Creutzfeldt Jakob Disease and Blood Transfusion: proposal for a limited look-back study

Introduction

Creutzfeldt-Jakob disease (CJD) is a rare neuro-degenerative disease of humans. The classic clinical presentation consists of pre-senile dementia, involuntary muscle movement and progressive motor dysfunction. Diagnosis is based on the clinical presentation combined with electroencephalogram and confirmed with pathology, if available. Survival with CJD is short, averaging less than one year and most often between two and six months. There is no know prophylaxis or treatment for CJD, and the disease is fatal in 100% of cases after the onset of clinical signs and symptoms. There is no available screening assay suitable for asymptomatic general populations.

Background

International Epidemiology of Creutzfeldt-Jakob Disease

CJD occurs at a world-wide rate of between 0.5 and 1 case per million population per annum. There is an even distribution by sex. The peak age of onset is between 60 and 65 years of age. Cases in persons under 30 years of age are rare. There are known to be three main forms of Creutzfeldt-Jakob disease: sporadic, iatrogenic and familial. Most CJD occurs sporadically; approximately 5-10% of CJD occurs

with families; the remainder is iatrogenic (less than 1%). An unknown agent is thought to be the cause of a number of brain diseases of animals and man called "Transmissible Spongiform Encephalopathies" (TSE). Bovine spongiform encephalitis (BSE, or 'mad cow disease') is an example of an non-human TSE. While scientific discussions continue to consider the hypothesis that TSE are caused by a virus, it is widely believed that prions (proteinaceous infectious particle) are responsible. Iatrogenic forms of CJD are believed to be caused by these prions. While some countries have higher rates of CJD, at this time there is no evidence that this is due to transmissible forms of CJD - rather, the higher rates are due to surveillance biases following intensified surveillance for CJD among clusters in which very high proportions of the cases are familial. Cases have been found in every country in which they have been sought. There has been no evidence of increase or decrease in the frequency during the decade of the 80's. The following sections review each of the transmission modalities more closely.

Familial CJD

The familial form of CJD is the cause of between five and ten percent of reported cases and is due to an autosomal dominant pattern of inheritance. Considerable literature has described a number of families with CJD and has also described the DNA sequences considered causative of the person's CJD.

Sporadic CJD

The sporadic form of CJD, which accounts for the vast majority of CJD occurrences, has an unknown etiology. It occurs in the population at a rate between 0.5 and 1 per million per year.

Iatrogenic CJD

Fewer than 1% of CJD reports can be attributed to direct transmission between persons with and without CJD. There are three basic circumstances in which CJD has been transmitted between people: instrumentation, tissue transfer and tissue extract transfer. These circumstances are distinguished from transfusion in that they feature either peripheral administration of brain tissue (a highly concentrated source), or direct introduction of the infectious agent into the brain. Studies of populations of people acquiring iatrogenic CJD have provided information regarding the time from exposure to CJD to the development of symptoms. Where CJD exposure was central (i.e. direct application of CJD to the brain), the incubation periods were quite short, ranging from 16 months (stereotactic EEG) to 45 months (dura mater implant). However, when the route of exposure was peripheral, as with hGH exposure, the incubation period was greatly extended. No cases were reported less than five years after exposure, and the mean incubation period was 13 years. The longest incubation period was 21 years. It would be reasonable to anticipate that if a highly concentrated source of the infective agent delivered peripherally has a very long incubation period (as occurred with hGH), then a low concentration

source of infective agent (as might occur with blood) delivered peripherally (as during transfusion) would also have an extended incubation period.

Creutzfeldt Jakob Disease and Blood Transfusion

1. Experimental Animal Data

Whole blood and plasma buffy coat taken from patients with CJD were inoculated intracerebrally in mice and guinea pigs and resulted in CJD-like changes. However, scientists have been unable to transmit CJD to chimpanzees using blood or buffy coats from eight patients.

2. Transmission by Blood Transfusion

In brief, CJD has not been shown to be transmitted by transfusion of blood or plasma products in humans. Studies have attempted to find evidence whether CJD is transmitted by this means, but none has been found. There is not a single reported case where a person was proven to have been infected with CJD by having received a blood transfusion or having used a blood-derived product.

The incidence of CJD is not elevated in patients who have received transfused blood or in the haemophiliac population.

Two studies involving small populations of transfusion recipients have been published. In one, no association between exposure to blood from a person with CJD and subsequent development of CJD was found; in the other development of CJD was not found to be associated with the receipt of blood. Both studies involved relatively small numbers.

