Is Creutzfeldt–Jakob disease transmitted in blood?

Is the absence of evidence of risk evidence of the absence of risk?

Maura N. Ricketts, MD, MHSc

Résumé

DANS CE NUMÉRO (page 1389), Timothy Caulfield et ses collaborateurs abordent la question difficile que constitue la notification des patients exposés à la maladie de Creutzfeldt–Jakob (MCJ) à la suite d'une transfusion sanguine. Même si la transmission iatrogène de la MCJ par certaines voies a été démontrée, on comprend mal le risque que pose la transfusion sanguine. Ce risque est reconnu comme théorique, mais on sous-estime les difficultés que pose l'évaluation des écrits publiés dans ce domaine. Les études épidémiologiques sont presque invalidées par les difficultés qui se présentent l'orsqu'il s'agit de déterminer s'il y a eu vraiment exposition et par le lien complexe entre la voie d'exposition, la dose et la vulnérabilité génétique dans l'établissement de la période d'incubation. Les résultats d'études sur des animaux sont aussi équivoques. La MCJ continuera peut-être d'intriguer les chercheurs pendant quelque temps encore et c'est pourquoi il faut pouvoir faire face à l'incertitude dans l'élaboration de politiques sur la MCJ et les transfusions sanguines.

In this issue (page 1389) Timothy Caulfield and colleagues tackle the difficult question of patient notification after exposure to blood or blood products taken from donors at risk for Creutzfeldt-Jakob disease (CJD). It is perhaps extraordinary that a disease with a stable annual incidence of 1 to 2 cases per million population and normally allocated only a few paragraphs in neurology textbooks has triggered such extensive review. The rarity and rapidly progressive nature of the disease make it somewhat hard to imagine that a person with CJD could donate blood. However, the fact that someone with CJD may deteriorate from apparent perfect health to akinetic mutism within 6 months, the lack of a suitable screening test for blood donations, and possibly a very long incubation period conspire to ensure that such donations can be made. In 1995 the discovery that CJD had developed in a single donor whose blood had been added to a large pool used to produce various immune globulins and albumin led to a massive recall that reduced the Canadian supply of certain essential products to nearly zero. Among the many recipients of the product was a man who developed CJD 8 months after transfusion (Dr. David G. Patry, Department of Neuroscience, University of Calgary, Calgary: personal communication, 1997). Given the uncertainty about the potential for infectivity, not least during the preclinical stages of the disease, the Canadian Red Cross Society and Health Canada concluded that blood banks must take remedial action when they learn of donations taken from a person with CJD, even if he or she was well at the time of donation. Health Canada has instructed the Red Cross to inform the consignee of the implicated products but does not require notification of the recipients. Participants at a conference on CJD held in Toronto by Health Canada in June 1996 concluded that recipient notification could not be mandated and that community participation in policy decisions of this kind is essential. Whether look-back programs are in fact an effective means of recipient notification is itself controversial.[1]

However, what is really at issue is whether CJD can be transmitted through blood or blood products. Epidemiologic studies — including population-based

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Dr. Ricketts is a Medical Specialist with the Blood-borne Pathogens Division, Bureau of Infectious Diseases, Laboratory Centre for Disease Control, Health Canada, Ottawa, Ont.

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surveillance studies, case–control studies and cohort studies — have been conducted in an effort to demonstrate the absence of risk from transfusion. None has found a link between CJD and exposure to blood or blood products. In fact, investigators have failed to find clusters or outbreaks associated with blood transfusion or to publish a single report that strongly supports the assertion that a case of CJD was caused by blood transfusion. This evidence is often offered to support the contention that CJD cannot be transmitted through blood transfusion. Indeed, most people with CJD have not been exposed to blood or blood products. However, the most we can conclude is that if CJD is transmissible by blood, such occurrences are rare.

