NEW VARIANT CREUTZFELDT JAKOB DISEASE AND THE RISK OF TRANSMISSION BY BLOOD TRANSFUSION*

G.E. Stewart†
P.K. Stockman‡

INTRODUCTION

The last two decades have seen major changes in the practice of transfusion medicine due to the emergence of new blood-borne diseases. The possibility that variant Creutzfeldt Jakob Disease (CJD) could be transmitted by blood transfusion has led to precautionary changes in blood transfusion policy over the last 12 months, including the introduction of universal leucodepletion and a ban on the use of UK-derived plasma for the production of medicinal products. This symposium was organised to examine the scientific and clinical background to variant CJD, the strength of the evidence that this disease may be transmissible by blood and the potential beneficial and detrimental impact of proposed changes in transfusion policy.

In his introduction to this symposium Professor James Petrie, President at the Royal College of Physicians of Edinburgh, urged the participants to concern themselves with a discussion and analysis of the evidence base rather than speculative theories. This was certainly a challenge, since our current understanding of the transmission of CJD by blood transfusion is based on limited information.

BIOLOGY OF THE TRANSMISSIBLE SPONGIFORM ENCEPHALOPATHIES

Bovine Spongiform Encephalopathy (BSE), a novel transmissible spongiform encephalopathy (TSE), was first identified in cattle in the UK in 1985. It is thought to have arisen from the practice of feeding cattle with ruminant-derived meat and bone meal. It spread rapidly through the UK herd reaching a peak in 1992. Current figures for BSE are under 300 cases per month. Smaller numbers of cases have been recorded in other European countries, some of which appear to have an increasing rate of diagnosis.

CJD is the commonest TSE in man (see Table 1). In 1996 a new form of CJD was first reported in the UK. This was shown to be distinct both clinically and neuropathologically from the other forms of CJD (see Table 2) and has become known as variant CJD. To date, there have been 40 confirmed cases in the UK and one in France.

PRIONS

Transmissible spongiform encephalopathies are also known as prion diseases because of the role played in their pathophysiology by an abnormal form of prion protein. The prion protein gene, which is on chromosome 20, encodes a 30-35 kilodalton glycoprotein expressed in man in many tissues. The function of the normal form of the protein (PrP^{c}) is uncertain. The presence of an abnormal form, termed PrP^{sc}, is pathognomic for TSE. PrP^{sc} has the

TABLE 1
Transmissible spongiform encephalopathies (TSE).

HUMAN	ANIMAL
Idiopathic	**Naturally Occurring**
Sporadic CJD	Scrapie
	Chronic wasting disease (deer, elk)
Genetic	
Gerstmann Straussler Sheinker	**Acquired**
Familial CJD	Bovine Spongiform Encephalopathy (BSE)
Fatal Familial Insomnia	Feline Spongiform Encephalopathy (FSE)
Acquired	TSE in exotic ungulates
Kuru	
Iatrogenic CJD	
Variant CJD	

TABLE 2
Comparison of sporadic and variant CJD.

	SPORADIC CJD	VARIANT CJD
Age Range at Onset	Usually over 50	16 - 51
Median Duration	4.5 months	14 months
Clinical Presentation	Rapidly progressive dementia with cerebellar features, cortical blindness and akinetic mutism	Initial presentation with psychiatric and sensory symptoms progressing to cognitive impairment and cerebellar problems
Neuro-pathology	Plaques in < 10%	Florid plaques universal
EEG	Periodic, triphasic complexes in 60 - 80%	Normal or slow
DNA Studies	80% MM at codon 129	100% MM at codon 129

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†Research Fellow, UK CJD Surveillance Unit, Western General Hospital, Edinburgh
‡Specialist Registrar, Department of Transfusion Medicine, Royal Infirmary of Edinburgh

same amino acid sequence but is conformationally different to PrP^{c}. The abnormal form, PrP^{sc} is resistant to protease, is tightly membrane-bound and precipitates the formation of amyloid plaques. In sporadic and familial forms of CJD PrP^{sc} is found only in neural tissue. In variant CJD it has also been detected in tonsil, appendix and in follicular dendritic cells in germinal centres of lymph nodes and spleen.

EVIDENCE LINKING BSE AND VARIANT CJD

Transmission experiments have been performed on a panel of inbred mice used to strain type the ovine TSE, scrapie. The pattern of incubation periods and neuropathological lesions produced were identical in those inoculated with BSE and variant CJD and significantly different to those produced by scrapie and sporadic CJD. Further evidence came from PrP glycoform patterns obtained on Western blotting; variant CJD and BSE produced patterns different from those seen in sporadic CJD.

PERIPHERAL ROUTES OF INFECTION

Kuru is thought to been have been peripherally transmitted during cannibalistic funeral rituals. CJD has been transmitted through the inoculation of pooled, cadaveric derived growth hormone as well as via infected dura mater grafts in iatrogenic CJD. Most information on the route of peripheral infection comes from scrapie models. PrP^{sc} has been detected in the early stages of incubation of scrapie in spleen and lymph nodes with relatively late detection in neural tissue. Follicular dendritic cells show high levels of expression of PrP and seem to be critical in this process. Immune deficient animals survive peripheral infection but succumb to centrally inoculated disease

STUDIES OF CJD AND VARIANT CJD TRANSMISSION BY TRANSFUSION OF BLOOD PRODUCTS

No evidence has been found to date that sporadic CJD has been transmitted to humans by transfusion.

