

# Human Prion Diseases

## (Rare Disease of Public Health Significance)

### 1. DISEASE REPORTING

#### A. Purpose of Reporting and Surveillance

1. To monitor trends in the epidemiology of human prion diseases in Washington State.
2. To maximize laboratory confirmation of suspected cases and facilitate testing.
3. To promote awareness of available resources.
4. To detect the emergence of variant Creutzfeldt-Jakob Disease or novel prion diseases in the United States.
5. To prevent potential iatrogenic transmission.

#### B. Legal Reporting Requirements

1. Health care providers: notifiable to local health jurisdiction within 3 business days.
2. Health care facilities: notifiable to local health jurisdiction within 3 business days.
3. Laboratories: no requirements for reporting.
4. Local health jurisdictions: notifiable to the Washington State Department of Health (DOH) Communicable Disease Epidemiology Section (CDES) within 7 days of case investigation completion or summary information required within 21 days.

#### C. Local Health Jurisdiction Investigation Responsibilities

1. Encourage providers to discuss the role of autopsy in the diagnosis of prion disease with the patient's family.
2. Inform providers of the autopsy and laboratory services provided by the National Prion Disease Pathology Surveillance Center (NPDPSC).
3. Discuss the importance of appropriate infection control procedures if surgical procedures are being considered.
4. Report all *definite, probable, and possible* cases to CDES (see definitions below). Complete the case report form for Human Prion Disease ([www.doh.wa.gov/notify/forms/prion.pdf](http://www.doh.wa.gov/notify/forms/prion.pdf)) and fax the completed form to CDES.
5. Enter the data into the Public Health Issues Management System (PHIMS) as a Rare Disease of Public Health Significance.
6. Perform a more extensive investigation for suspect variant CJD, iatrogenic CJD, a novel prion disease, and suspected disease clusters.

## 2. THE DISEASE AND ITS EPIDEMIOLOGY

### Background

Prion diseases, also known as transmissible spongiform encephalopathies (TSEs), are a family of rare, fatal neurodegenerative diseases of animals and humans. These diseases have long incubation periods, and cause characteristic spongiform changes, neuronal loss, and gliosis without provoking an inflammatory reaction. Death usually occurs within a year after onset of illness.

Sporadic Creutzfeldt-Jakob disease (CJD) occurs worldwide and is the most common human prion disease (estimated incidence: 1–2 cases per million population per year). Variant CJD was recognized in the United Kingdom in the 1990's and is associated with consumption of cattle products contaminated with the agent causing bovine spongiform encephalopathy. Less common prion diseases include Gerstmann-Sträussler-Scheinker syndrome and fatal familial insomnia.

Animal prion diseases include bovine spongiform encephalopathy (BSE, “mad cow disease”) in cattle, scrapie in sheep, chronic wasting disease in deer and elk, and transmissible mink encephalopathy.

### A. Etiologic Agent

Prion diseases are thought to result from a change in conformation of normal prion proteins into an abnormal, pathologic form. The term prion is derived from the phrase “proteinaceous infectious particle.” Prions are resistant to routine physical and chemical sterilization measures.

### B. Description of Illness

Sporadic CJD is a fatal neurodegenerative disease that primarily occurs in people over 55 years of age. It usually begins with cognitive and behavioral changes (e.g., memory difficulties) and progresses to include physical neurologic abnormalities (e.g., myoclonus, ataxia, rigidity). Death is often caused by aspiration or sepsis and usually occurs within one year of onset.

Familial CJD results from inherited mutations in the prion protein gene. Compared to sporadic CJD, patients with familial CJD are generally younger and have a family history of prion disease.

In the 1990s, a new variant of CJD was recognized in the United Kingdom (UK). The pathology of variant CJD is strikingly similar to that of cattle with BSE. Consumption of BSE-infected cattle products is the likely mode of transmission. In contrast to sporadic CJD, variant CJD is characterized primarily by behavioral changes (e.g., psychosis, depression), painful sensory symptoms, a younger age of onset (teens, 20s), and a longer duration of illness (Table 1).

