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Creutzfeldt-Jakob disease (CJD) & Variant Creutzfeldt-Jakob disease (vCJD)

Overview^{1,2,3,5,6,8}


Prion diseases also known as transmissible spongiform encephalopathies (TSEs) are a family of rare progressive neurodegenerative disorders that affect both humans and animals. Human prion diseases include: Creutzfeldt-Jakob disease (sporadic sCJD) which comprises approximately 85-90% of all human prion disease, Gerstmann-Sträussler-Scheinker syndrome (GSS), fatal familial insomnia (FFI), Kuru and variant Creutzfeldt-Jakob disease (vCJD) which has been causally linked with bovine spongiform encephalopathy (BSE), a disease of cattle. Prion diseases affecting animals include scrapie, BSE (commonly called "mad cow" disease) and chronic wasting disease of mule deer and elk.

"Prion" usually pronounced "PREE-on" in the U.S. and "PRY-on" in the U.K. was coined to mean "proteinaceous infectious particle" an abnormal form of a normally harmless protein found in the brain. For reasons not fully understood, these pathogenic agents are able to induce abnormal folding of specific normal cellular proteins which clump together and accumulate in the brain. This abnormal accumulation of protein in the brain can cause memory impairment, personality changes, and difficulties with movement. The diseases are characterized by long incubation periods, sponge-like holes in brain tissue, associated with neuronal loss, and a failure to induce inflammatory response. Prion diseases can be difficult to diagnose, treatment of prion diseases remains supportive; no specific therapy has been shown to stop the progression of these diseases, prion diseases are ultimately fatal.

CJD has four different categories: sporadic (spontaneous), iatrogenic (associated with medical use of infected pituitary-derived hormones and dura mater), familial (inherited), and vCJD, which is believed to be associated with dietary consumption of tissue from cattle infected with BSE or "mad cow" disease. Starting in 1989, the USDA began taking steps to prevent BSE from entering the U.S., including severe restrictions on the importation of live ruminants, such as cattle, sheep and goats, and certain ruminant products from countries where BSE was known to exist. These restrictions were later extended to include importation of ruminants and certain ruminant products from all European countries. vCJD is also thought to have been spread to people receiving cornea transplants from infected donors and from contaminated medical equipment.

Typically patients with sCJD onset later in life (mean age at onset 57 to 66 years)³ and occur worldwide at approximately 1 case per million population annually. Most victims of sCJD die in their late sixties after developing relatively slow-onset mental deterioration. In vCJD, most deaths have occurred among young adults in their late twenties and are often preceded by sudden behavior changes initially diagnosed as psychiatric illness.

Currently, the only method for a definitive diagnosis of CJD is to examine the affected individual's brain tissue. However, there are several clinical tests that aid clinicians in making a

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diagnosis of probable CJD; which include: cerebrospinal fluid analysis (obtained by "spinal tap") to measure certain proteins, electroencephalogram (EEG), and magnetic resonance imaging (MRI) of the brain.

For a more information on CJD, refer to the following texts:

- *Control of Communicable Diseases Manual (CCDM)*. 20th ed. Washington, D.C.: American Public Health Association, 2015.
- American Academy of Pediatrics. *Red Book: 2015 Report of the Committee on Infectious Diseases*. 30th ed. Elk Grove Village, IL. American Academy of Pediatrics; 2015.
- *Mandell, Douglas, and Bennett's Principles and Practices of Infectious Diseases*: 8th ed. 2015.

2010 CDC's Diagnostic Criteria for CJD and vCJD⁴ – (5/16)

1. Sporadic CJD (sCJD)

Confirmed:

- Diagnosed by standard neuropathological techniques; and/or
- Immunocytochemically; and/or
- Western blot confirmed protease-resistant PrP; and /or
- Presence of scrapie-associated fibrils.

Probable:

Rapidly progressive dementia; **and** at least **two** out of the following four clinical features:

- Myoclonus – seizure-like severe muscle contractions.
- Visual or cerebellar signs – double or blurred vision, and/or inability to visually recognize familiar objects.
- Pyramidal/extrapyramidal signs – poor control or poor initiation of skilled movement (primarily hands and fingers), poor control of speech, and difficulty forming words.
- Akinetic mutism - no spontaneous movement or attempt to formulate speech.

⇒**AND** a positive result on at least **one** of the following laboratory tests:


- A disease-typical EEG (periodic sharp wave complexes) during an illness of any duration; and/or
- A positive 14-3-3 cerebrospinal fluid (CSF) assay in patients with disease duration of less than 2 years.
- Magnetic resonance imaging (MRI) high signal abnormalities in caudate nucleus; and/or a putamen on diffusion-weighted imaging (DWI), or fluid attenuated inversion recovery (FLAIR).

