2 | HUMAN PRION DISEASES (OTHER THAN vCJD)

2.1 | Disease agent

- Human prion proteins

2.2 | 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): a group of neurodegenerative diseases that include kuru, sporadic Creutzfeldt–Jakob Disease (sCJD), variant CJD (vCJD; discussed in a separate fact sheet), Gerstmann-Sträussler-Scheinker syndrome (GSS) and fatal familial insomnia (FFI). 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 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. PrP^{Sc} (Sc is an abbreviation for scrapie), 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 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).
- PrPTSE forms aggregates that precipitate as diffuse accumulations or as amyloid plaques in the CNS; these are a histopathological hallmark of the TSEs. Generally, PrP^{TSE} is identified in the form of PrP^{res} using immunohistological and immunochemical techniques, or by immunoblotting after the treatment of tissues by proteinase K.
- Human prion diseases are transmissible to susceptible experimental animals: sCJD mainly to primates, bank voles, guinea pigs and genetically engineered mice.
- Propagation of sCJD in cell culture has been accomplished using iPSC-derived astrocytes.
- 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 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.

2.3 | Disease names

Human transmissible spongiform encephalopathies (TSEs) include:

- CJD
  - Variant CJD (see separate sheet)
  - Sporadic CJD (sCJD)
  - Familial CJD (fCJD)
- Gerstmann-Sträussler-Scheinker syndrome (GSS)
- Fatal familial insomnia (FFI)
- Kuru

2.4 | Priority level

- Scientific/epidemiologic evidence regarding blood safety: Theoretical; a number of epidemiologic studies do not demonstrate transfusion transmission of sCJD or fCJD to humans.
- Public perception and/or regulatory concern regarding blood safety: Very low.
- Public concerns regarding disease agent: Absent.

2.5 | Background

- Human PrP^{C} is encoded by a gene (*PRNP*) located on the short arm of chromosome 20.
- Sporadic CJD has been recognized since the 1920s, with a stable incidence in the population at about one

case per million population per year. The causative mechanism of sCJD is unknown. A common polymorphism at *PRNP* codon 129 encoding methionine (Met) or valine (Val) influences the susceptibility to sCJD. Most Caucasians with sCJD are homozygous carriers of Met-encoding allele. However, homozygous carriers of Val-encoding allele or heterozygous carriers of both alleles are also known to develop sCJD.

- Iatrogenic CJD results from infection through prion-contaminated human growth hormone or gonadotropin and transplantation of dura mater or cornea from patients who died of sCJD. It also occurs following neurosurgical procedures: this happened when brain penetrating electrodes or neurosurgical instruments used on sCJD patients were not effectively sterilized and then reused on subsequent patients.
- Familial CJD results from multiple variations of insertion mutations and point mutations of the *PRNP* gene.

2.6 | Common human exposure routes

- Sporadic: 85% of cases
- Familial: 10%–15% of cases
- Iatrogenic: Majority of cases are related to dura mater transplants and treatments with human pituitary-derived growth hormone. A few cases developed after treatments with human pituitary-derived gonadotropin, corneal transplants and after neurosurgery where instruments were contaminated by prior use on TSE patients
- Kuru: Historic interest as it was associated with ritual cannibalism in Papua New Guinea

2.7 | Likelihood of secondary transmission

- Transmission by surgical instruments and tissue implants, and pituitary hormones

2.8 | At-risk populations

- Those with known genetic susceptibility
- Those exposed to ineffectively sterilized surgical instruments during neurosurgery (e.g., intraoperative EEG electrodes) or who received a contaminated dura mater transplant or cornea or who received injections of human pituitary growth hormone derived from deceased infected donors

2.9 | Vector and reservoir involved

- Human reservoir
- Ineffectively sterilized surgical instruments, intraoperative EEG electrodes, tissue implants, and human-tissue–derived hormones

2.10 | Blood phase

- Identified in some experimentally infected animal models prior to clinical disease
- Not specifically identified in humans

