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The Risk of vCJD Transmission by Blood and Suggested Public Policy Response

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Abstract

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*ith the discovery of variant Creutzfeldt-Jakob Disease (vCJD), commonly known as human mad cow disease, in 1996, there has been a significant attention on diagnosis, treatment, and containment of this rare degenerative disease. To date, however, attempts to treat vCJD have been unsuccessful. Since the disease remains invariably fatal, therefore, public policy focus has shifted toward identification of transmission mechanism and containment of the disease. While there is no doubt that consumption of contaminated cattle can spread the disease, there is no evidence of direct human-to-human transmission with the exception of a small number of suspected cases of transmission through blood transfusion. Based on current research on the topic, this paper seeks to assess whether vCJD is transmissible through blood transfusion. This paper will then evaluate the current deferral policies—those who have travelled or lived in Europe for a certain period of time cannot donate blood—to restrict blood donation from those in risk of vCJD. The findings indicate that while there is some evidence that transmission of vCJD through blood transfusion is possible, the current donor deferral policy is misguided.*

Introduction and Historical Background

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NCE A LITTLE KNOWN DISEASE, EVEN WITHIN THE MEDICAL community, Creutzfeldt-Jakob Disease (CJD), particularly its variant type (variant Creutzfeldt-Jakob Disease, or vCJD), has recently risen to the forefront of popular attention. With this emergence, public health authorities have sprung to curb the spread of vCJD from cattle to humans, placing bans on certain agricultural practices. Yet, the fear of possible human-to-human transmission remains, and the focal point of this fear has been transmission through blood. As a precautionary measure, therefore, the U.S. Food and Drug Administration has implemented indefinite deferral policies on blood donors who have spent more than a certain period of time in Europe. Despite lower risk of transmission by blood, however, the evidence available so far suggests that this measure does more harm than good, considering its effectiveness (or lack thereof) and its costs.

Features of Variant Creutzfeldt-Jakob Disease and Prions

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ompared to other infectious diseases, very little is known about the nature of variant Creutzfeldt-Jakob Disease. What is known so far is that vCJD is caused by a type of protein known as prions. A product of a gene named PRNP, prions exist in our body in a normal, harmless state (PrPC), although the function of PrPC is not known for certain (Silveira, 2004). However, prions become deadly infectious agents once they experience a conversion into a misfolded state. Normally, PrPC composed mostly of alpha-helix structure with a minority of beta-sheets. However, in a pathological prion, PrPSc, beta-sheet conformation dominates, at the expense of unstructured and alpha-helix portions of the protein. When PrPSc comes in contact with PrPC, the pathological protein converts PrPC into PrPSc, thereby propagating the malignant structures (Soto, 2006). These pathological prions are resistant to protease activity and accumulate in the central nervous system. Abnormal PrPSc accumulation leads to amyloid plaque deposits, neuronal apoptosis, vacuolation of the brain (giving it sponge-like appearance), and eventual death.

Variant Creutzfeldt-Jakob Disease is a subset of a broad range of prion diseases. Many species are affected by prion diseases, including sheep (scrapie), cows (bovine spongiform encephalopathy, commonly known as mad cow disease), and humans (kuru and Creutzfeldt-Jakob Disease). More specifically, vCJD is one of four types of Creutzfeldt-Jakob Disease (Zou, 2008):

* Sporadic (sCJD): Accounting for the vast majority (85%) of CJD cases, sCJD is caused by spontaneous conversion of PrPC to PrPSc.
* Familial: inherited cases of CJD
* Iatrogenic (iCJD): caused by contaminated transplants
* Variant (vCJD): acquired mainly through consumption of contaminated cattle

Clinical characteristics vary between different types of CJD and between CJD and other human prion diseases. Incubation period ranges from months to half a century, and mean age at onset varies from 26 in the case of vCJD to 66 in the case of sCJD (Tyler, 2003). In the case of vCJD, symptoms are primarily neurological, including cognitive impairment, paresthesias, and gait abnormalities, and it is 100% fatal as there is no cure or treatment available (Tyler, 2003). Fortunately, the incidence of vCJD has remained exceedingly low, with only about 200 cases reported worldwide and vast majority clustered in UK.