⇒**AND** without routine investigations indicating an alternative diagnosis.

Suspect:

Progressive dementia; **and** at least **two** out of the following four clinical features:

- Myoclonus.

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- Visual or cerebellar signs.
 - Pyramidal/extrapyramidal signs.
 - Akinetic mutism.
- ⇒**AND** the absence of a positive result for any of the three laboratory tests that would classify a case as “probable” (see laboratory tests above for bullets **a**, **b** and **c**).
- ⇒**AND** duration of illness less than two years
- ⇒**AND** without routine investigations indicating an alternative diagnosis.

***COMMENT:** A death certificate indicating CJD as a cause of death (this means the mention of CJD anywhere on the death certificate) should be investigated to determine status.*

2. Iatrogenic CJD

- Progressive cerebellar syndrome in a recipient of human cadaveric-derived pituitary hormone; **OR**
- sCJD with a recognized exposure risk (e.g., antecedent neurosurgery with dura mater implantation.)

3. Familial CJD

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

4. Variant CJD


Confirmed:

Neuropathologic examination of brain tissue is required to confirm a diagnosis of vCJD. The following confirmatory features should be present:

- Numerous widespread kuru-type amyloid plaques surrounded by vacuoles in both the cerebellum and cerebrum-florid plaques **AND**
- Spongiform change and extensive prion protein deposition shown by immunohistochemistry throughout the cerebellum and cerebrum.

Suspect:

- a. Current age or age at death <55 years (*a brain autopsy is recommended, for all physician-diagnosed CJD cases*) **AND**
- b. Psychiatric symptoms at illness onset and/or persistent painful sensory symptoms (frank pain and/or dysesthesia) **AND**
- c. Dementia, and development ≥ 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; ≥ 4 months delay in the development of the neurologic signs is not required*) **AND**
- d. A normal or an abnormal EEG, but not the diagnostic EEG changes often seen in classic CJD **AND**
- e. Duration of illness of over 6 months.

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- f. Routine investigations of the patient do not suggest an alternative, non-CJD diagnosis **AND**
- g. No history of receipt of cadaveric human pituitary growth hormone or a dura mater graft **AND**
- h. No history of CJD in a first degree relative or prion protein gene mutation in the patient.

NOTE: All of the suspect criteria (a–h) for CJD may not be available at the initial report of the patient, however without the above information it will be difficult to make a diagnosis. If a patient has the typical bilateral pulvinar high signal on MRI scan, a suspected diagnosis of vCJD requires the presence of a progressive neuropsychiatric disorder, **d, e, f** and **g** of the above criteria, and four of the following five criteria:

- Early psychiatric symptoms (anxiety, apathy, delusions, depression, withdrawal);
- Persistent painful sensory symptoms (frank pain and/or dysesthesia);
- Ataxia;
- Myoclonus or chorea or dystonia; and
- Dementia.

COMMENT: 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.

Information Needed for Investigation


Verify the diagnosis. Obtain a copy of the CD-1 or death certificate. What laboratory tests were conducted? If a biopsy and/or an autopsy were performed, obtain results. If laboratory tests were not conducted, are specimens available? What are/were the patient’s clinical symptoms?

IMPORTANT: In order to provide effective surveillance for CJD and other prion diseases, it is strongly recommend that an effort be made to have an autopsy performed for all suspected cases of prion disease (a brain autopsy is recommended for all physician-diagnosed CJD cases). The National Prion Disease Pathology Surveillance Center (NPDPS) **is available to coordinate autopsies**. Please contact one of their Autopsy Coordinators at 216-368-0587 for more information.

⇒**For patients diagnosed with CJD (all categories) that are deceased.**

Perform a chart extraction and obtain copies of the following:

1. Discharge summary
2. Neurology consultation notes
3. Psychiatric consultation notes
4. EEG reports
5. MRI reports
6. Pathology report from brain biopsy or autopsy
7. Obtain demographic, clinical, laboratory information, and other epidemiological information necessary to complete the [Disease Case Report](#) (CD-1) and the [CJD Case Report](#) form. Affix the above chart extraction documents to the CJD Case Report

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Form. **NOTE:** *The Local Public Health Agency (LPHS) should inform the District Communicable Disease Coordinator immediately if a vCJD or iCJD case is reported.*

