

Classical Creutzfeldt–Jakob Disease (CJD) Human Prion Diseases (Other Than vCJD)

Disease Agent:

- Human prion proteins

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; 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 as a result 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 Names:

- Sporadic CJD, classical CJD
- Infectious CJD (kuru and iatrogenic CJD)
- Familial or heritable CJD (Gerstmann–Sträussler–Scheinker syndrome or GSS; familial CJD; fatal familial insomnia or FFI)

Priority Level:

- Scientific/Epidemiologic evidence regarding blood safety: Theoretical; after extensive study, transfusion-transmission to humans has not been demonstrated despite proven risk from human tissue (e.g., dura mater, pituitary growth hormone)
- Public perception and/or regulatory concern regarding blood safety: Very low
- Public concerns regarding disease agent: Absent

Background:

- Human PrP is encoded by a gene (*PRNP*) located on chromosome 20.
- Sporadic CJD (sCJD) has been recognized since the 1920s, with a stable incidence in the population at about one case per million population per year. The mechanism of sCJD is unknown. A methionine/valine polymorphism at PRNP codon 129 influences the expression of Creutzfeldt–Jakob disease (CJD) prion proteins because most Caucasians with sporadic CJD are homozygous for methionine or valine at codon 129.
- Iatrogenic CJD (iCJD) results from prion-contaminated human growth hormone or gonadotropin, from dura mater grafts, or from corneal transplants from patients who died of CJD. It also occurs following neurosurgical procedures in which penetrating electrodes or instruments contaminated by contact with affected tissues were ineffectively sterilized and reused on subsequent patients.
- Familial CJD (fCJD) results from mutations of the PrP gene. At least five mutations are genetically linked to disease in humans. These inherited prion proteins are infectious and have been transmitted to experimental animals.

Common Human Exposure Routes:

- Sporadic: 85% of cases
- Familial: 10–15% of cases
- Iatrogenic: Neurosurgery, dura mater transplants, human pituitary-derived growth hormone (HGH), corneal transplants from people who died of CJD (extremely rare)

- Kuru: Historic interest as it was associated with cannibalism in Papua New Guinea

Likelihood of Secondary Transmission:

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

At-Risk Populations:

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

Vector and Reservoir Involved:

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

Blood Phase:

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

Survival/Persistence in Blood Products:

- Unknown

Transmission by Blood Transfusion:

- Demonstrated in animal model systems
- Transfusion transmission in humans has not been demonstrated despite multiple studies of this issue.
 - No cases of CJD have been observed among 436 recipients of blood components from 36 donors subsequently diagnosed with CJD (2096 person-years of observation) including 91 living recipients, 144 who survived 5 years or longer following transfusion, and 68 of whom received blood components 60 months or less prior to the onset of CJD in the donor.
 - No cases of CJD were observed following autopsies of hemophilia patients over the past 20 years.

Cases/Frequency in Population:

- Global incidence is one per million annually.
- Prevalence is unknown but is likely to be at least 10-fold higher, considering the very long presumed incubation period.

Incubation Period:

- Unknown in sporadic cases
- Incubation periods for iatrogenic CJD secondary to human pituitary-derived growth hormone are

between 4 and 38 years (median of 12 years) with the longest incubation periods of 20-30 years being similar to what was seen with kuru, although up to 0.4% of kuru cases had incubation periods of 40 years or more.

Likelihood of Clinical Disease:

- Unknown as presymptomatic infection not readily detectable

Primary Disease Symptoms:

- Neurodegenerative disease (dementia, ataxia, myoclonus, coma). In FFI, adults usually older than 50 years develop a progressive sleep disorder and die within 1 year.

Severity of Clinical Disease:

- High (progressive, invariably fatal)

Mortality:

- 100% for symptomatic disease

Chronic Carriage:

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

Treatment Available/Efficacious:

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

Agent-Specific Screening Question(s):

- Several current questions are required by FDA and AABB Standards:
 - Diagnosis of CJD or transmissible spongiform encephalopathy
 - Potential iatrogenic exposure (dura transplant, human pituitary growth hormone)
 - Familial history, unless shown free of susceptibility gene(s)

Laboratory Test(s) Available:

- No FDA-licensed blood donor screening test exists.
- No readily accessible presymptomatic test available

Currently Recommended Donor Deferral Period:

- Permanent per FDA Guidance and AABB Standard

Impact on Blood Availability:

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

Impact on Blood Safety:

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

Leukoreduction Efficacy:

- In animal models, 42-72% reduction in prion content (two different studies) was observed.

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 upon inadvertent inclusion of plasma from an at-risk donor.
- To date, there is no epidemiologic evidence of transmission of classical human TSEs (or vCJD) by pooled plasma derivatives.
- Nanofiltration is effective in model systems.

Other Prevention Measures:

- Affinity-based removal filters (for red blood cell 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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