As of April 2010, more than 200 cases of variant CJD have been reported worldwide, mostly in the UK and Europe. Although three cases of variant CJD have been reported in the United States, all are thought to have been exposed to the disease outside of the United States.

**Table 1: Clinical and pathologic characteristics distinguishing variant and sporadic CJD**

Characteristic	vCJD	sCJD
Median age at death	28 years	68 years
Median duration of illness	13–14 months	4–5 months
Clinical signs and symptoms	Prominent psychiatric/behavioral symptoms; painful dysesthesia; delayed neurologic signs	Dementia; early neurologic signs
Periodic sharp waves on EEG	Absent	Often present
“Pulvinar sign” on MRI*	Present in >75%	Not reported
Presence of “florid plaques” on neuropathology	Present in large numbers	Rare or absent
Immunohistochemical analysis of brain tissue	Marked accumulation of PrP <sup>†</sup>	Variable accumulation
Presence of agent in lymphoid tissue	Readily detected	Not readily detected

\*An abnormal signal in the posterior thalami on T2- and diffusion-weighted images and fluid-attenuated inversion recovery sequences on brain MRI; in the appropriate clinical context, this signal is highly specific for vCJD.

† Protease-resistant prion protein

Source: Centers for Disease Control and Prevention. Creutzfeldt-Jakob disease not related to a common venue—New Jersey, 1995–2004. *MMWR* 2004;53(18):392–6. Adapted from Belay E, Schonberger L. Variant Creutzfeldt-Jakob disease and bovine spongiform encephalopathy. *Clin Lab Med* 2002;22:849.

### C. Human Prion Diseases in Washington State

Prior to 2005, surveillance for human prion diseases in Washington was primarily conducted by death certificate review. This surveillance method detected 3–9 clinical cases of CJD per year; however, less than half had a laboratory confirmed diagnosis. After implementation of initiatives to increase neuropathological analysis of brain tissue collected at autopsy in 2007–2008, 80% of CJD cases identified in Washington were laboratory confirmed.

### D. Reservoirs

It is unknown whether a reservoir exists for sporadic CJD.

### E. Modes of Transmission

The mode of transmission of sporadic CJD is not known. Approximately 5–15% of human prion disease is familial (i.e., inherited) and <1% is acquired through iatrogenic transmission or consumption of BSE-infected animal tissues. Rare cases of human prion disease have been acquired during medical procedures from contaminated human-derived pituitary hormones, dura mater grafts, corneal grafts or neurosurgical equipment.

Acquisition of variant CJD has been associated with consumption of tissue from cattle with BSE. Food protection measures have been implemented to prevent meat products from suspected or confirmed BSE-infected cattle from being sold for consumption.

Recent cases of variant CJD in the United Kingdom show that transmission of this disease can occur through blood transfusion. However, other human prion diseases are not known to be transmitted by transfusions. Prion diseases of humans are not transmitted through casual or intimate person-to-person contact.

### F. Incubation Period

The incubation period for the few prion diseases with known sources (i.e., variant CJD, iatrogenically-acquired prion disease) is variable and extremely long, on the order of years to decades.

### G. Period of Communicability

There is no evidence that prion disease is transmitted through casual or intimate person-to-person contact. However, in very rare circumstances, CJD has been acquired by contaminated neurosurgical instruments, transplanted dura mater and corneas, human-derived pituitary hormones, and transfused blood (for variant CJD only).

### H. Treatment

These diseases are invariably fatal. Supportive care is needed and medications may be used to control aggressive or agitated behaviors.

