Published in final edited form as:

Transfusion. 2017 August ; 57(8): 1875–1878. doi:10.1111/trf.14145.

Creutzfeldt-Jakob disease lookback study: 21 years of surveillance for transfusion transmission risk

Lauren A. Crowder[1], **Lawrence B. Schonberger**[2], **Roger Y. Dodd**[3], and **Whitney R. Steele**[1]

[1]Scientific Affairs, American Red Cross, Rockville, Maryland; [2]National Center for Emerging and Zoonotic Infectious Diseases, Division of High-Consequence Pathogens and Pathology, US Centers for Disease Control and Prevention, Atlanta, Georgia; [3]American Red Cross, Medical Office, Gaithersburg, Maryland.

Abstract

BACKGROUND: Transfusion transmission of human prion diseases has been observed for variant Creutzfeldt-Jakob disease (vCJD), but not for the classic forms of prion disease (CJD: sporadic, genetic, and iatrogenic). Although the presence of prions or misfolded prion proteins in blood has been documented in some patients with the most common form of CJD, sporadic CJD, no transfusion-transmitted cases of CJD have been recognized. Since 1995, the American Red Cross has conducted a lookback study of the recipients of blood products from donors who develop CJD to assess the risk of blood-borne CJD transmission in the United States.

STUDY DESIGN AND METHODS: Blood donors subsequently diagnosed with confirmed or probable CJD were enrolled and the consignees were asked to identify the recipients of their blood products. These donors' transfusion recipients are traced annually with the National Death Index to see if they subsequently die of CJD.

RESULTS: To date, 65 CJD donors have been enrolled along with 826 of their blood recipients. These recipients have contributed 3934 person-years of follow-up and no transfusion-transmitted cases of CJD have been recognized.

CONCLUSION: From this study, as well as other epidemiologic studies, there is no evidence of CJD transfusion transmission; this risk remains theoretical.

Creutzfeldt-Jakob disease (CJD) is a rapidly progressing, invariably fatal, neurodegenerative transmissible spongiform encephalopathy. Current research indicates that the infectious agent is composed of an abnormally misfolded prion protein.[1] The vast majority of CJD

Address reprint requests to: Whitney R. Steele, PhD, American Red Cross, 15601 Crabbs Branch Way, Rockville, MD 20855; Whitney.Steele@redcross.org.

Publisher's Disclaimer: This article was published online on 25 April 2017. After online publication, revisions were made in Table 1 and the Results section. This notice is included in the online and print versions to indicate that both have been corrected on 05 June 2017.

CONFLICT OF INTEREST

The authors have disclosed no conflicts of interest.

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

cases are thought to occur sporadically, with familial (5%−15%) and iatrogenic (<1%) types making up a minority of cases. The pre-1996 described subtypes of sporadic, genetic (fCJD), and iatrogenic CJD (iCJD) are commonly referred to as classic CJD[1] to distinguish them from the variant form of CJD (vCJD) that emerged in the United Kingdom with the outbreak of bovine spongiform encephalopathy or “mad cow disease.”

In recent years, between 400 and 500 CJD cases have been reported annually in the United States,[1] numbers that reflect, in part, increased awareness of this disease and improved diagnostic techniques. While a probable diagnosis can be made from clinical symptoms and certain tests, a confirmatory diagnosis requires pathologic examination of brain tissue.[2,3]

Whereas there have been three cases of symptomatic transfusion-transmitted vCJD in the United Kingdom, as well as one asymptomatic transmission, to date there have been no documented cases of CJD in recipients of blood components from donors who later died from classic CJD (CJD donors).[4–9] Because prion diseases are always fatal and prion infectivity[10] or misfolded prion proteins[11] have been reported in the blood of four CJD patients, epidemiologic studies have been ongoing to determine if disease is transmitted person to person through blood component transfusion. The recently updated UK study identified no cases in 1194 person-years of survival after transfusion from CJD donors.[5] Although an epidemiologic study in Italy suggested that blood transfusion may be a risk factor for later development of CJD,[12] this finding has not been confirmed by UK or US studies.[5,6,9,13] In this report we provide an update on the US lookback study that includes data on donors and recipients collected over 21 years.

MATERIALS AND METHODS

In 1995, the American Red Cross (ARC) with support from the US Centers for Disease Control and Prevention (CDC) established a lookback study to assess the risk of transfusion transmission of CJD. Blood donors with a later diagnosis of CJD are reported to ARC study investigators by family members, physicians, health departments, and blood centers. The study investigators work with the reporting entity to collect information on the donor that allows for prior donation tracing (e.g., full name, date of birth, donation center) and establishing evidence of the donor’s diagnosis (confirmed or probable CJD). The blood centers where the donor provided donations are contacted to verify the donor’s donation history, and if the donor’s status is confirmed, the center is asked to participate. Blood center staff identify the consignees for all the donor’s components. The consignees are asked to provide demographic information on the recipients of the enrolled donor’s blood using a standard form. All recipients with a completed report, and their donors, are enrolled.