Transmission of vCJD

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he vast majority of vCJD cases reported so far contracted the disease through consumption of cattle infected with bovine spongiform encephalopathy (BSE). It has been hypothesized that the remains of sheep infected with scrapie were fed to cows to increase their growth rate and milk yield. The cows, in turn, were infected with PrPSc, developing bovine spongiform encephalopathy, commonly known as mad cow disease (Yam, 2003). Some humans who consumed these infected bovines acquired the pathological prions from them, thereby developing vCJD. As a result of this revelation, authorities in affected nations—most of western Europe, US, and Canada—have slaughtered a great number of cattle in risk areas and banned ruminant feed. These measures, in large part, has succeeded in reducing BSE among cows and cutting off the transmission route of vCJD from cattle to humans, and incidence of both BSE and vCJD has declined in recent years (Donnelly, 2004).

However, in 2004, the possibility of human-to-human transmission of vCJD through blood transfusion surfaced seriously, with potential to greatly affect public policy regarding vCJD. Since 2004, four suspected cases of vCJD infection through blood transfusion were reported—all in United Kingdom—providing empirical support that vCJD is transmissible by blood transfusion. In these four cases, the donors developed vCJD 17-40 months after blood donation, and the recipients developed vCJD about 7 years after transfusion (Zou, 2008). Given that a human clinical study on the possibility of transmission by transfusion is not possible due to ethical consideration and that there is much unknown about the nature of vCJD, whether vCJD can be transmitted by blood transfusion depends on the interpretation of these four cases.

There are two possible interpretations of these four cases: either they are coincidences (i.e. the infections actually occurred through dietary exposure) or they are evidence of possible transmission of vCJD by blood transfusion. The evidence available so far seems to support the latter. For one, given the low incidence of vCJD in general, blood donor-recipient connect between four pairs of vCJD patients is highly unlikely. As an example, Llewelyn, Knight, Amar, Cousens, Mackenzie & Will (2004), considering only the first two cases (there were only two suspected cases at the time), concluded that the chance of observing two pairs of vCJD patients with blood donor-recipient relationship is between 1/15,000 and 1/30,000. As this study does not even consider the two suspected cases reported in 2006 and 2007, the chance of observing four pairs of vCJD patients linked through donor-recipient relationship likely is extremely low. Furthermore, the third and fourth suspect cases of vCJD transmission by blood were linked to the same donor, a highly unlikely scenario if the sole transmission route was through consumption of contaminated beef. Is it *possible* that the four cases occurred by chance? Certainly yes. Is it even remotely *probable*? Certainly no.

Further evidence of vCJD transmission by blood is the fact that the recipient-patient age in the four suspected cases are much higher than the average age of onset for vCJD patients. In contrast to sporadic CJD patients, vCJD patients develop the disease at a relatively young age; For vCJD, the average age of onset, as mentioned above, is 26 (Tyler, 2003). Yet, in three of the four suspected cases of vCJD transmission by blood, the recipient-patient was older than 60 at the time of onset (Zou, 2008). This sharp contrast provides further support for the interpretation that the four suspected cases represent vCJD transmission by blood transfusion.

In order to further ascertain the possibility of vCJD transmission by blood transfusion, it is helpful to consider the clinical studies regarding the issues. Unfortunately, no human clinical study is available since the disease is invariably fatal, but animal studies shed some light onto whether vCJD is transmissible by blood. Cervenakova et al. (2003) reported that 2 out of 6 mice inoculated intravenously with vCJD buffy coat and 6 out of 15 mice inoculated with vCJD plasma were infected. Similarly, Zou et al. (2008) reported that 4 out of 21 sheep inoculated IV with scrapie-infected whole blood developed the disease. While, of course, we must be wary of blindly generalizing animal test results to humans, these results seem to suggest that vCJD can be transmitted by blood. These animal test results are further reinforced by the findings of Zou et al. (2008); they found that in spleens of vCJD-infected primates, PrPSc level reached up to 4% of the level in the brain. While we do not know the threshold level of PrPSc for a person to develop vCJD and it is unequivocal that blood has lower infectivity than the brain does, the results indicate that blood is capable of transmitting PrPSc and leading to vCJD infection.

