

# Creutzfeldt-Jakob disease (CJD)

(Considered by National Center for Vital Statistics as a death due to rare disease)

## PROTOCOL CHECKLIST

- Enter available information into Merlin on receipt of initial report (Note: case not reportable until death)
- Review disease epidemiology, case definition, laboratory testing and need for referral to National Prion Disease Pathology Surveillance Center at Case Western Reserve University if not already done
- Contact provider
- Determine if patient is alive or deceased (if alive and symptoms are compatible with CJD, consent for autopsy should be arranged as soon as possible, [see 5.A.3](#))
- Review medical records and if appropriate, interview family member(s)
  - Review disease facts
    - Background and epidemiologic information on prion disease, specifically CJD
    - Clinical symptoms of dementia, early neurologic signs
    - Disease course and fatal outcome
  - Ask about relevant risk factors (information collected for case report form)
    - Age <55 years
    - History of receipt of human-derived pituitary growth hormone, dura mater graft or corneal graft
    - History of receiving a blood transfusion
    - History of neurosurgery prior to onset of symptoms
    - History of CJD in a first-degree relative
    - History of living outside the United States >3 months since 1985
  - Determine whether case has the following records available for review:
    - History and physical exam, neurology/infectious disease consultation notes, and discharge summary
    - MRI and EEG reports
    - Tau protein, 14-3-3 protein, and RT-QuIC assay results from CSF
    - Results from evaluation of brain tissue, including, histopathological/immunohistochemical examination, Western blot, PCR, and gene sequencing of the prion protein (PrP)
  - Identify if neurosurgical procedures (e.g., brain biopsy) were performed and ensure that appropriate infection control precautions were followed
- Education of patient's family:
  - Review services provided by the National Prion Disease Pathology Surveillance Center (NPDPSC), Division of Neuropathology, and Case Western Reserve University
  - Review the need for autopsy for definitive confirmation, encourage further discussion with their physician regarding consent for autopsy
  - Address family's questions/concerns and make sure they are aware of the CJD Foundation, a patient/family support organization
- Enter additional data obtained from interview into Merlin

## Creutzfeldt-Jakob disease (CJD)

### 1. DISEASE REPORTING

#### A. Purpose of reporting and surveillance

1. To monitor trends in the epidemiology of CJD
2. To detect cases of variant or other forms of CJD in Florida
3. To maximize laboratory confirmation of suspected cases and facilitate testing
4. To promote awareness of available resources
5. To prevent potential iatrogenic transmission

#### B. Legal reporting requirements

Physicians and laboratories are required to report cases of infection to their county health department (CHD) within one working day of identification or diagnosis. Reporting should not be delayed for confirmatory testing.

Since case definitions for human prion diseases are complex, the following criteria were developed to identify patients that warrant notification to CHDs:

- A lack of diagnosed etiological agent and
    - Rapidly progressive dementia with one or more of the following features:
      - Myoclonus
      - Visual or cerebellar signs
      - Pyramidal/extrapyramidal signs
      - Akinetic mutism
      - EEG findings of periodic, synchronous sharp-wave complexes superimposed on a slow background rhythm
      - Elevated tau or 14-3-3 protein in cerebrospinal fluid (CSF)
      - Magnetic resonance imaging (MRI) high signal abnormalities in caudate nucleus and/or putamen on diffusion-weighted imaging (DWI) or fluid attenuated inversion recovery (FLAIR)
    - Recent onset of cognitive impairment in a younger adult (<55 years old) with progressive neuropsychiatric disease, persistent painful sensory symptoms (e.g., dysesthesia), or MRI findings of bilateral pulvinar high signal
    - Progressive cerebellar or other neurological syndrome in patient with a recognized CJD risk factor (e.g., received human-derived pituitary hormone or dura mater graft, definite or probable prion disease in a first degree relative)
- OR
- Prion disease suspected by a neurologist or neuropathologist.

#### C. County health department investigation responsibilities

1. Begin investigation within two business days of receiving a report from a provider.
2. Report all suspect and confirmed cases in Merlin. The case report form for CJD is found at: [www.floridahealth.gov/diseases-and-conditions/disease-reporting-and-](http://www.floridahealth.gov/diseases-and-conditions/disease-reporting-and-)

[management/disease-reporting-and-surveillance/surveillance-and-investigation-guidance/index.html](http://www.cjdsurveillance.com/management/disease-reporting-and-surveillance/surveillance-and-investigation-guidance/index.html).

3. Discuss the importance of appropriate infection control procedures if surgical procedures are being considered. (Note: Brain biopsy is not recommended for confirmation of CJD. Autopsy should be considered in place of biopsy.)
4. Inform and assist the providers in arranging for autopsy and laboratory services provided by the National Prion Disease Pathology Surveillance Center (NPDPSC). Their web site is found at: [www.cjdsurveillance.com/](http://www.cjdsurveillance.com/) and their national toll free phone number is (800) 659-1991.
5. Cases aged <55 years should be evaluated for the variant form of CJD. Brain tissue for diagnosis and CSF for the tau and 14-3-3 protein should be sent to the National Prion Disease Pathology Surveillance Center at Case Western Reserve University. Information about the center, shipping and mailing instructions can be found on their web site, listed above. Please notify the Bureau of Epidemiology to assist with case evaluation and laboratory testing.