A number of factors make it difficult to conclude that there is no risk at all. For example, virtually all published studies have used interviews with family members rather than medical records in trying to ascertain whether patients with CJD had been exposed to blood. However, recollections of blood exposure are almost certainly inaccurate. In a study conducted in Britain, 14% of cases and 19% of controls claimed exposure to blood or blood products,[2] and in a survey conducted in Alberta, 22.1% of respondents claimed exposure.[3] Yet, in an Ontario study, only 6.1% of inpatients had received blood products,[4] and an investigation of the risk of acquiring HIV by blood transfusion showed that only approximately 1.0% of the population of Canada had received blood or blood products.[5] A US population-based study revealed that less than 1% of the population received a blood transfusion per annum.[6] Since the lifetime risk of transfusion could accumulate to 10% or 20%, the claimed rates of exposure are not impossible. However, there are no data to support the validity of oral history, and there is evidence that oral history is in fact inaccurate. Look-back programs conducted in Canada have found that many recipients are unaware of their transfusions: several programs in Canada found that only about 60% to 75% of transfusion recipients (or their parents) knew that they had received a blood transfusion[7,8] (Ms. Carolyn Kennelly, Children's Hospital of Eastern Ontario, Ottawa: personal communication, 1997). Errors in recollection would tend to bias the results toward the null hypothesis. It must be added that even if recipients had been perfectly informed as to their exposure, these studies do not determine whether the blood received was from donors who developed CJD, and hence whether there was any risk from the transfusion. Finally, none of these studies would have been of sufficient statistical power to detect a risk, especially if both the disease and the exposure are rare.

When human data are lacking, animal studies can sometimes be illuminating. In this case, however, even the data from animal studies are equivocal. Such experiments have involved direct injection of blood into the brains of animals, making the application of findings to blood transfusion as a route of infection strained. In addition, transmission via infected blood was claimed in some laboratories and denied in others.[9] More recent, although unpublished, experiments appear to confirm that blood and many of its fractions may act as a vehicle for the transmission of CJD and may demonstrate the possibility of transfusion as a route for infection (Dr. Paul Brown, National Institutes of Health, Bethesda, Md.; Dr. Robert Rohwer, Veterans Affairs Medical Center, Baltimore, Md.: personal communication, 1997).

Animal studies have, however, provided epidemiologically useful information about the incubation period of CJD. These studies indicate that the incubation period is linked both to the dose and to the route of exposure. First, the lower the dose, the longer the incubation period. Scientists place sufficient confidence in this correlation to use the incubation period in calculating the dose of the infective innoculum. Second, there is evidence that the more peripheral the innoculation, the longer the incubation period.[10] This appears to be validated by data from

Table 1: Route of infection, number of patients, entry route and incubation for transmissible Creutzfeldt–Jakob disease*

Mode of infection	Number of patients	Agent entry into brain	Mean incubation period (range)	
Instrumentation				
Neurosurgery	4	Intracerebral	20 mo	(15–28)
Stereotactic EEG	2	Intracerebral	18 mo	(16, 20)
Tissue transfer				
Corneal transplant	1†	Optic nerve	18 mo	
Dura mater implant	68†	Cerebral surface	5.5 yr	(1.5–12)‡
Tissue extract transfer				
Growth hormone	76	Hematogenous	12 yr	(5–30)
Gonadotrophin	4	Hematogenous	13 yr	(12–16)

*Adapted with permission from Brown.[9]
†Number of cases updated from original to reflect new information.
‡Incubation period based on data for 25 patients.

human studies. Table 1 illustrates the differing incubation periods for known iatrogenic transmission of CJD. Note the progressively longer incubation period as the route of exposure becomes more peripheral. The incubation period lengthens to 30 years after intramuscular or subcutaneous injection. When we consider the risk from exposure to blood, we might wonder if the "dose" in blood will eventually be considered to be very low and the route peripheral, thus possibly lengthening the incubation period beyond the survival of many recipients of contaminated product. Identifying outbreaks could be impossibly difficult if the disease develops only after the recipients of blood or blood products have survived virtually all other assaults on their lives — possibly 30 or more years. Both of these assumptions may be found to be inaccurate; yet, if blood is even modestly infective and if blood exposure, given its circulatory connection to the brain, is even a modestly effective route, it is difficult to believe that we would not have detected outbreaks by this time.