Further complicating these results is the uncertain incubation period of human prion diseases. The incubation period of vCJD is currently expected to be around a decade (Smith, 2004), but it is possible that the incubation period is actually much longer. It is very difficult to ascertain the incubation period of vCJD at this point as it is a relatively new disease with first case identified in 1996. Thus, any case with incubation of more a few decades would not have been identified so far. Should the incubation period of vCJD turn out to be much longer than we thought, there is a significant possibility that the number of suspected cases of vCJD transmission by blood would increase in the future.

In particular, there are two plausible reasons as to why the incubation period of vCJD may be longer than the scientists currently think. First, some human prion diseases have been known to have incubation periods as long as half a century. One of these is kuru, a disease prevalent among Fore tribe of Papua New Guinea. It is likely that kuru was transmitted from human to human through Fore tribe’s cannibalistic rituals, and thus, cessation of cannibalism in late 1950s should have cut off human-to-human transmission route of kuru. However, even now, half a century after cannibalistic practices stopped, kuru patients are occasionally observed in Papua New Guinea, suggesting that the incubation period of the disease may be as long as fifty years or more (Zou, 2008). Since kuru and vCJD are both human prion diseases and share many similar characteristics, it is possible that vCJD incubation period may be as long as that of kuru.

Secondly, many scientists have accepted the hypothesis that certain genetic types are more resistant to vCJD and may have longer incubation period, and if this hypothesis is true, we may be leaving out a big segment of the population that carries certain types of genes. Among the patients with sporadic type of CJD, those who are homozygous for methionine at the codon 129 of PRNP are overrepresented. Compared to only 40% of the general white population, 70% of sCJD patients are methionine-homozygous at the codon 129, suggesting that they are more susceptible to human prion diseases (Bishop, 2009). We find similar results with kuru; not only are individuals homozygous for methionine at codon 129 overrepresented among kuru patients, those homozygous for valine or heterozygous at codon 129 have longer incubation period (Goldfarb et al. 2004).

At this moment, it seems appropriate to generalize the results of DNA study on sporadic CJD and kuru to variant CJD. To date, all 172 confirmed cases of vCJD in UK have been found to be homozygous for methionine at codon 129. There has been only one suspected case of a vCJD patient not methionine-homozygous at codon 129, and this patient died of a nonneurological cause before exhibiting symptoms of vCJD (Bishop, 2009). These results show that the genetic susceptibility and resistance present in sCJD and kuru are also present in vCJD. Given the results of existing studies on sporadic CJD and kuru, it is possible that those not homozygous for methionine at codon 129 have longer incubation period. Should this be the case, there could be a number of cases of vCJD transmission by blood transfusion that have been undetected so far.

Even among patients homozygous for methionine at codon 129, many cases of vCJD transmission by blood transfusion may have gone undetected. The condition that necessitated the transfusion in the first place is likely to kill the patient even before symptoms of vCJD arise; in the U.S., only about 50% of transfusion recipients survived past the first year (Zou, 2008). Since the only definitive test for vCJD is brain biopsy performed during autopsy, those patients infected with vCJD but asymptomatic may have been overlooked. It is clear from the current evidence that transmission of vCJD through blood transfusion is possible, but there may be more cases of this type of transmission that have been unnoticed. Thus, the evidences outlined above indicate that it is possible (although with lower infectivity than brain matter) for blood transfusion to transmit vCJD from human to human and that this route of transmission may be nontrivial.

**Public Health Measures**

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his possibility of vCJD transmission by blood has triggered a series of stringent measures from the United States Food and Drug Administration and the American Red Cross regarding blood safety. As a precautionary measure, the American Red Cross indefinitely defers donors who have spent more than 3 months in UK or more than 5 years in Europe between 1980 and 1996, and FDA banned the import of blood products from European nations. FDA predicted that this ban would theoretically reduce the risk of vCJD transmission by 87% (Senior, 2001), a potentially large benefit.

However, in order to assess whether these measures are justified, we must weigh not only the benefits but also the costs. The upsides of this policy are countered by its adverse impact on the American blood supply. The United States already has a thin supply of blood, and this measure, according to Senior (2001), would reduce the blood supply by up to 8%. Even more detrimental would be the ban on blood import from Europe, especially in the New York area; for example, the New York Blood Center draws a quarter of its blood supply from imported European blood, and cutting off this supply would threaten the adequate supply of blood.