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## 2. THE DISEASE AND ITS EPIDEMIOLOGY

### A. Etiologic agent

Classic CJD is a human prion disease that is a neurodegenerative disorder with characteristic clinical and diagnostic features. It is rapidly progressive and always fatal. Death usually occurs within a year after onset of illness.

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.

Classic CJD is not related to bovine spongiform encephalopathy (BSE, or ‘mad cow’ disease). It is also distinct from variant CJD (vCJD), another prion disease that is associated with consumption of cattle products contaminated with the agent causing BSE.

Classic CJD has been recognized since the early 1920s. The most common form of classic CJD is believed to occur sporadically, caused by the spontaneous transformation of normal prion proteins into abnormal prions. Sporadic CJD occurs worldwide and is the most common human prion disease (estimated incidence: 1–2 cases per million population per year). The risk of CJD increases with age; in persons aged 60 years and older, the average annual rate is approximately 4.6 cases per million.

About 85% of CJD cases occur as sporadic disease, with a smaller proportion (5-15%) developing CJD because of inherited mutations of the prion protein gene. These inherited forms include Gerstmann-Sträussler-Scheinker syndrome and fatal familial insomnia.

### B. Description of Illness

**Sporadic CJD** is a fatal neurodegenerative disease that primarily occurs in people aged >55 years. 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.

**Variante CJD (vCJD)** was first recognized and described in 1996 in the United Kingdom (U.K.). There is now strong scientific evidence that the agent responsible for BSE in cattle is the same agent responsible for the outbreak of vCJD in humans. Consumption of cattle products contaminated with the agent of BSE 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 June 2, 2014, more than 229 cases of variant CJD have been reported worldwide, mostly in the U.K. and Europe. *Although four cases of variant CJD have been reported in the United States, including one case in Florida, 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	Often 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
Increased glycoform ratio on Immunoblot analysis of protease-resistance prion protein	Marked accumulation of protease-resistance prion protein	Not reported

\* 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. Reservoirs**

Humans are the only known reservoir for classic CJD. For vCJD there is evidence that cattle with BSE are reservoirs for the disease.

### **D. Modes of transmission**

There is no recognizable pattern of transmission for sporadic CJD (85% of patients). Approximately 5–15% of CJD cases are due to inherited forms of the disease and <1% are acquired through iatrogenic transmission. 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. Recent cases of variant CJD in the U.K. show that transmission of this disease can occur through blood transfusion. Other human prion diseases are not known to be transmitted by transfusions. Human prion diseases are not transmitted through casual or intimate person-to-person contact.

### **E. 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.

### **F. 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).

### **G. Treatment**

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

### **H. Prophylaxis**

None available.

### **I. CJD in Florida**

Monitoring of CJD did not begin until after the first report of variant CJD in Great Britain in 1996 and was not reportable in Merlin until 2003. Since the first year of complete reporting in 2004, the number of cases including confirmed, probable and suspect has ranged from 12 to 25. The first reported case of variant CJD in the United States occurred in Florida in 2002. The case-patient was a young woman who was born and lived most of her life in Great

Britain where she likely was exposed to the disease. Death certificates are another source of CJD case information with records dating back to 1979. However, these reports should be interpreted with caution as not all information has been verified.

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### 3. CASE DEFINITION

#### A. Clinical description

A progressive uniformly fatal dementia characterized by: myoclonus, visual or cerebellar signs, akinetic mutism, and pyramidal or extrapyramidal signs. There is rapid cognitive impairment following the presentation of neurologic symptoms for most prion disease. Almost all patients with sporadic CJD develop myoclonic jerks that involve either the entire body or a limb.

Prior human CJD epidemics were caused by iatrogenic human-to-human transmission of CJD following intramuscular injection of human growth hormone with clinically silent latency periods of 12-17 years. Therefore, intervening exposures to the index case's blood or other body tissues during that period carry public health risks.

Sporadic CJD is characterized by a rapidly progressive multifocal neurological dysfunction, myoclonic jerks, a terminal state of global severe cognitive impairment, and death in about eight months. Charts tend to document rapidly progressive cognitive impairment as frequently as cerebellar dysfunction. The clinical picture will generally include behavioral abnormalities, higher cortical dysfunction, cortical visual abnormalities, cerebellar dysfunction, and both pyramidal and extrapyramidal signs.

