



## Prion Disease Information for Wisconsin Medical Providers

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### Introduction

Human cases (suspect or confirmed) of transmissible spongiform encephalopathy (TSE) are legally reportable to the Wisconsin Division of Public Health (DPH) under Wis.Admin. Code ch. DHS 145 Appendix A.

TSEs include any prion-related disease, including sporadic Creutzfeldt-Jakob disease (sCJD), familial CJD, variant Creutzfeldt-Jakob disease (vCJD), fatal familial insomnia and Gerstmann-Sträussler-Scheinker syndrome. Of these, only sCJD is known to occur with any frequency in the U.S. (incidence approximately 1-1.5 per million).

A workgroup consisting primarily of Wisconsin neurologists and neuropathologists was convened to develop the clinical criteria that should elicit a report of a possible TSE case. This workgroup has also developed these guidelines to assist health care providers in the management/diagnosis of suspected prion-related dementias.

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### Criteria for Reporting a Suspect Case of TSE in Wisconsin

A prion-related disorder, such as Creutzfeldt-Jakob disease (CJD), should be suspected and reported to DPH in any patient with dementia of early onset (<55 years) OR rapidly progressive dementia occurring at any age with one or more of the following:

- Movement disorders (e.g., myoclonus, ataxia)
- Painful sensory symptoms
- Visual disturbances

To report a case or arrange an autopsy on a suspect CJD case, contact:

- Lorna Will 608-267-0401
- Jim Kazmierczak 608-266-2154

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### Diagnosis and Workup

A careful neurological history and examination may reveal findings supportive of a diagnosis of a TSE, such as an insidious, nonspecific prodrome (fatigue, behavioral change, depression, weight loss, sleep disturbance), leading to progressive dementia within weeks to months, with prominent neurological signs such as myoclonus, ataxia, visual disturbance, corticospinal, and extrapyramidal dysfunction and akinetic mutism.

It is the choice of the clinician whether to manage a patient with a suspected prion disease or to refer the patient to a specialty center or neurologist. Treatable causes, as in any patient with dementia, should first be sought. Routine blood work would include a CBC, electrolytes, hepatic and renal function tests, B12 level, and thyroid testing.

Diagnostic studies include:

- **Cerebrospinal fluid:** Constituents are usually normal, except for elevated levels of tau protein and 14-3-3 protein. The sensitivity and specificity of these CSF markers may approach 90 percent; however, the usefulness of these tests is questionable in early disease. We **strongly** recommend specimens be sent to the National Prion Disease Pathology Surveillance Center (NPDPS) at Case Western Reserve University, Cleveland, Ohio.
  - Phone: 216-368-0587
  - Email: [cjdsurv@po.cwru.edu](mailto:cjdsurv@po.cwru.edu)
  - Test protocols/submission forms: <http://case.edu/med/pathology/centers/npdpssc/index.html> (within *Resources for professionals*)

The NPDPS is currently performing the second-generation RT-QuIC (real-time quaking-induced conversion) assay on clinical specimens. The RT-QuIC is a test recently developed to detect the abnormal prion protein. Autopsy-verified data indicate 98.5 percent specificity and 89-92 percent sensitivity of this assay performed by the NPDPS for detection of all human prion diseases.

CSF should be obtained by lumbar puncture. The first 2ml of CSF that flows from the tap should be discarded. Collect 2-5ml of CSF, avoiding bloody tap. The CSF specimen should be frozen as quickly as possible (preferably within 20 minutes) and stored in a -80 C freezer (or, lacking that, in a -20 C freezer) until shipment on dry ice.