What is even more problematic about the measures that FDA and the American Red Cross have implemented is their misguided target. Currently, the donor deferral and the blood import ban affect not only those who travelled to UK, where the vast majority of vCJD cases are clustered, but also entire Europe. Even those who lived for more than five years in Eastern Europe, where there has never been a case of vCJD, are subject to the deferral policy. Moreover, the import ban affects continental Europe—where there have been few cases of vCJD—more than the United Kingdom. New York Blood Center’s imported blood came from Germany, the Netherlands, and Switzerland; in all these nations combined, there have only been three cases of vCJD so far. While the donor deferral and import ban policies may be well-intentioned, low incidence of vCJD in continental Europe suggest that they are misguided.

Alternatives to Donor Deferral and Import Ban

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he most obvious solution to the problem of misguided policy outlined above is modifying the policy to target the most risky nation, the United Kingdom. However, it is also true that public health policy must be conservative and cautious; it is possible that should there be a few cases of vCJD transmission by blood, the public would lose faith in the blood system. As such, we cannot leave imported blood from continental Europe unmonitored. In order to balance the costs and the benefits of public health policy regarding vCJD and blood supply, we need to reinforce the current system in place, and there are two possible additions:

***i. Blood tests***

A blood test is the most direct solution to the problem of tainted blood supply. If the American Red Cross could identify the blood units that are contaminated, we would be able to reducing the risk of transmission to near zero while minimizing the detrimental effects on the blood supply. However, developing a blood test for vCJD is no easy task. The greatest obstacle lies in the fact that currently the only known marker of vCJD in blood is PrPSc. The concentration of PrPSc is high enough to be infectious but low enough to be practically undetectable—in the order of pg/mL of blood (Grassi, 2008). Furthermore, given the immense psychological, social, and economic impact of vCJD on the society, the blood test must be extremely sensitive and specific.

For example, even if we were to assume 99% sensitivity and specificity and 1 in 10,000 prevalence (a very conservative figure given that the incidence of sCJD is 1 in 1 million), the test would yield a hundred times as many false positives than true positives (Turner, 2009). Due to ethical concerns, those testing positive would have to be notified as such, and this would have immense impact on the society. For instance, in the case of Japan, mere three cows infected with BSE are estimated to have cost the economy $2.76 billion (Yam, 2003). Therefore, given this potentially explosive impact, universal blood tests seem neither feasible nor desirable.

***ii. Component Processing***

Component processing of leukocytes and plasma can offer a less dangerous alternative. According to Murphy (1999), it is likely that host B lymphocytes are involved in the transport of prions from the periphery to the central nervous system. Zou et al. (2008) added further that plasma seems to be another transmission route for PrPSc, while rejecting the hypothesis that red blood cells carry PrPSc. These results suggest that reduction of leukocytes and plasma fractionation can lower the risk of vCJD transmission by blood.

Of course, these measures applied alone are insufficient. Leukodepletion by itself reduces only about half of the infectivity. However, there are prion removal devices under development that would significantly decrease the infectivity of the contaminated blood, and leukocyte reduction is an important first step. Plasma fractionation also seems to help prevent transmission of vCJD through blood; no case of vCJD by plasma products has been reported (Turner, 2009). While universal adoption of these procedures would be expensive—estimated at $400 million/year for the US— selective administration on geographically risky blood units is desirable (Murphy, 1999).

Conclusion

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t is, of course, without doubt that the vast majority of vCJD cases are transmitted through consumption of contaminated beef. Of nearly two hundred cases reported worldwide, only four have been suspected cases of transmission by blood. However, the current evidence indicates that this possibility is present and may even be greater than we think. Since it is difficult to know for certain how long the incubation period of vCJD is or how many cases of vCJD transmission by blood have gone undetected, therefore, it is advisable that public health measures be as conservative as possible and restrict potentially risky blood donors. But to adopt overly stringent measures would be to do more harm than good; particularly when the blood supply in the United States is stretched thin and threatens the health of many that need the transfusions, import ban and donor deferral policy that encompasses even the relatively vCJD-free nations of Europe is detrimental. Thus, given the current research on vCJD and its transmission mechanism, the current FDA policies regarding blood supply and vCJD should be modified to 1) target the core nation in the crisis, UK, and 2) reduce as much infectivity in blood supply as possible through leukocyte reduction and plasma fractionation.

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