3 | VARIANT CREUTZFELDT–JAKOB DISEASE (vCJD)

3.1 | Disease agent

- Prion agent causing vCJD.

3.2 | 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 proteinaceous infectious agents causing transmissible spongiform encephalopathies (TSE). This includes a group of neurodegenerative diseases that include kuru, sporadic Creutzfeldt–Jakob Disease (sCJD), variant CJD (vCJD), Gerstmann-Sträussler-Scheinker syndrome (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 sCJD is unknown. 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 are devoid of detectable nucleic acid.
- Mammalian prions replicate by recruiting the normal cellular prion protein PrP^{C} to form a disease-causing isoform. PrP^{Sc} (Sc is an abbreviation for scrapie) or PrP^{res} abbreviation for misfolded core PrP 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) as well as to physical and chemical denaturing agents.
- 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 leaflet of the plasma membrane through a glycosylphosphatidylinositol anchor. It is present on a variety of cells but also circulates in plasma and has a molecular weight of about 35–36 kDa.
- PrP^{TSE} has a more restricted tissue range than does PrP^{C}; mainly in the central nervous system (CNS)
- PrP^{TSE} forms aggregates that precipitate as diffuse accumulations or as amyloid plaques in the CNS; these are a histopathological hallmark of the TSEs. So called "florid" plaques (amyloid plaques surrounded by a crown of vacuoles in brain tissue) are a typical feature of vCJD. Generally, PrP^{TSE} is identified in the form of PrP^{res} using immunohistological and immunochemical techniques, or by immunoblotting after the treatment of tissues with proteinase K.
- vCJD prions are transmissible to susceptible experimental animals, specifically to nonhuman primates, mice, and guinea pigs.
- Propagation of vCJD in cell culture has been accomplished using iPSC-derived astrocytes.
- Physicochemical properties: Resistance of prions to commonly used disinfectants such as 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 h can be partially effective. High concentrations of NaOH (1–2 N) or heat in a gravity displacement autoclave at 121°C or higher or in a porous load autoclave at 134°C for 1 h are advocated for disinfection.

3.3 | Disease name

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

3.4 | Priority level

- Safety/epidemiologic evidence regarding blood safety: Very 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 United Kingdom.
- Public perception and/or regulatory concern regarding blood safety: Low and declining with FDA removing most remaining donor deferrals in May 2022.
- Public concern regarding disease agent: Low.

3.5 | Background

- Emergent; first case identified in United Kingdom in 1994; recognized as a distinct disease in 1996.
- As of April 2021, there have been 232 cases reported worldwide with 178 cases in the United Kingdom.

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 United Kingdom. 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 United Kingdom. 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 sCJD 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^{C} is encoded by a gene (*PRNP*) located on the 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 a vCJD-implicated blood transfusion and one received vCJD-implicated-plasma-derived products.
- It is postulated that vCJD originated from the transmission of BSE to humans. BSE has an incubation time of approximately 5 years and was apparently caused by the feeding of ruminant derived MBM to cattle. 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 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.

3.6 | Common human exposure routes

- Consumption of beef products contaminated with tissue(s) from cattle infected with BSE prions

3.7 | Likelihood of secondary transmission

- Tissue implants and ineffectively sterilized instruments may pose a risk of iatrogenic 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.

3.8 | At-risk populations

- Individuals who ingest beef products from animals infected with BSE are at risk. 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 are exposed to surgical instruments previously used on patients with vCJD remain at risk.
- Genetic predisposition: most vCJD patients studied to date who have dietary and transfusion exposures have been homozygous for Met at codon 129. The most recent vCJD case in the United Kingdom was Met/Val heterozygous at codon 129 of the *PRNP* gene. Prior to that, two asymptomatic individuals, Met/Val heterozygous at codon 129, were 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.

3.9 | Vector and reservoir involved

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

3.10 | Blood phase

- Identified in experimentally infected animal models prior to development of clinical disease.
- Infectivity has been demonstrated in erythrocytes, leukocytes, and plasma.
- Unlike sCJD, 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.