## 3. CASE DEFINITIONS

### A. Sporadic CJD\* (2011)

1. **Definite:** Diagnosed by standard neuropathological techniques; and/or immunocytochemically; and/or Western blot confirmed protease-resistant PrP; and /or presence of scrapie-associated fibrils.
2. **Probable:**
  - Rapidly progressive dementia; and
  - At least two out of the following four clinical features: 1) myoclonus, 2) visual or cerebellar signs, 3) pyramidal/extrapyramidal signs, or 4) akinetic mutism; and
  - A positive result on at least one of the following laboratory tests; and
    1. A typical EEG (periodic sharp wave complexes) during an illness of any duration;
    2. A positive 14-3-3 cerebrospinal fluid (CSF) assay in patients with a disease duration of less than 2 years; and/or
    3. Magnetic resonance imaging (MRI) high signal abnormalities in caudate nucleus and/or putamen on diffusion-weighted imaging (DWI) or fluid attenuated inversion recovery (FLAIR)
  - The absence of an alternative diagnosis after routine investigation.
3. **Possible:**
  - Progressive dementia; and
  - At least two out of the following four clinical features: 1) myoclonus, 2) visual or cerebellar signs, 3) pyramidal/extrapyramidal signs, or 4) akinetic mutism; and

- The absence of a positive result for any of the three laboratory tests that would classify a case as “probable” (see tests 1-3 above) AND
- Duration of illness less than two years AND
- The absence of an alternative diagnosis after routine investigation.

**B. Iatrogenic CJD\* (2011)**

Progressive cerebellar syndrome in a recipient of human cadaveric-derived pituitary hormone; or sporadic CJD with a recognized exposure risk, e.g., antecedent neurosurgery with dura mater implantation.

**C. Familial CJD\* (2011)**

Definite or probable CJD plus definite or probable CJD in a first degree relative; and/or Neuropsychiatric disorder plus disease-specific PrP gene mutation.

**D. Variant CJD (2003)**

- 1. Definite:** Neuropathologic examination of brain tissue is required to confirm a diagnosis of variant CJD. The following confirmatory features should be present.
  - a. Numerous widespread kuru-type amyloid plaques surrounded by vacuoles in both the cerebellum and cerebrum - florid plaques.
  - b. Spongiform change and extensive prion protein deposition shown by immunohistochemistry throughout the cerebellum and cerebrum.
- 2. Suspected:**
  - a. Current age or age at death <55 years (a brain autopsy is recommended, however, for all physician-diagnosed CJD cases).
  - b. Psychiatric symptoms at illness onset and/or persistent painful sensory symptoms (frank pain and/or dysesthesia).
  - c. Dementia, and development  $\geq 4$  months after illness onset of at least two of the following five neurologic signs: poor coordination, myoclonus, chorea, hyperreflexia, or visual signs. (If persistent painful sensory symptoms exist,  $\geq 4$  months delay in the development of the neurologic signs is not required).
  - d. A normal or an abnormal EEG, but not the diagnostic EEG changes often seen in classic CJD.
  - e. Duration of illness of over 6 months.
  - f. Routine investigations of the patient do not suggest an alternative, non-CJD diagnosis.
  - g. No history of receipt of cadaveric human pituitary growth hormone or a dura mater graft.
  - h. No history of CJD in a first degree relative or prion protein gene mutation in the patient.

**NOTE**

1. If a patient has the typical bilateral pulvinar high signal on MRI scan, a suspected diagnosis of variant CJD requires the presence of a progressive neuropsychiatric disorder, d, e, f and g of the above criteria, and four of the following five criteria: 1) early psychiatric symptoms (anxiety, apathy, delusions, depression, withdrawal); 2) persistent

painful sensory symptoms (frank pain and/or dysesthesia); 3) ataxia; 4) myoclonus or chorea or dystonia; and 5) dementia.

2. A history of possible exposure to bovine spongiform encephalopathy (BSE) such as residence or travel to a BSE-affected country after 1980 increases the index of suspicion for a variant CJD diagnosis.

\*These CDC diagnostic criteria for Creutzfeldt-Jakob Disease (2010) have been adapted from: 1) Global Surveillance, diagnosis, and Therapy of Human Transmissible spongiform Encephalopathies: Report of a WHO consultation, February 9-11, 1998, Geneva, Switzerland; and 1) Zerr I, Kallenberg K, Summers DM, et al. Brain 2009, 132; 2659-2668.