Our current understanding is based on:

- Animal models. In rodents, transmission of CJD has been demonstrated by intracerebral inoculation of blood or buffy coat from animals and humans with clinical evidence of CJD. There is no evidence of transmission by intravenous injection.
- Epidemiological studies. In the case of sporadic CJD it is estimated that approximately 15% of patients have previously acted as blood donors. Case control, lookback and surveillance studies have failed to demonstrate definitive evidence of transmission of CJD. However, the small number of cases involved make it difficult to determine the significance of these results.

However, it should not be assumed that variant CJD will behave in the same way as sporadic CJD. There is evidence of abnormal prion protein outwith the nervous system in variant CJD that has not been found in sporadic CJD. Furthermore, the prevalence of variant CJD in the donor population may be significantly higher and it is likely that insufficient time has elapsed for cases arising by secondary transmission to present with clinical signs or symptoms.

RISK ASSESSMENT

A risk assessment was commissioned to inform decisions on any measures necessary to protect recipients of blood and blood products from the transmissible agent of variant CJD. This assumed that variant CJD was transmissible by blood transfusion and that:

- Infectivity in blood from variant CJD cases was assumed to be 1 human i/v ID50/ ml human blood.
- Infectivity was assumed to be constant throughout the incubation period.
- The incubation period of variant CJD was assumed to have a median of 15 years.
- The infectivity in blood components was assumed to vary linearly with the white cell content.
- The infectivity in plasma derivatives was assumed to have the same infectivity per gram of protein as in the plasma fraction from which they are made.
- Leucodepletion soon after donation was assumed to reduce the infectivity by two orders of magnitude.
- The dose response curve was assumed to be linear.

This predicted about 0.75 new variant CJD cases per infected blood donation.

The report recommended that leucodepletion and the elimination of UK plasma products would provide significant risk reductions.

CURRENT STRATEGIES TO REDUCE THE RISK OF TRANSMISSION BY BLOOD TRANSFUSION

Following a precautionary policy, the UK Blood Transfusion Services and regulatory authorities have taken the following steps to reduce the risk from blood transfusion:

- **Donor selection**. Selection of donors is an important means to improve the overall safety of the blood supply. Donors in the UK are permanently deferred if they have a personal or close family history of CJD or a medical history of corneal or dura mater grafting, neurosurgical intervention or human pituitary-derived hormone exposure. These selection criteria are intended to exclude donors at risk of contracting CJD. However, these selection criteria will not identify individuals at increased risk of variant CJD. Consideration has been given to excluding those donors who themselves have received blood components or products. Since an estimated 8% of the donor population have received blood components and 20-25% have received plasma products, implementation of such an exclusion policy would seriously undermine the UK blood supply. Furthermore, if donors who are homozygous for methionine at codon 129 of the PrP gene were excluded this could lead to a loss of up to 40% of the donor pool.
- **Donor screening.** No screening assay is available for CJD. Conventional serological and molecular biological screening assays are not applicable to the detection of the abnormal prion protein. The difficulty lies in the fact that there is no systemic serological response to CJD and no nucleic acid has been found in association with the CJD agent. If a screening assay were developed the psychological and social impact on the population must be considered since there is no scope for disease prophylaxis or treatment.
- **Universal leucocyte depletion of blood products.** Leucocytes are thought to represent the main source of infectivity in the peripheral blood of CJD-infected

individuals. This is based on the following: (a) infectivity can be demonstrated in the immune system before the neurological system, (b) whole blood and buffy coat from individuals with sporadic CJD have transmitted infection on intracerebral inoculation into experimental animals, (c) B lymphocytes and follicular dendritic cells facilitate early replication of the disease and (d) abnormal prion proteins are found in the lymphoid tissue of patients with variant CJD.

The efficacy of leucocyte depletion in preventing transmission of CJD is unproven. No data is currently available on the presence, titre and distribution of infectivity in the peripheral blood of individuals in the preclinical phase of variant CJD.

Leucocyte depletion filters reduce the concentration of leucocytes and other cellular components in blood products by 3-4 log and may reduce PrP load and/or infectivity by a similar amount. Other important factors which require to be considered are (a) platelets express large amounts of PrP^c and this is released into the plasma following platelet activation, (b) leucocyte fragments and certain leucocyte subsets expressing PrP^c pass through the leucocyte filters. Both these could be a potential source of infectivity.

Leucodepletion is known to have other proven benefits namely:

- reduction in transmission of cell associated viruses,
- reduction in the rate of alloimmunization,
- imunomodulatory effects.

Indeed, universal leucodepletion is already employed in some European countries for these reasons. The estimated cost of introducing universal leucodepletion in the UK is £70-80 million per annum. Safety and quality assurance measures are currently being evaluated.