Surviving recipients are tracked annually through the National Center for Health Statistics’ National Death Index (NDI) for vital status and the multiple causes of death. Because death certificate data are filed immediately after death and do not always take into account findings from subsequent autopsy, the possibility of miscoding cause of death remains a concern. Any identified recipients with neurologic disease code(s) on the death certificate are cross-checked by CDC against records from the National Prion Disease Pathology

Surveillance Center to verify if the cause of death was later determined to be prion disease related. The last search of the NDI identified deaths through December 31, 2014.

Comparison of UK and US studies was carried out using Fisher's exact statistics; a p value of less than 0.05 is considered significant. This study has been approved by ARC and CDC Institutional Review Boards.

RESULTS

To date, 65 blood donors who were subsequently diagnosed clinically with CJD by a neurologist have been enrolled; 42 (64.6%) had pathologic confirmation of their CJD diagnosis. Of the 65 donors, 63 are classified as sporadic CJD, one fCJD (E200K mutation), and one iCJD (dura mater transplant). The fCJD donor made one donation of record and contributed two transfusable units, one of which had a traceable recipient who received red blood cells (RBCs). The iCJD donor made eight donations, contributing 21 transfusable units, which had eight traceable recipients (receiving a total of 5 platelet [PLT] units, 2 plasma units, and one RBC component). The recipient associated with the fCJD case has survived 12.73 years. One recipient associated with the iCJD case has survived for 19.48 years; however, the other seven recipients have a combined survival time of 10.8 person-years and none were reported to have a neurologic cause of death.

Most (73.8%) of the enrolled donors were male. The mean numbers of donations and donated components by the enrolled donors were 21 and 31, respectively (Table 1).

Overall, the 65 donors contributed 1816 total components to the blood supply, from which 826 (45.5%) had available recipient information. Of the 826 recipients, 572 (69.2%) had specified components: 170 PLT units, 291 RBC units, 77 plasma units, 11 whole blood units, and 23 other. Of the 826 recipients, 27 had insufficient information to track using the NDI, but did contribute to person-time. Annual tracking through the NDI of the vital status of the 799 other recipients indicated that through December 2014, a total of 154 were alive and 645 were deceased (Table 1).

Given the unknown, yet potentially long incubation period for prion diseases, and the likelihood that prion diseases are theoretically more infectious proximal to the onset of symptoms, certain recipient groups are of special interest.[8] These groups include 264 recipients who were long-term survivors: that is, they survived for 5 or more years posttransfusion (131, 89, and 44 recipients survived 5–9, 10–19, and 201 years, respectively), 414 recipients who received blood components donated 60 months or less prior to the donor's CJD diagnosis or symptom onset, and 105 recipients who fit into both of those categories. We compared the CJD risk of the third group from this study's recipients with the risk of vCJD among the long-term survivors in the UK study. There were no clinical cases of CJD from the 105 recipients in this third group, compared to three such cases of the 33 long-term survivors in the UK study (Fisher's exact, p 5 0.013). In addition, one asymptomatic vCJD infection was documented among the 33 UK long-term survivors.

DISCUSSION

This study is assessing the transfusion transmission risk of CJD from specific donors to the enrolled recipients. Although we recognize that our enrolled donors and recipients are not random samples of the universe of such persons, we believe that for the described relevant time intervals (the period between donation and onset of CJD for the donors and the period blood recipients were followed after transfusion), our observed best estimate of no transfusion transmission risk is likely reasonably unbiased. However, the number of donors and recipients and the periods the recipients have been followed may be too small to detect a long latent period risk from a rare infectious donor. Because only a limited number of blood recipients live for long periods after transfusion,[14] com bined with the long incubation period for the disease, we are unlikely to see any cases except in recipients with many years of posttransfusion survival or when we have acquired enough years of follow-up to see a case by chance alone. This study has a large percentage of recipients who lived for 5 years or longer posttransfusion (32%) allowing for an increased chance of recognizing a case that developed over this time period were it to have occurred.

A limitation of this study is that 35.4% of the enrolled donors did not undergo a brain biopsy or autopsy to confirm the neurologist's clinical diagnosis of CJD. Nevertheless, because approximately 90%[15] of CJD cases are recognized clinically, we believe that it is reasonable to assume that each of these enrolled donors most likely truly had the disease.

The additional years of data presented in this US study update combined with the published UK study data on the transfusion transmission risk associated with classic forms of CJD include 94 donors, 1037 recipients, and 5128 person-years of observation, with no reported cases of CJD in the traced recipients. We believe that these findings further support our conclusion that the risk of trans-fusion transmission of classic CJD remains theoretical. However, due to ongoing concern that CJD may be transmitted by blood, study enrollment and follow-up will continue.