## 4. DIAGNOSIS AND LABORATORY SERVICES

### A. Diagnosis

**Confirmatory diagnosis of prion diseases requires laboratory examination of brain tissue.** The importance of autopsy and laboratory testing should be discussed with the patient's family. Arrangements for autopsy and laboratory testing can be made through the National Prion Disease Pathology Surveillance Center (NPDPS, see below). This national reference center provides state-of-the-art prion disease diagnostics, including histopathology, immunohistochemistry, Western blot, and genetic analysis to confirm and determine the type of prion disease. These services are offered free of charge.

**Antemortem indicators are not confirmatory.** Antemortem indicators that support but cannot confirm the diagnosis of CJD include certain findings on EEG and MRI (see Table 1) and elevated levels of 14-3-3 or tau protein in cerebral spinal fluid (CSF). Testing CSF for the protein markers 14-3-3 or tau may be helpful in patients exhibiting rapidly progressive dementia. However, these markers cannot confirm sporadic CJD, and sensitivity decreases as the illness progresses. The 14-3-3 immunoassay is not a screening test and should be used only when a diagnosis of CJD is strongly suspected. The NPDPS performs 14-3-3 and tau immunoassays free of charge.

### B. Services Available at DOH Public Health Laboratories (PHL)

PHL does not perform diagnostic testing for prion diseases. All specimens should be sent directly to the NPDPS.

### C. Specimen Collection

For details regarding the collection and shipment of clinical specimens, see the NPDPS website (<http://www.cjdsurveillance.com>) or call (216) 368-0587.

## 5. ROUTINE CASE INVESTIGATION

Cases of possible, probable, and definite prion disease are primarily identified from three sources: 1) reports from health care providers; 2) National Prion Disease Pathology Surveillance Center (NPDPS) lab reports; and 3) death certificates.

### A. Evaluate the Diagnosis

1. Determine the status (alive or deceased) of the patient. There is no need to interview the next of kin unless variant CJD, iatrogenically-transmitted CJD, a novel prion disease, or a CJD cluster is suspected.

2. Interview the provider and/or review medical records to collect information on the patient's clinical presentation and antemortem test results (see above). See Appendix A for definitions of neurologic terms found on the case report form.
3. If CJD is suspected and the patient is still alive, strongly encourage the provider to discuss the essential role of autopsy for diagnosis with the patient's family when appropriate. If the family consents to having an autopsy performed, they should complete the NPDPSA autopsy consent form (available at <http://www.cjdsurveillance.com/pdf/consent-autopsy.pdf>) and send or fax it to the NPDPSA. All arrangements and expenses including transport of the body to a facility that can perform a brain-only autopsy, collection of brain tissue, return of the body, and specimen shipping and testing are covered by the NPDPSA. NPDPSA is the national reference laboratory for human prion diseases. The Center performs advanced neuropathologic and biochemical diagnostics, including histopathology, immunohistochemistry, Western blot, and prion gene analysis to confirm the diagnosis of prion disease and distinguish the type (e.g., familial vs. sporadic).
4. If the patient is deceased, determine the date of death and whether postmortem samples of brain tissue were collected. Ascertain which laboratory has the tissues and forward any pathology report with the case report form.

#### **B. Identify Potential Sources of Infection**

Ask the provider and/or review records to determine if the patient ever received human-derived pituitary hormones (especially human-derived growth hormone), dura mater or corneal grafts, had neurosurgery, or is biologically related to a person with heritable prion disease.

If a patient is suspected to have iatrogenically-acquired prion disease, variant CJD or another novel acquired prion disease, contact Communicable Disease Epidemiology Section. An extensive investigation including an interview with the next of kin will need to be initiated.

#### **C. Identify Potentially Exposed Persons**

Determine if the patient had surgery, in particular, surgery on the brain, spinal cord or posterior eye, during this illness or before becoming ill. If so, contact CDES. The hospital where the procedure was performed should be contacted to determine if equipment, surfaces, and other objects were properly decontaminated.

#### **D. Environmental Evaluation**

None.