International policies regarding blood or blood products from a person with CJD

In the US, the policy of the FDA (memoranda to Registered Blood and Plasma Establishments, August 8th, 1995) is to withdraw and quarantine all blood donated by persons known to have CJD, donors receiving pituitary-derived human growth hormone injections, donors who are blood relatives of a person with known CJD and donors receiving dura mater transplants. Persons receiving the blood of a person known to have CJD are not being informed as a matter of policy, although the consignees of products are notified for the purpose of enabling them to inform physicians and others responsible for the care of product recipients.

The policy of the European Community has been to not withdraw or quarantine plasma derived product that originated from a person with CJD.

Neither Australia nor New Zealand have formal policy documents. At this time, neither country is notifying patients of their exposure to blood from a person with CJD nor systematically removing persons with CJD from the donor pool. In Canada,

a Health Protection Branch Information Leaflet, October 28, 1995 revised November 1, 1995, stipulated that products would be removed from the market when they are identified as being for a person at risk for CJD. Manufacturers are required to notify the hospital or other agency if blood is determined to have been donated by a person with CJD, to permit notification of recipients as considered appropriate.

The UK position

At a special meeting of the UK Transfusion Services to discuss the possible implications of the likely new variant of Creutzfeldt Jakob Disease for UK Transfusion Services (9th April 1996) it was agreed that UK Transfusion Services should take urgent action to ensure that direct questioning of donors in relation to a family history of CJD should be instituted but that it would be inappropriate to consider extending current donor selection guidelines beyond the regulatory requirements until the position became clearer. It was also agreed that it is essential to ensure that accurate information is obtained to identify whether identified CJD patients have also donated blood and that this would require information to be provided to transfusion services to enable interrogation of donor databases. It was also agreed that there is a need to consider what action should be taken when a new case of CJD is identified in a current or lapsed donor. It was recommended that a form of look-back is instituted to assist in identifying the potential for transmissibility of this agent by blood. It is also required to investigate systematically whether recorded cases of CJD have received transfusions of blood or blood products.

UK proposal for limited CJD look-back

There is no evidence that CJD, in either its classical or new variant forms, is transmitted by blood transfusion. Nevertheless, information in relation to the potential transmissibility of CJD by blood transfusion is very limited. The absence of information severely restricts ability of the transfusion services to provide definitive reassurance of the new variant form of CJD does not possess a threat to the blood supply. Furthermore, further definition of donors who might be at risk of developing CJD is required. Until further evidence is available, it should be assumed that the newly described variant CJD syndrome is a new disease. It is inappropriate to assume that this would behave in a manner analogous to classical CJD. The potential impact of both CJD and the new variant on the safety of the blood supply is at present unclear. Nevertheless, it is obvious that further information must be accumulated for the purpose of planning resources for future care of individuals affected by CJD and for assisting transfusion services in planning future policies and resources.

The UK Transfusion Services are in an ideal situation to help accumulate knowledge about CJD and blood transfusion, both the classical and variant forms.

1. There is now a well established procedure for recipient look-back, put into place in 1995 when hepatitis C look-back commenced. The procedures for look-back are well established at both transfusion centres and hospitals and

the procedures will form a basis on which any subsequent look-back, for any potentially transmissible agent, can be superimposed.

2. The new variant type of CJD has currently been described only in the UK. Although the number of cases is currently small, the Health Department will need to be accumulating information about this new variant disease and its potential implications for public health. The potential, or lack of potential, for transmission through blood transfusion is an integral part of the information required for future planning.

3. The CJD Surveillance Unit in Edinburgh has clinical information in relation to reported cases of CJD in the UK.

It is proposed that a limited look-back programme would be conducted by the UK Transfusion Services in collaboration with the CJD Surveillance Unit. A key element to this proposal will be the exchange of donor/patient information only between the UK Transfusion Services and the CJD Surveillance Unit. The CJD Surveillance Unit would pass, in confidence, to the Transfusion Services the identity of CJD patients who have ever donated blood. The Transfusion Services will then, with the aid of the look-back protocol, obtain information from hospitals about the fate of individual donations from such donors. The information would include the identity of any recipient know to have received blood from such a case. The details of the recipient would then be passed back to the CJD Surveillance Unit, which could then check these names against the CJD register to ascertain whether any of the recipients are

know to have died of CJD. A further check on the OPCS register could be included, to ascertain whether any of these cases could possibly be linked to CJD , although not notified to the CJD register.

It is recommended that the limited look-back would take place without notification of the recipient. The reasons are as follows:

1. There is no screening test available which can detect the possibility of an individual being susceptible to development to CJD in the future.

2. There is no diagnostic test available to detect whether an individual has been infected with the agent which causes CJD.

3. The diagnosis of CJD can only be made with certainty by examination of pathology specimens post-mortem.

4. There is no intervention which can be offered to individuals detected to be at risk of developing disease, or to those who have already developed symptomatic disease.