⇒ **For patients diagnosed with CJD (all categories) that are not deceased.**

Obtain as much of the above information as is available (bullets **1** through **6** above) to complete the [Disease Case Report](#) (CD-1) and the [CJD Case Report](#) form. Affix the chart extraction documents to the CJD Case Report form. **NOTE:** *The LPHA should inform the District Communicable Disease Coordinator immediately if a vCJD or iCJD case is reported.*

IMPORTANT: *If diagnostic laboratory testing has not been performed on patients, inform the physician that laboratory services are available from:*

NPDpsc
 Institute of Pathology
 Case Western Reserve University
 2085 Adelbert Road, Room 418
 Cleveland, Ohio 44106-4907
 Tel: 216-368-0587 Fax: 216-368-2546
 Email: cjdsurv@case.edu

NOTE: *The NPDpsc charges for CSF and genetic testing, as well as brain biopsy examinations, including Western blot and immunohistochemistry. Refer to the NPDpsc web site for more information: <http://case.edu/med/pathology/centers/npdpssc/contact.html>.*


N.B.: *However, if the patient is accepted for autopsy assistance, all autopsy related costs are covered by the NPDpsc. These costs included the autopsy itself, any transportation or use-of-facility fees associated with the autopsy, and the testing for prion diseases (CJD). For additional information: <http://case.edu/med/pathology/centers/npdpssc/resources-autopsyfaqs.html>.*

Establish the extent of illness. Early onset of CJD should prompt a thorough search for iatrogenic sources of infection and is characteristic of some cases of vCJD and fCJD.

Provide information on CJD to persons at risk for disease and the general public. Efforts should be made to promote CJD awareness and educate the public on sources of infection. Additional information on CJD and other prion diseases can be found at:

- <http://www.cdc.gov/prions/>
- <http://case.edu/med/pathology/centers/npdpssc/aboutprion.html>
- http://www.cjdfoundation.org/webfm_send/76.

CJD Surveillance. The Centers for Disease Control and Prevention (CDC) will enhance its current program to identify and investigate possible cases of vCJD. Through cooperative agreements with state and local health departments, CDC also will enhance and expedite the oversight of illness and deaths from CJD so that any possible vCJD cases will be rapidly detected. CDC will also increase its technical assistance to state and local health personnel

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develop new laboratory capacity to support its investigations and enhance its current collaborative agreement with the NPDPC at Case Western Reserve University.

Notification

- Immediately contact the [District Communicable Disease Coordinator](#), the [Senior Epidemiology Specialist](#) for the District, or the Missouri Department of Health and Senior Services (MDHSS) - BCDCP, phone (573) 751-6113, Fax (573) 526-0235, or for afterhours notification contact the MDHSS/Emergency Response Center (ERC) at (800) 392-0272 (24/7) upon notification of a case of vCJD or iCJD.

Control Measures


To monitor the prevalence of prion diseases in Missouri and investigate possible cases in which the disease has been acquired from other persons or from animals.

- The Medical Certifier should clearly indicate the diagnosis of CJD on the patient's death certificate when the clinical diagnosis applies because CJD is also monitored from mortality data.
- Performing a brain autopsy in patients with suspected or clinically diagnosed CJD is encouraged to confirm the diagnosis and detect other emerging forms of CJD.

Testing is available from the NPDPC. If the patient is accepted for autopsy assistance, all autopsy related costs are covered by the NPDPC; these costs included the autopsy itself, any transportation or use-of-facility fees associated with the autopsy, and the testing for prion diseases (CJD). However, the NPDPC is only funded to test for prion diseases (CJD). If negative, the NPDPC can send any remaining tissue to a physician or medical center for further neuropathological workup. *N.B.: The NPDPC cannot cover funeral or embalming charges.* For additional information you may contact the NPDPC at: 216-368-0587 or visit their web site at: <http://case.edu/med/pathology/centers/npdpcc/resources-autopsyfaqs.html>.

- Information for Funeral and Crematory Practitioners can be found at: <http://www.cdc.gov/prions/cjd/funeral-directors.html>.
- The "WHO infection control guidelines for transmissible spongiform encephalopathies. Report of a WHO consultation, Geneva, Switzerland, 23-26 March 1999" can be found at: http://www.who.int/csr/resources/publications/bse/WHO_CDS_CSR_APH_2000_3/en/.
- The "Guidance for Industry - Revised Preventive Measures to Reduce the Possible Risk of Transmission of Creutzfeldt-Jakob Disease (CJD) and Variant Creutzfeldt-Jakob Disease (vCJD) by Blood and Blood Products" can be found at: <http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Blood/ucm074089.htm>.
- CDC's Infection Control web site is located at: <http://www.cdc.gov/prions/cjd/infection-control.html>.