## **6. CONTROLLING FURTHER SPREAD**

#### **A. Infection Control Recommendations**

1. Standard precautions are recommended for hospitalized patients; additional special precautions are necessary during some surgical procedures, including surgery on the brain, spinal cord and posterior eye.
2. Surgical procedures: Prions are resistant to routine physical and chemical sterilization measures used in medical facilities. As a result, surgical equipment, surfaces and other

objects in contact with certain tissues, including nervous tissue or posterior eye tissue, of a person with suspected or confirmed prion disease require special decontamination measures. The brain, spinal cord and posterior eye of patients with prion disease are considered highly infectious.

If a patient with confirmed or suspected prion disease requires or recently had a surgical procedure or invasive EEG monitoring, contact the facility's infection control division so that appropriate infection control measures can be implemented, if needed. Information about infection control measures related to prion disease is available from the Centers for Disease Control and Prevention

([http://www.cdc.gov/ncidod/dvrd/cjd/qa\\_cjd\\_infection\\_control.htm](http://www.cdc.gov/ncidod/dvrd/cjd/qa_cjd_infection_control.htm)) and the World Health Organization (<http://whqlibdoc.who.int/publications/2003/9241545887.pdf> and <http://www.who.int/bloodproducts/tablestissueinfectivity.pdf>).

3. **Autopsy:** The World Health Organization (WHO) Infection Control Guidelines for Transmissible Spongiform Encephalopathies should be followed during autopsy of a patient with confirmed or suspected human prion disease. WHO infection control guidelines can be found at: <http://whqlibdoc.who.int/publications/2003/9241545887.pdf>
4. **Embalming:** The Centers for Disease Control and Prevention guidelines 'Information on Creutzfeldt-Jakob Disease for Funeral Home, Cemetery and Crematory Practitioners' should be followed (see [http://www.cdc.gov/ncidod/dvrd/cjd/funeral\\_directors.htm](http://www.cdc.gov/ncidod/dvrd/cjd/funeral_directors.htm)).
4. **Tissue/Organ Donation:** Tissues and organs from patients with confirmed or suspected prion disease should not be donated for transplantation or teaching purposes.

Note: Additional infection control measures are recommended in some circumstances for persons 'at risk' for developing prion disease. These persons are defined as asymptomatic persons who meet any of the following criteria: 1) received dura mater *or* human-derived pituitary hormones, especially human-derived growth hormone *or* cornea transplants, 2) have undergone neurosurgery, or 3) are members of families with heritable prion disease.

Source: World Health Organization Communicable Disease Surveillance and Response. WHO Manual for surveillance of human transmissible spongiform encephalopathies including variant Creutzfeldt-Jakob disease. Geneva, Switzerland: 2003.

## B. Case Management

If routine case investigation activities have been completed, no case follow-up is needed after an autopsy is arranged. Once pathology results are available, they will be sent to the patient's physician and to the Communicable Disease Epidemiology Section which, in turn, will send the pathology results to the local health jurisdiction. Using these results, the case can be classified.

## C. Contact Management

No follow-up is needed for close contacts of the patient since there is no evidence that any human prion disease is transmitted through casual or intimate person-to-person contact. If the patient had a surgical procedure when the hospital was unaware of the suspected disease status, contact CDES.

## **7. ROUTINE PREVENTION**

### **A. Immunization Recommendations**

There is no vaccine to prevent human prion diseases.

### **B. Prevention Recommendations**

There are no prevention measures for the majority of human prion diseases. See the infection control section above for precautions in hospital and other special settings.

## **UPDATES**

April 2010: The guideline was reviewed. No significant revisions were made.

January 2011: The legal reporting requirements were revised to reflect the 2011 Notifiable Conditions Rule revision. The case definitions were updated due to revisions to the CDC cases definitions.

**APPENDIX A**

The following terms and their definitions may assist with the questions on the prion disease case report form and terms that you may find during Creutzfeldt-Jakob Disease (CJD) chart reviews.

