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Risk of acquiring Creutzfeldt-Jakob disease from blood transfusions: systematic review of case-control studies

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Abstract

Objective To determine the strength of association between history of blood transfusion and development of Creutzfeldt-Jakob disease.
Data sources English and non-English language articles published from January 1966 to January 1999 were retrieved using a keyword search of Medline and Embase. These were supplemented by handsearching key journals and searching bibliographies of reviews.
Study selection Two independent reviewers selected the relevant abstracts and articles. Articles were chosen that reported the results of case-control studies trying to identify rates of prior blood transfusion in patients with Creutzfeldt-Jakob disease and in controls.
Data extraction Odds ratios and information on study quality were extracted from the selected articles by two independent reviewers.
Data synthesis Five studies containing data on 2479 patients were included. Three of the five studies used medical or neurological patients as controls, the other two used population controls. Odds ratios for developing Creutzfeldt-Jakob disease from blood transfusion ranged from 0.54 to 0.89. Four of the five studies had confidence intervals that crossed 1.0. The combined odds ratio was 0.70 (95% confidence interval 0.54 to 0.89).
Conclusions Case-control studies do not suggest a risk of developing Creutzfeldt-Jakob disease from blood transfusion. Rather, a trend seems to exist towards a lower frequency of previous blood transfusion in patients with Creutzfeldt-Jakob disease than in controls. However, it is important to be aware of these studies' methodological limitations—primarily the choice of control population and reliability of recall of transfusion status.

Introduction

The possibility of iatrogenic transmission of Creutzfeldt-Jakob disease via blood transfusion has recently attracted increased attention owing to the known transmissibility of hepatitis C and HIV via blood.[1] Owing to the rarity of Creutzfeldt-Jakob disease and the potentially long latency period case-control studies are well suited to determine if an association exists between Creutzfeldt-Jakob disease and blood transfusion. We have conducted a systematic review of the evidence of blood transmission of sporadic Creutzfeldt-Jakob disease from case-control studies. Studies of variant Creutzfeldt-Jakob disease were not included in the review.

Methods

We conducted a search of English and non-English language articles in the Medline database from January 1966 to January 1999. We also searched the Embase database from 1988 to 1999. We supplemented this search by handsearching key journals and searching bibliographies of reviews.

Two authors independently evaluated the abstracts and the retrieved articles and also extracted data. Articles selected for the systematic review had to meet two criteria. They had to have studied patients with Creutzfeldt-Jakob disease and controls, and they had to have determined the rate of blood transfusion in patients with Creutzfeldt-Jakob disease and controls. Odds ratios were calculated using the Meta-analyst program.[2]

Results

Study selection and characteristics

The Medline and Embase searches yielded 302 citations, including 14 case-control studies. Of these studies, four met the inclusion criteria.[3–6] A fifth study released after the searches were conducted was later identified and included in this analysis.[7] Thus five studies, involving 2479 patients, were included in the final analysis. Two studies were conducted in the United Kingdom,[4 5] one in Japan,[3] one in Europe,[6] and one in Australia.[7]

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Table 1 Study characteristics

	Kondo et al, 1982[3]	Harries-Jones et al, 1988[4]	Esmonde et al, 1993[5]	Van Dujin et al, 1998[6]	Collins et al, 1999[7]
Primary goal to determine the odds of receiving transfusion	No	No	Yes	No	No
Criteria for diagnosing CJD	Masters	Masters	Masters	Masters	Masters
Source of controls	Population	Hospital	Hospital	Hospital	Population
Strategy for identifying cases	Request for notification	Request for notification or death certificates	CJD registers	Request for notification or death certificates	CJD registers, death certificates, hospital coding
Assessment of transfusion history	Surrogate report	Surrogate report	Surrogate report	Surrogate report	Surrogate report
Matching of cases and controls	Age and sex	Age and sex	Age and sex	Age and sex	Age, sex, and community
Interval between transfusion and disease development	Five years	Not assessed	174 months (mean)	Not assessed	Not assessed
Dose-response relation	Not assessed	Not assessed	Not assessed	Not assessed	Decreased odds ratio with increased number of transfusions (not significant)

CJD=Creutzfeldt-Jakob disease.

Only one of the studies had a primary goal to determine the odds of receiving a blood transfusion.[5] The other four studies were looking more broadly for risk factors for Creutzfeldt-Jakob disease. All studies used the Masters criteria to define cases of Creutzfeldt-Jakob disease and included definite and probable cases.[8] All studies described a clear strategy for identifying cases. Two studies selected population controls[3 7]; the rest identified medical or neurological patients as controls. All studies used age and sex matched controls, and all relied on surrogate reporting of transfusion history, most frequently from a close relative (table 1).

Risk of Creutzfeldt-Jakob disease from blood transfusion

All studies showed a trend towards a lower risk of Creutzfeldt-Jakob disease in patients who had received a blood transfusion, with one study showing this association to be significant.[6] Odds ratios ranged from 0.54 to 0.89 (table 2). A combined odds ratio using a DerSimonion-Laird random effects model reached significance (odds ratio 0.70 (95% confidence interval 0.54 to 0.89)). A statistical test for heterogeneity was negative ($P=0.62$).[9] The combined odds ratio should be interpreted with caution owing to theoretical concerns relating to combining data from observational studies.[10]

Two studies provided information on the interval between transfusion and development of Creutzfeldt-Jakob disease. One study only identified cases in which transfusions had been received in the five years up to the development of Creutzfeldt-Jakob disease.[3] One study reported a mean interval of 174 months between transfusion and development of the disease.[5] Only one study examined for a possible dose-response relation, and it found a progressively lower odds ratio with increasing number of transfusions, although significance was never reached.[7]