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Laboratory Procedures

Physicians suspect a diagnosis of CJD on the basis of the typical signs and symptoms and progression of the disease. In most CJD patients, the presence of 14-3-3 protein in the cerebrospinal fluid and/or a disease-typical EEG pattern (periodic sharp wave complexes), both of which are believed to be diagnostic for CJD, have been reported. However, a confirmatory diagnosis of CJD currently requires neuropathologic and/or immunodiagnostic testing of brain tissue obtained either at biopsy or autopsy.⁵

***NOTE:** The NPDPSA charges for CSF and genetic testing, as well as brain biopsy examinations, including Western blot and immunohistochemistry. Please review the corresponding protocol pages for more information on specimen collection:*

<http://case.edu/med/pathology/centers/npdpssc/protocols.html>.

***N.B.:** If the patient is accepted for autopsy assistance, all autopsy related costs are covered by the NPDPSA. These costs included the autopsy itself, any transportation or use-of-facility fees associated with the autopsy, and the testing for prion diseases (CJD); for more information:*

<http://case.edu/med/pathology/centers/npdpssc/resources-autopsyfaqs.html>.

For the contact and shipping information for NPDPSA see their web site:

<http://case.edu/med/pathology/centers/npdpssc/contact.html>.

All shipments should be addressed to:

NPDPSA

Institute of Pathology

Case Western Reserve University

2085 Adelbert Road, Room 418

Cleveland, Ohio 44106-4907


Tel: 216-368-0587

Email: cjdsurv@case.edu

Reporting Requirements

Creutzfeldt-Jakob disease is a Category 3 disease and shall be reported to the [LPHA](#) or to the Missouri Department of Health and Senior Services within three days of first knowledge or suspicion by telephone, facsimile or other rapid communication. The MDHSS may be contacted by phone at (573) 751-6113, Fax (573) 526-0235, or for afterhours notification contact the MDHSS/ERC at (800) 392-0272 (24/7).

1. For all cases of sporadic CJD, iatrogenic CJD, familial CJD, or variant CJD complete a [Disease Case Report](#) (CD-1) and [CJD Case Report](#) form. Affix the chart extraction documents to the CJD Case Report Form. Send the forms and all chart extraction materials to the [District Health Office](#).
2. Contact the District Communicable Disease Coordinator immediately for all confirmed, probable, or suspect cases of variant CJD or iatrogenic CJD.
3. Entry of the complete CD-1 by the LPHA into WebSurv negates the need for the paper CD-1 to be forwarded to the District Health Office.

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4. All outbreaks or “suspected” outbreaks must be reported as soon as possible (by phone, fax or e-mail) to the District Communicable Disease Coordinator. This can be accomplished by completing the [Missouri Outbreak Surveillance Report](#) (CD-51).
5. Within 90 days from the conclusion of an outbreak, submit the final outbreak report to the Regional Communicable Disease Coordinator.

References

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4. Centers for Disease Control and Prevention’s (CDC). CDC’s Diagnostic Criteria for CJD and vCJD. <http://www.cdc.gov/prions/cjd/diagnostic-criteria.html> and <http://www.cdc.gov/prions/vcjd/diagnostic-criteria.html> (5/16).
5. CDC, National Center for Emerging and Zoonotic Infectious Diseases (NCEZID), Division of High-Consequence Pathogens and Pathology (DHCPP). *Prion Diseases*. <http://www.cdc.gov/prions/> (5/16).
6. U.S. National Library of Medicine, Bethesda, MD, U.S. Department of Health and Human Services, National Institutes of Health. *Creutzfeldt-Jakob Disease*. In: MedlinePlus. <https://www.nlm.nih.gov/medlineplus/ency/article/000788.htm> (5/16).
7. National Prion Disease Pathology Surveillance Center, Institute of Pathology, Case Western Reserve University, 2085 Adelbert Rd. Room 418, Cleveland Ohio, 44106. <http://case.edu/med/pathology/centers/npdpssc/> (5/16).
8. The Johns Hopkins University, The Johns Hopkins Hospital, and Johns Hopkins Health System. In: Johns Hopkins Medicine. http://www.hopkinsmedicine.org/psychiatry/specialty_areas/neuropsychiatry/frontotemporal_dementia/conditions/what_is_CJD.html (5/16).
9. Creutzfeldt-Jakob Disease Foundation, Inc. 341 W. 38th Street, Suite 501 New York, NY 10018. <http://www.cjdfoundation.org/> (5/16).

Acknowledgements

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