- Akinetic mutism: Akinetic mutism is the loss of the voluntary ability to speak and move. This term should be specifically stated. Unless it is clearly stated that the patient is awake and not comatose, do not substitute the term “unresponsive.”
- Cerebellar signs of CJD may include:
  - Ataxia: failure of muscular coordination. Affected patients have coordination, postural and balance problems early in the disease process and as the disease progresses, severe ataxia leads to loss of ability to walk.
  - Opsoclonus (horizontal and vertical oscillations of the eyes)
  - Nystagmus (involuntary rapid rhythmic movement of the eyeball)
  - Truncal titubation / truncal ataxia (staggering, stumbling gait with shaking of the trunk)
  - Appendicular ataxia (lack of coordination in a limb)
  - Movement tremor (involuntary trembling/quivering)
  - Termination or terminal tremor would be included in CJD signs, however “tremor” alone is not necessarily a cerebellar or CJD sign.
- Chorea: Writhing movements of the body / extremities. Rapid, highly complex jerky movements that appear to be well coordinated but occur involuntarily.
- Dementia: Dementia refers to cognitive decline.
- Dysesthesia and painful sensory symptoms: New onset of pain or other uncomfortable sensations unrelated to injury or stimulus.
- Dystonia: Abnormal tonicity in muscles resulting in impairment of voluntary movement.
- Hyperreflexia: Exaggerated reflexes
- Myoclonus: Sudden, involuntary contractions or jerking of a muscle or group of muscles. Terms such as “myoclonic jerks”, “myoclonic jerking”, “myoclonic activity” are also acceptable. These variants of myoclonus may be mentioned:
  - Nocturnal myoclonus
  - Facial myoclonus
  - Action myoclonus
  - Startle myoclonusTerms such as “twitching”, “tremulousness”, or “shaking / shakiness” are not equivalent and the term “clonus” represents a separate neurologic sign.
- Progressive Dementia: Ongoing cognitive decline. The development of dementia in CJD patients is very pronounced over a short period of time (weeks) unlike dementia associated

with Alzheimer's disease. Terms like "delirium", "altered mental status", or "unresponsiveness" should not be interpreted as representing progressive dementia, unless there is clear evidence in the chart that the condition has been ongoing for weeks / months and that the patient is progressively getting worse in terms of cognitive ability.

- Progressive neuropsychiatric disorder: Abnormalities in the nervous system and in mental processes. In the variant form of CJD, the first symptoms are psychiatric and patients experience a progressive neuropsychiatric disorder lasting at least 6 months. In the sporadic form, if neuropsychiatric disorders are present, they usually are concurrent with the physical manifestations of the disease.
- Pyramidal signs refer to disorders of the upper motor neuron pathway going from the motor cortex through the brainstem and down to the spinal cord. Pyramidal signs would include things such as:
  - Upper motor neuron weakness
  - Hemiplegia (paralysis of one side of the body)
  - Spastic (limb) paralysis / paresis
  - Hyperreflexia
  - Presence of Babinski's sign / "upgoing toes"
  - Spasticity
  - Clonus (alternate muscular contraction and relaxation in rapid succession)
- Extrapyramidal signs refer to disorders of brain structures controlling movement, mainly with reference to the basal ganglia and related structures. The most commonly recognized extrapyramidal signs are those associated with Parkinson's disease. Extrapyramidal signs of CJD may include:
  - Bradykinesia / hypokinesia (slowness of movement)
  - Rigidity (limb or neck)
  - Tremor
  - Hypomimia (flat facies, masked facies, lack of facial expression)
  - Postural instability
  - Shuffling gait
  - Ballismus / hemiballismus (sudden flinging movements of the extremities)
  - Chorea / choreoathetosis (writhing movements of the body / extremities)
- Visual Deficits: The visual abnormalities in CJD most commonly are complex visual disturbances, such as hallucinations or cortical blindness. Do not count terms such as "blurred vision" or "decreased visual acuity." Terms that may be to describe CJD-associated visual deficits include the following:
  - Visual hallucinations
  - Hemianopsia (defective vision or blindness in half of the visual field)

- Visual field cut / visual field deficit
- Blindness
- Opsoclonus (horizontal and vertical oscillations of the eyes)
- Diplopia / double vision