- **Electroencephalogram:** Early in sCJD, the EEG may be normal or may show non-specific slowing; later biphasic or triphasic synchronous complexes may be superimposed on a slow background; terminally, the EEG will show periodic sharp wave complexes in up to 90 percent of patients. These characteristic EEG findings are usually absent in cases of vCJD.
- **Magnetic resonance imaging:** CJD typically shows increased T2 and FLAIR signal in the basal ganglia and cerebral cortex in approximately 80 percent of patients at presentation. Diffusion-weighted MRI sequences are critical for optimal detection, with sensitivity and specificity approaching 100 percent in the appropriate clinical setting. For this reason, it is essential to order a diffusion-weighted-MRI study and consult with an experienced neuroradiologist when considering the diagnosis of CJD.
- **Brain biopsy and autopsy:** While conventional pathological investigation will show spongiform encephalopathy, we **strongly** recommend specimens be sent to the NPDPS at Case Western Reserve University, Cleveland, Ohio.
  - Phone: 216-368-0587
  - Email: [cjdsurv@po.cwru.edu](mailto:cjdsurv@po.cwru.edu)The NPDPS can also perform genotyping on frozen specimens to determine the type of CJD and diagnose related conditions such as GSS and FFI. They can also distinguish familial CJD from sCJD. Only frozen brain tissue examination definitely confirms or excludes the diagnosis of prion disease and provides the information to identify the type of prion disease. The immunohistochemical examination provides a definitive diagnosis only when positive and by itself cannot distinguish familial from sporadic CJD.
- **Infection control considerations—autopsy and embalming:** World Health Organization (WHO) Infection Control Guidelines for TSEs should be followed during autopsy. An autopsied or traumatized body of a suspected or confirmed TSE patient can be embalmed using the precautions in the WHO TSE Infection Control Guidelines: ([http://www.who.int/csr/resources/publications/bse/WHO\\_CDS\\_CSRAPH\\_2000\\_3/en/](http://www.who.int/csr/resources/publications/bse/WHO_CDS_CSRAPH_2000_3/en/)). Bodies that have not been autopsied or traumatized can be embalmed using Standard Precautions.
- **Arrangement of autopsies:** DPH can arrange autopsies and transport of remains for suspect TSE patients at no cost. Tissue is submitted to the NPDPS for analysis. An autopsy consent form and written consent for testing at NPDPS can be sent to the patient's POA for health care or the next of kin. DPH staff will also inquire about which mortuary service the family prefers to use so arrangements can be made for transport of remains to and from the pathology laboratory. For details contact:
  - **Lorna Will:** 608-267-0401
  - **Jim Kazmierczak:** 608-266-2154

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## Differential Diagnosis of CJD and Other Prion Dementias

The differential diagnosis of CJD includes treatable conditions such as B12 deficiency, hypothyroidism, syphilis, other central nervous system infections (HIV/AIDS, chronic meningitis, Whipple's disease, etc.), cerebrovascular disease, direct and indirect (paraneoplastic) effects of cancer (B cell lymphoma), Wilson's disease seizure disorder, tardic dyskinesia, normal pressure hydrocephalus, toxic exposure, organ failure, psychiatric disorders, unusual presentation of Parkinson's disease or Parkinson-plus syndromes, and others.

Incurable conditions, which may enter into the differential diagnosis of CJD, include unusual presentations of Alzheimer's disease, Pick's disease, diffuse Lewy body disease, MELAS syndrome, frontotemporal dementia, corticobasilar degeneration, mitochondrial diseases, leukodystrophies and spinocerebellar degenerations.

Variant CJD (vCJD) was linked to beef consumption during the occurrence of a large outbreak of bovine spongiform encephalopathy (BSE, commonly known as mad cow disease) among cattle in the United Kingdom in the 1990s. vCJD should not be confused with the classic form of sporadic CJD, which is endemic throughout the world. vCJD can be confirmed only through examination of brain tissue—the nature and location of brain lesions combined with western blot testing of prion protein (performed at the NPDPS) allow the definitive differentiation of vCJD from sCJD. Clinically, in contrast to sCJD, vCJD predominantly affects younger people, has a longer survival time after onset (>6 months), and has an atypical presentation, with prominent psychiatric or sensory symptoms at the time of presentation. Patients with vCJD usually have delayed onset of neurologic abnormalities, including ataxia within weeks or months, with dementia and myoclonus occurring late in the illness. Only four cases of vCJD have occurred in the U.S., none of which had been acquired indigenously in this country.