Also influencing the interpretation of epidemiologic studies are certain genetic factors affecting the host. Mutations and polymorphisms in the gene that encodes the prion protein can significantly alter the likelihood that disease will develop. Between 10% and 20% of disease may be caused by dominant, highly penetrant mutations in this gene; even genetic CJD is transmissible. Additionally, there is a polymorphism at codon 129 of the gene; this consists of a methionine/methionine, valine/valine or methionine/valine combination. In human populations it appears that homozygosity predicts either increased susceptibility or shortened incubation period.[11] Recently it has been suggested that the ability to transmit the disease between species is also dependent upon coding homology (i.e., bovine spongiform encephalopathy and new variant CJD [vCJD]).[12] Whether it predicts susceptibility or incubation period, homozygosity is an important confounding factor that future epidemiologic studies will have to account for by classifying both cases and controls according to their polymorphism.

Conclusion

Evidence indicates that the risk of transmission of CJD through blood and blood products is not simply rare or even exceedingly rare. It is theoretical. Nonetheless, an impartial review of the available information still leaves us with uncertainty, doubt and suspicion. It is difficult to imagine a more problematic issue: the agent is theorized but not identified; there is no test for exposure; there is no test for the agent; and there is no phenotypic, neuropathologic or pathophysiologic feature that clearly differentiates between blood-borne and sporadic CJD. Epidemiologic studies are almost crippled by difficulties in determining whether a true exposure occurred and by the complex relationship between route of exposure, dose and genetic susceptibility in determining incubation period. A prolonged incubation period makes the identification of point-source outbreaks extremely difficult. Successful investigations in this area have depended on specific epidemiologic or pathophysiologic characteristics such as previously established and closely monitored cohorts (e.g., children exposed to human growth hormone), identifiable clusters of cases (as has been seen after dura mater transplantation), epidemiologic markers of sentinel events (e.g., relative youth in the first cases of dura mater transmission), and novel neuropathologic findings (as seen in vCJD).

In the face of equivocal information, the regulatory authorities and the Red Cross in Canada have undertaken measures to protect the recipients of blood and blood products. People with CJD in their family or who have been exposed to cadaver-derived growth hormone and other iatrogenic risks are excluded from donation. Notably, the receipt of blood from a person with CJD does not lead to exclusion. If a person with CJD or at risk of CJD is found to have donated blood, any stored product is withdrawn and destroyed. However, the protection these strategies afford is limited simply because there is no useful test for screening for CJD in blood donors.

Animal and human studies currently under way may eventually provide answers. The hunt for an antibody or test for pathogenic prions is highly competitive and may produce results in the near future. Epidemiologic investigations continue in Australia, Canada, Europe, the UK and the US. In Canada, a surveillance system for CJD with the specific goal of assessing the risk following exposure to blood has recently been implemented.[13] Other initiatives, such as the long-term studies implemented by the US Centers for Disease Control and Prevention to follow recipients of blood from donors with CJD, and neuropathologic studies of hemophiliac populations will also contribute to our understanding. Despite this research, it is possible that answers will not be found soon and that we will continue to have to make extremely difficult, highly controversial decisions in the absence of decisive information on risk. CJD may be but the first of a number of theoretical or very slight risks that will challenge, and even threaten, regulators, policy-makers, blood banks and physicians in the post-HIV era. We need methods that will free us from decision-making paralysis when demands for answers lead only to more questions.

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Reprint requests to: *Dr. Maura N. Ricketts, Blood-borne Pathogens Division, Bureau of Infectious Diseases, LCDC, Locator address 3005A, 5th Fl., Tower A, Holland Cross, Ottawa ON K1A 0L2*