For all the above reasons, it is considered unethical to notify any individual who has received blood from a donor who subsequently developed CJD. Furthermore, to avoid a possible compromising situation for hospital staff, it is recommended that the reason for the look-back enquiry is not stated anywhere on look-back

documentation. For public health purposes. it would be necessary to distinguish the new variant form of CJD from the classical cases. The need to establish transmission or lack of it for the new variant form will be very urgent if there is continuing evidence of an epidemic. The look-back procedure would therefore be crucially important in this case.

It should be noted that, should there be any change in the capacity to diagnose the disease, or if any intervention becomes available in the future, then the transfusion services should have in place a mechanism for contacting the identified recpients.

There should also be consideration of detailed investigation of all individuals reported to the CJD Surveillance Unit, to ascertain whether there is a history of blood transfusion in such cases. In that situation, it should be possible to identify all donations given to the recipient, including product batch numbers where fractionated blood products are concerned. These details would then be passed to the Transfusion Services, who would carry out a standard investigation linking these donations to named donors. The identity of these donors would also be passed to the CJD Surveillance Unit, for possible linkage between donors and recipients.

The proposed two way limited CJD look-back study would have the potential to provide:

1. Information on any linkage between donors and recipients.

2. The accrual of data relating to the number of donations originating from donors subsequently identified as suffering from CJD, and how many units have not resulted in development of CJD in the recipient.

Issues arising out of the look-back proposal

1. Confidentiality.

   There is a duty of confidentiality owed to individual donors who have been involved with the blood transfusion services. There is no standard consent by donors to pass on personal medical information to other parts of the NHS. The exchange of information between the CJD unit and the transfusion services would therefore need to be considered in the light of this lack of consent.

2. Exclusion of donors considered at risk of developing CJD.

   The transfusion services must exercise a high level of suspicion about possible transmissibility of CJD by blood and err on the side of caution in deciding whether to accept donations from individuals believed to be at risk of developing CJD. To wait until a causal connection is established on a scientific basis may not be regarded as acting with reasonable care. Thus, decisions about selection of donors must not be delayed pending results of the limited look-back, but must be taken in the light of current knowledge and guidelines.

Jack Gillon
Patricia Hewitt
Bob Will

PEH/mm/25jun96
peh/paper/cjd

Dr Robinson

Copy just in case Dr Will has not already sent you one.

30th Jan.
ability to progress
- clarify with Angela
keep for look-

GRO-C

31/2/97

With compliments

NHS Executive

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15th January 1997

Dr J. Gillon,
Blood Transfusion Service,
41 Lauriston Place,
Edinburgh. EH3 9HB

Dear Jack,

I have just received the formal approval for the retrospective look-back study in CJD and hopefully we can now proceed. Perhaps you would like to come across here to the Unit so that we can discuss how to take matters on.

Kind regards,

Yours sincerely,

GRO-C

Dr R.G. Will
Consultant Neurologist

cc: Dr A Wight, Senior Medical Officer, Department of Health ✓

D' Rejman.
MS Turner - with papers.

We will need to report this → to MSBT. Presumably D'will has also advised D'Robinson.

GRO-C 30-1-97

cc Dr Metters
Dr Rejman
M Skinner
Dr Wrigfield.

29/1

MSBT - CJD + transfusion link

1702/96/4/169

6 January, 1997

Dr R G Will
Consultant Neurologist
CJD Surveillance Unit
Western General Hospital
Edinburgh EH4 2XU

Dear Dr Will,

Request for Ethical Approval - 1702/96/4/169: A retrospective study to examine a possible link between Creutzfeld-Jakob Disease (CJD) and blood transfusion.

Thank you for submitting the amendments or additional information requested by the Sub-Committee for the above protocol. The Chairman of the Medicine/Clinical Oncology Research Ethics Sub-Committee has now agreed to grant ethical approval. This approval encompasses all aspects of the application including the Patient/Subject Information Sheet and other accompanying documentation.

Under the terms of the Scottish Office Home and Health Department Guidelines on Local Research Ethics Committees this decision has been notified to the NHS body under the auspices of which the research is intended to take place. It is that NHS body which has the responsibility of deciding whether or not the research should go ahead taking account of the advice of the Research Ethics Sub-Committee.

A condition of this approval is that you are required to notify the Sub-Committee, in advance, of any significant proposed deviation from the original protocol. Reports to the Sub-Committee are also required once the research is underway if there are any unusual or unexpected results which raise questions about the safety of the research.

Please quote the above reference on all correspondence

9030 9009

In addition, researchers are required to report on success, or difficulties, in recruiting subjects in order to provide useful feedback on perceptions of the project among patients and volunteers.

Yours sincerely,

GRO-C

Linda Semple
Secretary
Medicine/Clinical Oncology
Research Ethics Committee

Please quote the above reference on all correspondence

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