Table 2 History of blood transfusion, with odds ratios for developing Creutzfeldt-Jakob disease if having received blood transfusion

		Cases		Controls		
Study (year)	Subjects	Yes	No	Yes	No	Odds ratio (95% CI)
Kondo et al, 1982[3]	163	1	59	3	100	0.56 (0.06 to 5.56)
Harries-Jones et al, 1988[4]	276	15	77	37	147	0.77 (0.40 to 1.50)
Esmonde et al, 1993[5]	402	21	134	46	201	0.68 (0.39 to 1.20)
Van Dujin et al, 1998[6]	719	38	303	71	307	0.54 (0.35 to 0.83)*
Collins et al, 1999[7]	919	27	118	158	616	0.89 (0.57 to 1.40)†

*Results of matched analyses: 0.56 (0.37 to 0.97).
†Results of matched analyses: 0.89 (0.57 to 1.40).

Discussion

This systematic review does not support an association between blood transfusion and development of sporadic Creutzfeldt-Jakob disease. A trend seems to exist, however, towards a protective effect of transfusion. An excluded study that did not provide raw data reported an odds ratio of 0.6 for having received a blood transfusion, which was consistent with the findings of this review.[11]

Limitations

Although case-control studies are well suited for determining associations in conditions that have low frequency and long latency periods, they are susceptible to bias. The major source of bias contributing towards the apparent beneficial effect of blood transfusion involves selection of controls in the primary studies. Three of the five studies used medical patients or neurological patients as controls.[4–6] Presumably, these individuals would be at higher risk than the average population of having received a blood transfusion.

Bias may also occur as a result of inaccurate ascertainment of transfusion status. Studies have found that 25-40% of transfusion recipients do not recall having received transfusions.[12] The necessary reliance on reporting from surrogates, usually relatives, also contributes to inaccurate ascertainment. However, for recall bias to produce a decreased association between Creutzfeldt-Jakob disease and blood transfusions, family members of patients with Creutzfeldt-Jakob disease would have to be less likely to recall transfusion history than family members of controls.

Three of the five primary studies did not provide the results of matched analyses.[3–5] This is an important methodological limitation and illustrates the need for caution if using data from case-control studies. The failure to use matched analyses generally produces a bias towards the null effect.[13]

Other studies

Despite the limitations of the primary studies it seems unlikely, from the results presented in this systematic review, that blood transfusions contribute towards

development of sporadic Creutzfeldt-Jakob disease. Evidence from other sources also seems to support the lack of an association. Results from animal studies have been equivocal, although a study from the US National Institute of Health concluded that the human blood could not transmit Creutzfeldt-Jakob disease to animals.[14] This may, however, be more a function of the species barrier than of infectivity. A study of preserved brain samples of 25 haemophilic patients—who have high exposure to blood transfusions and potentially higher exposure to blood infected with the agent responsible for Creutzfeldt-Jakob disease—found no evidence of the disease.[15] "Look back" studies have not identified any cases of Creutzfeldt-Jakob disease developing in recipients who received blood from a donor in whom the disease was later diagnosed.[16 17] No extended controlled cohort studies have been conducted to determine if blood transfusion recipients are at increased risk of Creutzfeldt-Jakob disease.

Generalisability

The results of this systematic review pertain to the transmissibility of sporadic Creutzfeldt-Jakob disease and should not be generalised to variant Creutzfeldt-Jakob disease. Variant Creutzfeldt-Jakob disease differs from the sporadic form in several respects: a shorter latency period, presentation with behavioural symptoms, and longer duration of disease before death. In particular, the lymphoreticular system seems to be a site for collection of the prion protein in variant Creutzfeldt-Jakob disease, with large amounts found in the appendices and tonsils of affected individuals. This affinity for the lymphoreticular system may increase the likelihood of variant Creutzfeldt-Jakob disease being transmitted via blood.[18] One case-control study examining the risk of transmission of variant Creutzfeldt-Jakob disease from blood transfusions did not find any association (UK Creutzfeldt-Jakob Disease Surveillance Unit, www.cjd.ed.ac.uk/rep98.html (accessed 1 September 1999)).

Conclusion

This study illustrates some of the difficulties in attempting to determine causal relations in the area of infectivity of blood products. Despite the methodological advantages of case-control studies in studying rare diseases with long latency periods, potential exists for significant levels of bias that can produce apparently spurious results. It is important to recognise these limitations when attempting to address the question of infectivity of variant Creutzfeldt-Jakob disease via blood transfusion.

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Contributors: KW designed the study, selected the included papers, extracted data, conducted the statistical analysis, and prepared the manuscript. He will also act as guarantor for the paper. CC selected the included papers, extracted data, and reviewed the final manuscript. MNR provided background information on Creutzfeldt-Jakob disease and indicated potential sources of bias in the primary studies. She also reviewed the final manuscript.

What is already known on this topic

Potential blood transmission of sporadic Creutzfeldt-Jakob disease has been a concern in several countries

Current evidence suggests that no link exists between blood transfusion and development of sporadic Creutzfeldt-Jakob disease

What this study adds

This systematic review summarises the results from five case-control studies examining the risk of developing sporadic Creutzfeldt-Jakob disease from blood transfusions

No study shows an association

Patients with Creutzfeldt-Jakob disease were less likely to have received blood transfusions than controls, suggesting a protective effect of transfusions; this apparently spurious result is probably the consequence of methodological limitations of the primary studies

The study draws attention to the importance of having well designed case-control studies when trying to assess the risk of developing variant Creutzfeldt-Jakob disease from blood transfusion

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