- **Plasma Products.** There is concern that variant CJD could be transmitted by fractionated plasma products. It is known that transmission of sporadic CJD has occurred by parenteral administration of pooled human cadaveric growth hormone and gonadotrophins.

  Fractionated plasma products are prepared from up to 20,000 donations and are widely used as prophylactic and therapeutic agents in the treatment of healthy individuals, for example in the form of anti-D and normal human immunoglobulin. They are also used as excipients in other medicinal products. The processing of plasma involves a series of partitioning and filtration steps that are likely to result in a substantial reduction in CJD infectivity. Since TSEs are highly resistant to most physical and chemical agents, the steps currently employed to inactivate viruses in plasma products are unlikely to reduce infectivity and those processes known to be effective in reducing CJD infectivity are also likely to destroy the plasma product itself. There is no evidence that transmission of CJD by plasma products has occurred. None the less, as a precaution, the regulatory authorities and blood transfusion services in the UK and elsewhere have taken measures to discontinue or limit the use of UK plasma.

MEASURES TAKEN BY REGULATORY AUTHORITIES IN THE UK

- **1997** December. UK Haemophilia Centre Directors Organisation (UKHCDO) recommended that all patients with haemophilia A should be offered recombinant Factor VIII and that recombinant Factor IX should be the treatment of choice for those with haemophilia B when licensed. They also suggested using products derived from plasma from countries where variant CJD and BSE had not been identified.
- **1997** December. UK Committee for the Safety of Medicines (CSM) recommended that plasma products should be recalled where a donor confirmed as suffering from variant CJD was confirmed as having contributed to the pool. Five of the current UK variant CJD cases had previously acted as blood donors. In November/ December 1997 three product recalls occurred.
- **1998** February. Committee for Proprietary Medicinal Products (CPMP) recommended recall of plasma products where a donor subsequently diagnosed as a probable or confirmed case of variant CJD was found to have contributed to the pool. They also advised that human albumin from countries where clusters of variant CJD are known to have occurred should not be used as an excipient in medicinal products.
- **1998** May. CSM advised that plasma from UK donors should no longer be used to manufacture plasma fractionated plasma products.

The issue of notifying people who have been exposed to blood products that have been associated with variant CJD is the subject of considerable debate. There are variations in practice around the world.

OPTIMAL USE OF BLOOD COMPONENTS AND PRODUCTS

A complete ban on the use of blood components and products from UK donors would be impractical. Strategies to reduce or avoid the use of such products where possible need to be considered.

There is evidence of widespread variation in the clinical use of blood components. Rationalisation of clinical practice has the potential to reduce the risks to patients associated with transfusion by; (a) reducing unnecessary exposure to variant CJD contaminated blood products and (b) conserving blood at a time when supplies may be limited by implementation of donor selection or screening policies.

PERSPECTIVES IN THE TREATMENT OF HAEMOPHILIA

Haemophiliacs are a special group of patients to consider when discussing blood-borne infections because:

- They have a long history of exposure to blood borne infections e.g. Hepatitis B, C and HIV.
- Factor concentrates are prepared from donor pools of up to 20,000 donations.
- They receive repeated treatment i.e. up to 150 injections per year.

Sporadic CJD is probably not transmitted by blood transfusion to haemophiliacs since none have been affected in the last 30 years. Retrospective neuropathology studies of prion disease show no evidence of disease in the brains of 33 haemophiliacs from 1962-1995. There is, however, no evidence to conclude that variant CJD cannot be transmitted by blood transfusion. As a precaution the UKHCDO made the recommendations regarding use of recombinant Factor VIII as a treatment of choice in their statement of December 1997.

PROPHYLACTIC AND THERAPEUTIC INTERVENTION FOR PRION EXPOSURE

No agent is currently recommended for prophylaxis or treatment for prion exposure. Several candidates are currently under investigation. Sulphated polyanions such as dextran sulphate 500 and pentosan sulphate have been shown to inhibit the accumulation of PrP^{SC} in *in vitro* model systems and to lengthen incubation periods and reduce disease susceptibility *in vivo*. It might be possible to reduce the infectivity of CJD by administering agents that interfere with replication of PrP^{SC}. Alternatively, these agents could be added to blood components to achieve the same effect.

Experimental models of disease transmission are currently under investigation for testing of these compounds.

CONCLUSION

Professor Roddy MacSween, President of the Royal College of Pathologists, thanked the speakers for their contributions and concluded the discussion with a concise summary of the meeting:

- Sporadic CJD appears to be rarely, if ever, transmitted by blood transfusion. Unfortunately, the same cannot be assumed to hold true for variant CJD. Good evidence about transmissibility of this illness is not available.
- Precautions must be taken in an attempt to ensure the safety of blood products. Universal leucodepletion and the sourcing of plasma products from outside the UK may reduce risk and are being implemented.
- Further research into both transmissibility and treatment options is required. A multidisciplinary approach is clearly essential.

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FURTHER READING

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