

Variant Creutzfeldt–Jakob Disease (vCJD)

Disease Agent:

- Prion agent causing vCJD

Disease Agent Characteristics:

- Current evidence supports the theory that the infectious agent is a prion. However, the existence of accessory factors has not been excluded.
- Prions are proteinacious infectious agents causing transmissible spongiform encephalopathies (TSE): a group of neurodegenerative diseases that include kuru, Creutzfeldt–Jakob Disease (CJD), variant CJD (vCJD), Gerstmann–Sträussler–Scheinker disease (GSS) and fatal familial insomnia (FFI); other human prion diseases are discussed in a separate fact sheet. Prion diseases are either sporadic, genetic or infectious. The cause of sporadic CJD (sCJD) is unknown. The genetic prion diseases are associated with a germline mutation in the human gene, *PRNP*. The infectious disease occurs in people exposed to food, biologicals or instruments contaminated with prions.
- Prions differ from other infectious agents in that they are formed mostly of an abnormally folded prion protein and devoid of detectable nucleic acid.
- Mammalian prions replicate by recruiting the normal cellular prion protein PrP^C to form a disease-causing isoform designated PrP^{Sc} (Sc is an abbreviation for scrapie). PrP^{Sc} or PrP^{res} (abbreviation for misfolded core PrP protein resistant to proteinase K) or PrP^{TSE} (a wider definition accepted by WHO) are the designations for the pathogenic forms and are used interchangeably in the literature. Prion diseases represent disorders of protein conformation in which the tertiary structure of the native protein is profoundly altered. The transition occurs when the α -helical PrP^C changes into a β -sheet-rich molecule of PrP^{TSE} that is resistant to proteases (proteinase K, lysosomal enzymes).
- Prions are nonimmunogenic as a result of the sharing of epitopes with the normal cellular isoform.
- PrP^C is a glycosylated protein attached to the outer-layer of plasma membrane through a glycosylphosphatidylinositol anchor. It is present on variety of cells but also circulates in plasma and has a molecular weight of about 33–35 kDa.
- PrP^{TSE} has a more restricted tissue range than does PrP^C.
- PrP^{TSE} forms aggregates that precipitate as diffuse accumulations or as amyloid plaques in the central nervous system; these are a histopathological hallmark of the TSEs. So called “florid” plaques (amyloid plaques surrounded by crown of vacuoles) in brain tissue are typical feature of vCJD. Generally, PrP^{TSE} is identified in a form of PrP^{res} using immunohistological techniques or by immunoblotting after the treatment of tissues by proteinase K.
- vCJD prions are transmissible to susceptible experimental animals, specifically to nonhuman primates, mice and guinea pigs.

- vCJD prions cannot be tested for infectivity using cell cultures.
- Physicochemical properties: Resistance of prions to commonly used disinfectants (formaldehyde, glutaraldehyde, ethanol, and iodine [partially]) and other treatments that damage nucleic acids is well recognized. Prions are resistant to ultraviolet light and ionizing radiation, ultrasonication, nucleases, boiling, and heat. Immersion in undiluted bleach (60,000 ppm or mg/L of available chlorine) for 1 hour can be partially effective. High concentrations of NaOH (1–2N) or heat in a gravity displacement autoclave at 121°C or higher or in a porous load autoclave at 134°C for 1 hour are advocated for disinfection.

Disease Name:

- Variant Creutzfeldt–Jakob disease (vCJD)
- Human transmissible spongiform encephalopathy

Priority Level:

- Safety/Epidemiologic evidence regarding blood safety: Low: due to the absence of endogenous human infection in North America and the possible impact of stringent deferral policy. There is strong evidence for transfusion transmission in the UK.
- Public perception and/or regulatory concern regarding blood safety: High
- Public concern regarding disease agent: Moderate

Background:

- Emergent; first case identified in UK in 1994; recognized as a distinct disease in 1996
- As of October 2011, there have been 225 cases reported worldwide with 176 cases in the UK (3 are alive). Bovine spongiform encephalopathy (BSE) is thought to have been introduced outside of the UK through the exportation of ruminant-derived meat and bone meal (MBM). Most vCJD cases outside of the UK have been attributed to exposure to BSE-infected beef products locally or in the UK. Three confirmed cases with neurological disease and one asymptomatic case positive for PrP^{TSE} in lymphoid tissue related to transfusion of non-leukoreduced red cell concentrates from donors who later developed vCJD were reported in the UK. One hemophiliac patient who received multiple treatments with plasma-derived concentrates and showed no signs of neurological disease at death tested positive for PrP^{TSE} in the spleen.
- The average age at onset of vCJD is 28 years (range: 12–74 years) in contrast to CJD which develops in the late sixties. The increased prevalence of vCJD in teenagers and young adults relative to older age groups remains an enigma.
- Human PrP is encoded by a gene (*PRNP*) located on short arm of chromosome 20. A common polymorphism at PRNP codon 129 encoding methionine (Met) or valine (Val) influences the susceptibility to vCJD. All patients with vCJD are homozygous for Met. However, carriers of both alleles can

be infected: two cases identified with subclinical disease were heterozygous Met/Val carriers, one received vCJD-implicated blood transfusion and one received vCJD-implicated plasma-derived products.

- It is postulated that vCJD resulted from the transmission of BSE to humans. BSE has an incubation time of approximately 5 years and is apparently caused by the feeding of ruminant-derived MBM to cattle. The MBM was prepared from the offals of sheep, cattle, pigs and chickens. Changes in the rendering of offals in the late 1970s may have allowed prions to persist and initiate the epidemic. In 1988, the process of feeding ruminant-derived protein to ruminants was banned, and the bovine epidemic waned.

Common Human Exposure Routes:

- Consumption of beef products contaminated with neural tissue from cattle infected with BSE prions

Likelihood of Secondary Transmission:

- Tissue implants and ineffectively sterilized instruments may pose a risk of secondary transmission due to higher prevalence and titer of prions in lymphoreticular tissues.
- Non-leukoreduced RBCs have transmitted vCJD.
- In a single case, plasma derivatives might have been implicated.

At-Risk Populations:

- Individuals who ingest beef products (containing neural tissue) from animals infected with BSE
 - A CDC survey that inquired about travel to 9 BSE endemic countries by US residents since 1980 found that 29.5% had done so, with 19.4% visiting the UK for a median of 14 days.
- Individuals who have received blood transfusions in the UK and France, where asymptomatic infection with the vCJD agent may be present in the donor populations, are currently deferred from blood donation in the US.
- Individuals who are exposed to surgical instruments previously used on patients with vCJD
- Genetic predisposition: all vCJD patients studied to date (dietary and transfusion exposures) have been homozygous for Met at codon 129. Two asymptomatic individuals MV heterozygous at codon 129 have been identified as being positive for PrP^{TSE} in lymphoreticular tissue but not in the brain. One received non-leukoreduced RBCs and another received multiple treatments with plasma-derived factor VIII concentrates.

Vector and Reservoir Involved:

- No vector
- Humans and cattle serve as a reservoir.

Blood Phase:

- Identified in experimentally infected animal models prior to development of clinical disease

- Unlike sporadic CJD, there is widespread infectivity and deposition of PrP^{TSE} in lymphoreticular tissues, such as tonsils, spleen, and lymph nodes; lymphocytes traffic freely between blood and lymphoid tissues, probably contributing to the observed infectivity of blood.

Survival/Persistence in Blood Products:

- Unknown, but likely will survive for entire storage period by extension from known physicochemical properties of prions.

Transmission by Blood Transfusion:

- Transfusion transmission in experimental sheep model:
 - Documented for BSE (36% of BSE-exposed recipients) and for scrapie (43%). The majority of transmissions in the scrapie model resulted from blood collected from donor sheep during the late pre-clinical or clinical phase of infection (>50% of the estimated incubation period).
 - All non-leukoreduced components (i.e., red cell concentrates, plasma, buffy coats and platelet concentrates prepared according to standard blood bank methods) including whole blood from healthy BSE-infected sheep were capable of transmitting TSE infection and clinical disease in transfused recipient sheep following a single transfusion. Transmission occurred from blood collected early in pre-clinical phase. Leukoreduction of blood components in paired studies did not prevent disease transmission and in nearly all cases, little or no difference in the incubation period was observed in paired red cell and plasma recipient sheep. Of note, there was a 700-day delay in the incubation period of non-leukoreduced versus leukoreduced platelets. Rates of transmissions were: 37.5% for whole blood, 32.4% for buffy coats, 24.3% for platelets, 18.9% for red cells and 13.2% for plasma.
- Transfusion transmission to humans:
 - Documented transfusion transmission to four recipients of non-leukoreduced RBCs; three recipients developed vCJD. One recipient died from non-neurological disease but had PrP^{TSE} in spleen and lymph node. These were part of an ongoing study of 66 recipients followed after receiving labile blood components from 18 donors who subsequently developed vCJD. The four recipients represent 12.5% of the recipients surviving longer than 5 years.
 - The three recipients who developed vCJD died 6.5, 7.8 and 8.3 years following transfusion of implicated non-leukoreduced RBCs.
 - These four cases received blood components from three asymptomatic donors who subsequently developed clinical vCJD between 17 and 42 months after donation.
- An elderly hemophiliac in the UK was found to have PrP^{TSE} in his spleen at postmortem after death unrelated to vCJD.

This is the first time that abnormal prion protein has been found in a patient with hemophilia, or in any patient treated with plasma derivatives. The patient received almost 400,000 IU of Factor VIII lifetime, with 9000 IU of Factor VIII from two plasma pools that contained donations from a UK donor who went on to develop vCJD 6 months after donating the plasma in 1996. The hemophilia patient had no signs or symptoms of vCJD or other neurological disease at the time of death 11 years and 1 month after receiving the implicated factor VIII. The patient had, in addition, received 14 units of RBCs, had a large number of endoscopic procedures (including 5 with biopsies) and potential dietary exposure. A formal risk assessment by the UK Department of Health concluded that factor VIII exposure was the most likely source of vCJD infection, but the probability that exposure occurred from unimplicated lots was greater than from the lots to which the implicated donor had contributed.

Cases/Frequency in Population:

- Between January 1995 and October 2011, 176 cases (3 alive) of vCJD were reported in the UK.
- Elsewhere, there have been reports of 25 cases in France, five in Spain, four in Ireland, three in the US (two patients were long-time UK residents and one was a resident of Saudi Arabia), three in the Netherlands, two each in Portugal, Italy and Canada (one had a cumulative residence of more than 6 months in the UK and one was a resident of Saudi Arabia), and one each in Japan (resided in the UK for 24 days during 1980-1996), Saudi Arabia and Taiwan (cumulative residence of more than 6 months in the UK). A total of seven non-UK cases had a cumulative residence of greater than 6 months in the UK during 1980-1996.
- Screening of tonsils and appendix samples suggests there could be 4000 people in the UK who harbor the vCJD prion.
- Updated data are available at <http://www.cjd.ed.ac.uk/vcjdworld.htm>

Incubation Period:

- Unknown, but estimated at 5-15 years; one study cites the mean incubation period at 16.7 years, with a lower 95% confidence interval of 12.4 years. In transfusion-associated cases, the time between the implicated transfusion and appearance of symptoms has varied from 5 to 8 years.

Likelihood of Clinical Disease:

- Unknown but hypothesized to be high
- Precise estimates are not possible because presymptomatic infection is not readily detectable.

Primary Disease Symptoms:

- vCJD is an invariably fatal disease manifesting with psychiatric syndromes (withdrawal, anxiety, insomnia, and loss of interest); the neurologic deficits (memory loss, paresthesias, sensory deficits, dysarthria, ataxia, and myoclonus) not appearing until about 4 months later.

- Median duration of illness was previously reported at 14 months (range: 6.5-40 months); however; at present, the longest survivor died at 114 months after the disease onset.

Severity of Clinical Disease:

- High (progressive, invariably fatal)

Mortality:

- 100% for symptomatic disease

Chronic Carriage:

- Lengthy incubation period; infectious agent presumed present throughout, but not necessarily in blood at all times

Treatment Available/Efficacious:

- No treatments exist that can halt or reverse the neurodegenerative disease.