Acknowledgments

This work has been funded by Grant 2 U01 CK000360–03 from the US Centers for Disease Control and Prevention.

ABBREVIATIONS:

ARC	American Red Cross
fCJD	genetic (familial) Creutzfeldt-Jakob disease
iCJD	iatrogenic Creutzfeldt-Jakob disease
NDI	National Death Index
vCJD	variant Creutzfeldt-Jakob disease

REFERENCES

1. Creutzfeldt-Jakob Disease, Classic (CJD) [Internet]. Atlanta: Centers for Disease Control and Prevention; 2015 [cited 2016 Nov 9]. Available from: www.cdc.gov/prions/cjd
2. National Prion Disease Pathology Surveillance Center [Internet]. Cleveland (OH): Case Western Reserve University; c2010 [cited 2016 Nov 16]. Available from: http:/CJDsurveillance.com.
3. McGuire LI, Peden AH, Orru CD, et al. Real time quaking-induced conversion analysis of cerebrospinal fluid in sporadic Creutzfeldt-Jakob disease. Ann Neurol 2012;72:278–85. [PubMed: 22926858]
4. Hewitt PE, Llewelyn CA, Mackenzie J, et al. Three reported cases of variant Creutzfeldt-Jakob disease transmission following transfusion of labile blood components. Vox Sang 2006;91:348. [PubMed: 17105612]
5. Urwin PJ, Mackenzie JM, Llewelyn CA, et al. Creutzfeldt-Jakob disease and blood transfusion: updated results of the UK Transfusion Medicine Epidemiology Review Study. Vox Sang 2016;110:310–6. [PubMed: 26709606]
6. Hewitt PE, Llewelyn CA, Mackenzie J, et al. Creutzfeldt-Jakob disease and blood transfusion: results of the UK Transfusion Medicine Epidemiological Review study. Vox Sang 2006;91: 221–30. [PubMed: 16958834]
7. Peden AH, Head MW, Ritchie DL, et al. Preclinical vCJD after blood transfusion in a PRNP codon 129 heterozygous patient. Lancet 2004;364:527–9. [PubMed: 15302196]
8. Zou S, Fang CT, Schonberger LB. Transfusion transmission of human prion diseases. Transfus Med Rev 2008;22:58–69. [PubMed: 18063192]
9. Dorsey K, Zou S, Schonberger LB, et al. Lack of evidence of transfusion transmission of Creutzfeldt-Jakob disease in a US surveillance study. Transfusion 2009;49:977–84. [PubMed: 19170987]
10. Douet JY, Zafar S, Perret-Liaudet A, et al. Detection of infectivity in blood of persons with variant and sporadic Creutzfeldt-Jakob disease. Emerg Infect Dis 2014;20:114–7. [PubMed: 24377668]
11. Jackson GS, Burk-Rafel J, Edgeworth JA, et al. Population screening for variant Creutzfeldt-Jakob disease using a novel blood test: diagnostic accuracy and feasibility study. JAMA Neurol 2014;71:421–8. [PubMed: 24590363]
12. Puopolo M, Ladogana A, Vetrugno V, et al. Transmission of sporadic Creutzfeldt-Jakob disease by blood transfusion: risk factor or possible biases. Transfusion 2011;51:1556–66. [PubMed: 21214582]
13. Molesworth AM, Mackenzie J, Everington D, et al. Sporadic Creutzfeldt-Jakob disease and risk of blood transfusion in the United Kingdom. Transfusion 2011;51:1872–3. [PubMed: 21831186]
14. Dorsey KA, Moritz ED, Notari EP 4th, et al. Survival of blood transfusion recipients identified by a look-back investigation. Blood Transfus 2014;12:67–72. [PubMed: 24333056]
15. Will RG, Alpers MP, Dormont D, Schonberger LB. Infectious and sporadic prion disease. In: Prusiner SB, editor. Prion biology and diseases. Cold Spring Harbor (NY): Cold Spring Harbor Laboratory Press; 2004 p. 629–72.

TABLE 1.

CJD donor case and blood recipient information

Descriptors	Blood donors {n = 65}	Blood recipients {n = 826}
Number of donations		
Mean	21	
Median	13	
Number of components donated		
Total	1816	
Mean	31.0	
Mean age {years)		
Symptom onset	60.8	
Transfusion		59.9
Death		67.7
vital status		
Deceased		645
Alive, as of December 31, 2014		154
Not enough information to track annually		27
Person-years of follow-up		
Total		3933.9
Deceased		1918.6
Alive, as of December 31, 2014		1919.7
Not enough information to track annually		95.6