3.11 | Survival/persistence in blood products

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

3.12 | 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 preclinical 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 the preclinical 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 PrP^{TSE} was discovered in spleen and lymph nodes upon autopsy. 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 United Kingdom 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 was 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 9,000 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 five 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.

3.13 | Cases/frequency in population

- Between January 1995 and April 2021, 178 cases (0 alive) of vCJD were reported in the United Kingdom. The last reported case was in 2016 with onset in 2014.
- Elsewhere, there have been reports of 28 cases in France, five in Spain, four each in Ireland and the US (for the US cases, two were long-time UK residents, one was a resident of Saudi Arabia, and the fourth was a case who was infected prior to moving to the US), three each in the Netherlands and Italy, two each in Portugal and Canada (for the Canadian cases, one had a cumulative residence of more than 6 months in the United Kingdom and one was a resident of Saudi Arabia), and one each in Japan (resided in the United Kingdom for 24 days during 1980–1996), Saudi Arabia and Taiwan (cumulative residence of more than 6 months in the United Kingdom). A total of seven non-UK cases had a cumulative residence of greater than 6 months in the United Kingdom during 1980–1996.
- Screening of tonsils and appendix samples suggest there could be 1 in 4,000 people (250 per million) in the United Kingdom who harbor the vCJD prion. In the absence of controls, the relevance of this finding is unclear.
- Updated data are available at http://www.cjd.ed.ac.uk/sites/default/files/worldfigs.pdf

3.14 | 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.

3.15 | Likelihood of clinical disease

- Unknown.
- Precise estimates are not possible because presymptomatic infection is not readily detectable.

3.16 | 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 13–14 months (range: 6.5–40 months); however; at present, the longest survivor died at 114 months after disease onset.

3.17 | Severity of clinical disease

- High (progressive, invariably fatal)

3.18 | Mortality

- 100% for symptomatic disease

3.19 | Chronic carriage

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

3.20 | Treatment available/efficacious

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

3.21 | Agent-specific screening question(s)

- Questions about donor risks for exposure to BSE/vCJD have been required by FDA and AABB Standards.
- However, as of May 2022, according to revised FDA guidance, only a donor's diagnosis of vCJD (or another TSE) require deferral. All geographic vCJD deferrals, including those for transfusion in high-risk areas (the United Kingdom and France) have been rescinded, and many donors previously deferred under older guidances are eligible for reentry if they meet all other donor criteria.
- As of May 2022, permanent deferral is required only for a diagnosis of vCJD or another TSE.

3.22 | 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.
- Additionally, one report of using the protein misfolding cyclic amplification (PMCA) technique has shown that this method is successful and PrP^{TSE} can be detected with 100% sensitivity and specificity in a sample of 14 vCJD and 153 controls.

3.23 | Currently recommended donor deferral period

- As of May 2022, permanent deferral is required per FDA Guidance for a diagnosis of vCJD (or another TSE).

3.24 | Impact on blood availability

- Agent-specific screening question(s): Previously, the FDA estimated that 3% of the US donor base would be deferred for residence and travel to the UK; however, current FDA recommendations have mitigated the impact on blood availability.

3.25 | Laboratory test(s) available: None

- The impact of a hypothetical test is not known, but preliminary surveys suggested that testing would have a major impact on availability since asymptomatic

donors would be reluctant to be tested for a lethal disease that lacks effective interventions.

3.26 | Impact on blood safety

- Agent-specific screening question(s): Unknown; FDA's original modeling estimated a 90% risk reduction (as measured in person-days of potential exposure to BSE).

3.27 | Leukoreduction efficacy

- Leukoreduction was introduced as a control measure for vCJD in the United Kingdom 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.
- In a BSE-sheep model, leukoreduction of blood components did not prevent disease transmission.

3.28 | Pathogen reduction efficacy for plasma derivatives

- Inactivation data are not available; highly significant dilution and/or partitioning of infectivity away from the final derivatives by the fractionation process was observed 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.

3.29 | Other prevention measures

- None is currently effective.

SUGGESTED READING

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