Agent-Specific Screening Question(s):

- Several current questions are required by FDA and AABB Standards. These are based on epidemiologic risks for potential exposure to vCJD infection.
 - Residence in the UK for 3 months or more from 1980 through 1996
 - Members of the US military, civilian military employees, and their dependents stationed in the rest of Europe during time intervals chosen based on the estimated intensity of exposure to UK beef products
 - Five years in the rest of Europe since 1980
 - Transfusion since 1980 in UK or France
- Following identification of three cases related to long-term residence in Saudi Arabia, the FDA is considering a deferral policy similar to what is currently in place for travel/residence in Europe or military assignments to bases other than Northern Europe.
 - “Six months or more cumulatively in Saudi Arabia as US military personnel from the beginning of 1980 through the end of 1996, or otherwise spent more than five years cumulatively in Saudi Arabia from the beginning of 1980 through the end of 1996” was presented to the Transmissible Spongiform Encephalopathies Advisory Committee for discussion in August, 2011 and the TSEAC supported the proposal.
 - Although the FDA has not taken action on this consideration, at the time of this update, the Armed Services Blood Program announced a decision to begin phasing in an assessment of military blood donors for vCJD risks associated with time spent in Saudi Arabia.

Laboratory Test(s) Available:

- No FDA-licensed blood donor screening test exists.
- No validated or FDA-approved test is available to detect presymptomatic or symptomatic infection. A research whole blood test has been developed that differentiates

vCJD-infected individuals from healthy individuals or those with non-vCJD neurodegenerative disorders. PrP^{Sc} in whole blood is absorbed and concentrated on stainless steel particles (solid-state binding matrix), detected with a PrP-specific antibody and detected by chemiluminescence. Sensitivity was 71.4% (95% CI 47.8-88.7%) by the detection of 15 of 21 vCJD patient samples. Specificity was 100% (97.8-100%) by testing 169 samples including 27 with sCJD, 42 with other neurological diseases and 100 healthy controls.

Currently Recommended Donor Deferral Period:

- Permanent per FDA Guidance and AABB Standard

Impact on Blood Availability:

- Agent-specific screening question(s): The FDA estimated that 3% of the US donor base would be deferred for residence and travel to UK; one subsequent study predicted a donor loss of 3-13% in five diverse geographic regions. The travel deferrals are cumulative; that is, currently acceptable donors will be added continuously to the deferral list if they have been transfused in the UK or France or they pass a threshold for duration of residence in non-UK countries where control of the food chain is not yet considered to be adequate.
- Laboratory test(s) available: The impact of testing is not known, but preliminary surveys suggest that such a test would have major impact on availability in the UK because of the reluctance of asymptomatic donors to be tested for a lethal disease that lacks effective interventions.

Impact on Blood Safety:

- Agent-specific screening question(s): Unknown; the FDA estimated a removal of 90% of person-days of potential exposure to BSE (time spent in UK) from the donor population.
- Laboratory test(s) available: Not applicable

Leukoreduction Efficacy:

- Leukoreduction was introduced as a potential control measure for vCJD in the UK in 1999 due to preliminary data supporting infection of lymphocytes. Subsequently, in hamster scrapie models, a 42-72% reduction in prion content (two different studies) was observed. Recently, in a BSE-sheep model, leukoreduction of blood components did not prevent disease transmission.

Pathogen Reduction Efficacy for Plasma Derivatives:

- Inactivation data are not available; highly significant dilution and/or partitioning of infectivity away from final derivatives by fractionation process suggested in animal models.
- The FDA does not require recall of pooled plasma or final products on inadvertent inclusion of plasma from an at-risk donor.
- Excluding the one suspect hemophiliac case mentioned, there is no epidemiologic evidence of transmission of

vCJD or of other human prion diseases by pooled plasma derivatives.

- Nanofiltration is effective in model systems.

Other Prevention Measures:

- Affinity-based prion removal filters (for RBC products) under development; primarily considered for BSE/vCJD, but should be efficacious for other human TSEs if they are transmissible via this route.

Suggested Reading:

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