2.11 | Survival/persistence in blood products

- Unknown: probably stable if present

2.12 | Transmission by blood transfusion

- Demonstrated in animal models (other than sCJD: hamsters, mice, sheep, deer).
- Transfusion transmission in humans of TSE, other than vCJD, has not been demonstrated despite multiple epidemiological studies.
  - In three studies from the United States, United Kingdom, and Scandinavia (SCANDAT), no cases of CJD were observed among 2,316 recipients of blood components from donors subsequently diagnosed with sCJD, as of December 31, 2020. These recipients represent over 15,221 person-years of follow-up.
    - Among them are 1,780 deceased recipients, none of whom had a cause of death of CJD
    - Using the SCANDAT database, over 2 million blood recipients from Denmark and Sweden were studied. Of these, 883 patients had received blood from donors who subsequently developed CJD. None of the recipients developed CJD in 7,617 person-years of observation.
    - In the United Kingdom study, 29 sCJD blood donors, of 370 reported to May 31, 2015, had products transfused to 211 recipients. Five of these recipients were reported to have died from dementia but were not believed to be cases of CJD.
    - In the United States study, a total of 411 recipients survived 5 years or longer following transfusion: they include 143 recipients (77 alive and 66 deceased) who received blood components donated by the donors 60 months or less prior to the onset of CJD.

- No cases of CJD have been observed following autopsies of hemophilia patients over the past 20 years.

2.13 | Cases/frequency in population

- Global incidence is 1–1.5 cases per million population per year. Risk increases with age.
- Prevalence is unknown but may be at least 10-fold higher, considering the very long presumed incubation period.
- In the United States, about 1.2–3 deaths per 1,000,000 persons

2.14 | Incubation period

- Unknown in sporadic cases.
- Incubation periods for iatrogenic CJD secondary to human pituitary-derived growth hormone range between 5 and 42 years (from midpoint of hormone treatment); 47 years from start of hormone therapy being similar to what was seen with kuru.

2.15 | Likelihood of clinical disease

- Unknown in sCJD as presymptomatic infection is not readily detectable; high in familial and iatrogenic diseases

2.16 | Primary disease symptoms

- Neurodegenerative disease (behavioral changes, dementia, ataxia, progressive sleep disorder in case of FFI)

2.17 | Severity of clinical disease

- High (progressive, invariably fatal)

2.18 | Mortality

- 100% for symptomatic disease

2.19 | Chronic carriage

- Lengthy incubation period for many years; abnormal prions presumed present throughout, but not necessarily in the blood

2.20 | Treatment available/efficacious

- The few proposed treatments have not been effective in halting or reversing the neurodegenerative disease

2.21 | Agent-specific screening question(s)

- FDA Guidance (as of May 2022) provides for several deferrals, largely based on information spontaneously provided by the donor rather than specific required questions.
  - Diagnosis of CJD or any other TSE leads to permanent deferral, with quarantine and retrieval of in-date products based on post-donation information. No specific donor question is required, but these deferrals apply when the information is provided spontaneously by a donor).
  - No specific question is required for receipt of human growth hormone (cadaveric pituitary, available in the United States from 1958 to 1985). If information is volunteered, the donor is permanently deferred.
  - No question is required regarding a blood relative with CJD. However, potential donors who volunteer that they have blood relatives with familial prion disease (fCJD, GSS, or FFI) should be permanently deferred. Quarantine and retrieval of products based on post-donation information is recommended.
  - Donors who have received a human allograft of dura mater, which remains available in the United States, are permanently deferred. A specific question is required with quarantine and retrieval of in-date products based on post-donation information.

2.22 | Laboratory test(s) available

- No FDA-licensed blood donor screening test exists
- No readily accessible presymptomatic test is available
- Genetic tests to detect pathogenic mutations that are indicative of heritable disease may be performed in a limited number of research laboratories

2.23 | Currently recommended donor deferral period

- Permanent per FDA Guidance and AABB Standard

2.24 | Impact on blood availability

- Agent-specific screening question(s): Minimal
- Laboratory test(s) available: Not applicable

2.25 | Impact on blood safety

- Agent-specific screening question(s): Unknown
- Laboratory test(s) available: Not applicable

2.26 | Leukoreduction efficacy

- Leukoreduction was introduced as a potential 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. Recently, in a BSE-sheep model, leukoreduction of blood components did not prevent disease transmission.

2.27 | Pathogen reduction efficacy for plasma derivatives

- Inactivation data are not available for human plasma. 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 upon inadvertent inclusion of plasma from an at-risk donor.
- To date, there is no epidemiologic evidence of transmission of sCJD by pooled plasma derivatives.
- Nanofiltration is effective in model systems.

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