#### B. Laboratory criteria for diagnosis

- Standard neuropathological techniques; and/or immunocytochemically; and/or Western blot confirmed protease-resistant PrP; and/or presence of scrapie-associated fibrils conducted on brain tissue
- Tau proteins and/or 14-3-3 proteins in CSF (test not specific for CJD)
- Periodic sharp and slow wave complexes (PSWC) in EEG (test suggestive but not specific for CJD)

#### C. Case classification

Confirmed: A fatal outcome with a clinically compatible illness diagnosed by standard neuropathological techniques; and/or immunocytochemically; and/or Western blot confirmed protease-resistant PrP; and/or presence of scrapie-associated fibrils

Probable: A fatal outcome with a progressive dementia; and at least two out of the following four clinical features:

- Myoclonus
- Visual or cerebellar signs
- Pyramidal/extrapyramidal signs
- Akinetic mutism

**AND**

- A clinical duration of death <2 years WITH
- A typical EEG during; and/or a tau or 14-3-3 CSF assay results consistent with prion disease
- Routine investigations should not suggest an alternative diagnosis

Suspect: A fatal outcome with a progressive dementia; and at least two out of the following four clinical features:

- Myoclonus
- Visual or cerebellar signs
- Pyramidal/extrapyramidal signs
- Akinetic mutism

**AND**

- No EEG or atypical EEG and a clinical duration to death of <2 years

**D. Comment**

Cases under the age of 55 years old should be evaluated for the variant form of CJD. Brain tissue for diagnosis and CSF for the tau and 14-3-3 protein should be sent to the National Prion Disease Pathology Surveillance Center (NPDPSC) at Case Western Reserve University. Information about the center, shipping and mailing instructions can be found on their web site: [www.cjdsurveillance.com](http://www.cjdsurveillance.com). Please notify the Bureau of Epidemiology to assist with case evaluation and laboratory testing.

**A copy of laboratory test results must accompany the paper case report form.**

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**4. LABORATORY TESTING****A. Criteria for diagnosis**

**Confirmatory diagnosis of CJD requires laboratory examination of brain tissue.** The importance of autopsy and laboratory testing should be discussed with the physician and patient's family. Arrangements for autopsy and laboratory testing can be made through the NPDPSC (see NPDPSC as noted above). 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.

**Antemortem indicators are not confirmatory.** Antemortem indicators that support but cannot confirm the diagnosis of CJD include certain findings on EEG ([see table 1](#)), and elevated levels of 14-3-3 or tau protein in 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.

**B. Services available at Florida Department of Health Bureau of Public Health Laboratories (BPHL)**

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

### C. Specimen collection

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

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## 5. CASE INVESTIGATION

Cases of confirmed, probable, and suspect CJD are primarily identified from three sources: 1) reports from health care providers; 2) NPDPS lab reports; and 3) death certificates.

### A. Contact the physician or hospital

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](#)).
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 NPDPS autopsy consent form (available at [www.cjdsurveillance.com/pdf/consent-autopsy.pdf](http://www.cjdsurveillance.com/pdf/consent-autopsy.pdf)) and send or fax it to the NPDPS. 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 NPDPS. NPDPS 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, received a blood transfusion, has a history of living outside the U.S. 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 the Bureau of Epidemiology for further guidance.

### 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. 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

#### E. Merlin data entry

Create a case in Merlin under disease code CREUTZFELDT-JAKOB DISEASE (04610). Enter the data collected into Merlin, being sure to include all required fields on the data screen. Attach relevant medical records (e.g., history and physical, neurological consult), EEG and MRI reports, and the completed case report form in the case documents section of Merlin. Attach electronic laboratory reports. Scanned copies of related NPDPS letters should be located in the lab documents section of existing electronic laboratory reports. Note that cases do not meet the case definition until death has occurred.

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## 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 (CDC)

([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 [www.who.int/bloodproducts/cs/TSEPUBLISHEDREPORT.pdf](http://www.who.int/bloodproducts/cs/TSEPUBLISHEDREPORT.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 CDC guidelines 'Information on Creutzfeldt-Jakob disease for Funeral Home, Cemetery and Crematory Practitioners' should be followed (see [www.cdc.gov/ncidod/dvrd/cjd/funeral\\_directors.htm](http://www.cdc.gov/ncidod/dvrd/cjd/funeral_directors.htm)).
5. **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 Bureau of Epidemiology, which in turn, will enter the pathology results as an electronic laboratory report in Merlin. 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, the hospital where the procedure was performed should be contacted to determine if equipment, surfaces, and other objects were properly decontaminated.

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## 7. ROUTINE PREVENTION

### A. Immunization recommendations

There is no vaccine to prevent CJD.

### B. Prevention recommendations

There are no prevention measures for the classic form of CJD. The number of variant CJD cases is declining worldwide due to BSE surveillance and control efforts. See the infection control section above for precautions in hospital and other special settings.

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## 8. IMPORTANT LINKS

### A. CJD Case Report Form:

[www.floridahealth.gov/diseases-and-conditions/disease-reporting-and-management/disease-reporting-and-surveillance/index.html](http://www.floridahealth.gov/diseases-and-conditions/disease-reporting-and-management/disease-reporting-and-surveillance/index.html)

### B. National Prion Disease Pathology Surveillance Center (NPDPSC):

<http://www.cjdsurveillance.com/>

National toll free phone number: (800) 659-1991

## 9. REFERENCES

- A. Heymann, D.L. (Ed.) (2015) *Control of Communicable Diseases Manual* (20<sup>th</sup> ed.). Washington: American Public Health Association.
- B. Centers for Disease Control and Prevention: <http://www.cdc.gov/ncidod/dvrd/cjd/>