

Variant Creutzfeldt–Jakob Disease (vCJD)

Disease Agent:

- Variant Creutzfeldt–Jakob disease prion (vCJD prion)

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 considered members of the transmissible spongiform encephalopathy (TSE) group of agents that include kuru, Creutzfeldt–Jakob Disease (CJD), and variant CJD (vCJD); CJD is discussed in a separate fact sheet. Prion diseases are either sporadic, inherited, or infectious. Prions are the agent, whether heritable through a germline mutation in the human gene, *PRNP*, or infectious.
- Prions are infectious proteins that are devoid of nucleic acid that result in certain disorders through binding and accumulation of the abnormal disease-causing prion isoform to the normal prion protein.
- Mammalian prions replicate by recruiting the normal cellular isoform of the prion protein PrP^C to form a disease-causing isoform designated PrP^{Sc}. PrP^{Sc} or PrP^{res} are the designations for the pathogenic forms and are used interchangeably in the literature.
- Prions are nonimmunogenic because of the sharing of epitopes with the normal cellular isoform.
- PrP^C is soluble and circulates in plasma, is also present on many cell membranes, and has a molecular weight of about 33–35 kDa.
- PrP^{Sc} has a more restricted tissue range than does PrP^C.
- Prion diseases represent disorders of protein conformation in which the tertiary structure of the precursor protein is profoundly altered. The transition occurs when the α helical protein of PrP^C changes into a β -sheet-rich molecule of PrP^{Sc}. PrP^{Sc} or PrP^{res} is folded into a form containing 50% β sheet and is resistant to proteases (proteinase K, lysosomal enzymes).
- PrP^{Sc} can form aggregates that precipitate as amyloid plaques in the CNS; these are a histopathological hallmark of the transmissible spongiform encephalopathies.
- Physicochemical properties: Resistance of prions to commonly used disinfectants (formaldehyde, glutaraldehyde, ethanol, and iodine) is well recognized. Immersion in undiluted bleach (60,000 ppm or mg/L of available chlorine) for 1 hour is only partially effective. Prions are resistant to ultraviolet light and ionizing radiation, ultrasonication, nucleases, boiling, and heat. High concentrations of NaOH (1–2 N) and prolonged autoclaving (1–5 h) at high temperatures (120–135°C) 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 occurred in UK in 1994; recognized as a distinct disease in 1996
- As of Oct 2008, 206 cases and 203 deaths worldwide. Most have occurred in the UK or after alleged dietary exposure to exported UK beef products elsewhere.
- The average age of vCJD patients is 26 years (range: 12–74 years) in contrast to CJD. 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 chromosome 20. A methionine/valine polymorphism at codon 129 appears to influence the expression of vCJD because all patients with vCJD are homozygous for methionine.
- It is postulated that vCJD resulted from the transmission of bovine spongiform encephalopathy (BSE) to humans. BSE has an incubation time of approximately 5 years and is apparently caused by the feeding of meat and bone meal (MBM) to dairy cows. The MBM was prepared from the offal of sheep, cattle, pigs, and chickens. Changes in the rendering of offal in the late 1970s may have permitted prions to survive this process and initiate the epidemic. In 1988, the process of feeding offal to cattle was banned, leading to a waning of the bovine epidemic.

Common Human Exposure Routes:

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

Likelihood of Secondary Transmission:

- By analogy with CJD, tissues and surgical instruments may pose a risk of secondary transmission.
- Blood has been demonstrated to transmit the vCJD prion.

At-Risk Populations:

- Individuals who ingest beef products (containing neural tissue) from animals infected with BSE

- Individuals who receive blood transfusions in areas considered at increased risk of vCJD (i.e., UK and France)
- 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 methionine on codon 129 of PrP except for one transfused patient who remained asymptomatic. This patient was heterozygous (methionine/valine) on codon 129 of PrP and died of a nonneurologic disease with no clinical evidence of vCJD. vCJD prions were found in the spleen and a cervical lymph node but not in the brain of this patient.

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 CJD in humans, there is widespread replication of the prion protein and deposition of PrP^{Sc} 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:

- Documented experimentally in sheep for BSE (36% of exposed recipients). Transmissions occurred from donor animals at 50% of the estimated incubation period. Also documented for scrapie (43%) in the same experimental system.
- Relatively high rates of transmission by blood transfusion in humans:
 - Documented transfusion transmission to four recipients of nonleukoreduced RBCs; three had disease while one had prions in tissue, but no disease. 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 showed symptoms at 6.3-8.5 years.

- These four cases arose 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 evidence of infection with the vCJD prion, only in his spleen, at postmortem; the cause of death was unrelated to vCJD. The hemophilia patient was treated in the 1990s with several batches of UK-sourced clotting factors including one batch of factor VIII that was manufactured using plasma from a 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 batch. This is the first time that vCJD abnormal prion protein has been found in a patient with hemophilia, or in any patient treated with plasma products.

Cases/Frequency in Population:

- Between January 1995 and February 2009, 168 cases of vCJD were reported in the UK.
- Elsewhere, there have been reports of 23 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 in Portugal, and one each in Canada, Italy, Japan, and Saudi Arabia.
- 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 process manifested as psychiatric syndromes (withdrawal, anxiety, insomnia, and loss of interest), with neurologic deficits (memory loss, paresthesias, sensory deficits, dysarthria, ataxia, and myoclonus) not appearing until about 4 months later.

- Median duration of illness is 13 months (range: 6-69 months)

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, their dependents, and civilian military employees stationed in the rest of Europe with the time intervals 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

Laboratory Test(s) Available:

- No FDA-licensed blood donor screening test exists.
- No well-characterized test available to detect pre-symptomatic or symptomatic infection

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, current donors are continuously added to the deferral list as they accumulate time of residence in the implicated countries.
- 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 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:

- In animal models, a 42-72% reduction in prion content (two different studies) was observed; however, the impact of leukoreduction on vCJD transfusion transmission is speculative. Leukoreduction was introduced as a potential control measure in the UK in 1999.

Pathogen Reduction Efficacy for Plasma Derivatives:

- Inactivation data 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 classical human TSEs 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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