure to plasma-derived medicinal products [18]. The risk of plasma products in relation to vCJD is linked to the estimated prevalence of infection in the general population and the capacity of manufacturing processes to reduce infectivity. The country with the highest estimated prevalence of BSE/vCJD infection is the UK. The risk of vCJD in France is estimated to be about one tenth that of the UK and the risks in other Member States are likely to be lower.

In summary, the heterozygote case described in December 2009 was classified as ‘possible’ vCJD, and because of the uncertainty of this diagnosis it is still unclear if this case indicates the start of a second wave of cases.

The identification of potential transmission of vCJD through plasma-derived products is a new finding calling for a review of current assumptions on the number of people that may develop vCJD in the future. Although no clinical cases of vCJD have yet been connected to plasma-derived products, there remains a theoretical risk that such products are able to transmit infection. However, the evidence for such transmission is, as yet, weak.

Q2. Should the answer to question 1 be positive, would this have an impact on the current assumptions regarding: (1) transmissibility of vCJD through blood transfusion and tissue/cells transplantation; and (2) the number of individuals at risk of developing vCJD following a transfusion/transplantation?

There is compelling evidence that vCJD is transmissible through blood transfusion. However, to date there is no evidence of transmission of vCJD through tissue transplantation, although this should be considered feasible in the knowledge of transmission of CJD via corneal and dura mater grafts, and the wider distribution and higher level of infectivity/abnormal prion protein in peripheral tissues in vCJD compared with sporadic CJD.

The total number of cases of vCJD linked to blood transfusion in the UK has been estimated as 0–871, and, with effective leucodepletion and a ban on transfusion recipients acting as blood donors, 0–257 [19]. Assuming that the incubation period in secondary transmission is likely less than primary transmission, the estimate is 46–171 cases. Using plausible assumptions, a self-sustaining epidemic through blood transfusion is very unlikely. This conclusion is consistent with a similar analysis by a German group [20]. Cases of transfusion transmission of vCJD have not been identified outside the UK.

Q3. Should the answer to question 2 be positive, what steps would effectively reduce the risk of transmission through transfusion/transplantation in light of recent findings?

There is already a range of measures in place to minimise the risk of iatrogenic transmission of vCJD.

In the UK, measures to minimise the risk of transfusion and transmission through plasma products have already been taken. This includes the deferral of transfusion recipients as blood donors and the importation of plasma for plasma fractionation. Additional measures are being considered because of the estimated prevalence of silent infection in the UK population.

Deferral of transfusion recipients as blood donors is established policy in some Member States but not in others. An alternative approach is to defer people with a history of receiving transfusion in the UK after 1980. Deferral of blood recipients risks causing shortages of blood components and the absolute reduction in risk from transmission of vCJD may be very limited in countries with a low estimated prevalence of vCJD infection [20]. In such settings, the public health costs for deferral may outweigh the benefits.

Additional measures, such as the introduction of prion filters for blood transfusion, will have to be carefully assessed in relation to risk and benefit, particularly in Member States with low background risk of vCJD infection in the population. Retrieval from market of high-risk plasma derivatives prepared from donors later on diagnosed with vCJD should be considered early after reporting suspected vCJD to CJD surveillance units. This requires accurate diagnosis, without delay, in suspected cases. Since it is possible that life expectancy of plasma-products recipients can be long in many cases, incidents, particularly when a high number of recipients of high-risk plasma products are implicated, should be carefully assessed and managed long-term by experts.

As regards plasma- and urinary-derived medicinal products, the European Medicines Agency has a position statement [21]. This recommends that donors who have spent a cumulative period of one year or more in the UK between the beginning of 1980 and the end of 1996 are excluded from donating blood/plasma for fractionation. Manufacturers of plasma-derived medicinal products are required to estimate the potential of their manufacturing processes to reduce infectivity. The Agency has also published guidance for advanced therapy medicinal products based on human cells and tissues [22].
Areas of particular uncertainty

- The definite diagnosis of vCJD requires post-mortem examination of brain tissue. The estimation of the number of subclinical cases in a population is difficult due to lack of sensitive and specific laboratory tests.
- There is no validated test for screening of blood, blood products and tissue material.
- Individuals with non-MM background may be susceptible to infection, but it is still unknown if they will develop clinical disease and if they can transmit infection to others.
- Effectiveness of public health measures based on identification and follow-up of persons ‘at risk of vCJD for public health purposes’ may be very low if the prevalence of individuals susceptible to infection is low and change with age. Such uncertainties make estimations of potential benefits and decision difficult.

Next steps for ECDC/EFSA

Update this risk assessment when more data are available.

References


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