

Creutzfeldt-Jakob Disease (CJD)



Public Health Branch

Creutzfeldt-Jakob disease (CJD) is a human prion disease (also known as a transmissible spongiform encephalopathy, or TSE). It is believed to be caused by a misfolded form of a normal host protein, the prion protein (PrP). Case definitions for the three etiologic subtypes of classic CJD (cCJD) (sporadic, genetic and iatrogenic) and variant CJD (vCJD) are provided below.

Early consultation with the Canadian Creutzfeldt-Jakob Disease Surveillance System (CJDSS) (1-888-489-2999 or cjdss@phac-aspc.gc.ca) is recommended when CJD is suspected in a patient. The CJDSS offers support to health professionals through assistance with laboratory investigations, logistic support and education for case management and public health decision-making.

1. Case Definition

A. Sporadic Creutzfeldt-Jakob Disease (sCJD):

Definite sCJD:

- Rapidly progressive dementia PLUS one or more pathological features seen in brain tissue (1, 2) (refer to Table 1);
- AND
- No evidence of iatrogenic CJD or genetic prion disease (refer to sections B and C below) (1).

Probable sCJD: Routine investigations do not show alternate diagnosis;

AND

- Rapid cognitive decline PLUS two clinical features from Table 2, PLUS positive EEG (periodic triphasic sharp wave complexes at 1-2 Hz) OR diffusion-weighted magnetic resonance imaging (MRI) findings (restricted diffusion in basal ganglia or cortical ribboning) (1, 3);

OR

- Possible sCJD and at least one positive cerebrospinal fluid (CSF) protein assay [panel includes immunoassays for 14-3-3 protein and tau protein, and Quaking-induced Conversion (QuIC) assay disease-associated prion protein] in patients with disease duration < 2 years (1, 3, 4).

Possible sCJD:

- Rapid cognitive decline;
- AND
- Two clinical features from Table 2
- AND
- No supportive electroencephalogram (EEG) OR diffusion-weighted MRI (1).

Table 1: Pathological Features in Brain Tissue

1. Spongiform encephalopathy in cerebral and/or cerebellar cortex and/or subcortical grey matter.
2. Prion protein (PrP) immunoreactivity in plaque-like and/or diffuse synaptic and/or patchy/perivacuolar patterns by examination of tissue either directly or with assistance of capillary transfer from paraffin-embedded tissue (PET) to secondary support (PET blot).
3. Presence of protease resistant PrP by Western blot (1).

Table 2: Clinical Features

1. Myoclonus
2. Visual disturbances
3. Pyramidal or extrapyramidal features
4. Akinetic mutism
5. Cerebellar dysfunction (ataxia)
6. Higher cortical signs (neglect, aphasia, apraxia, acalculia)

B. Iatrogenic CJD (iCJD):

Definite iCJD:

- Rapidly progressive dementia PLUS one or more pathological features seen in brain tissue (2) (refer to section A, Table 1);

AND

- A recognized risk factor for iatrogenic transmission (refer to Table 3) (1).

Probable iCJD:

- Progressive predominant cerebellar syndrome in a recipient of cadaverically derived human pituitary growth hormone;

OR

- Probable sCJD (refer to section A) and a recognized risk factor for iatrogenic transmission (refer to Table 3) (1).

Table 3: Risk Factors for Iatrogenic Transmission of CJD

Note: Assessment of the relevance of any proposed risk factor to disease causation should take into account the timing of the putative exposure in relation to disease onset, especially where the putative exposure is recent. As well, this list is provisional, as the risks of iatrogenic transmission of prion disease by other routes are currently incompletely understood (1).

1. Treatment with human cadaveric pituitary growth hormone, human pituitary gonadotrophin or human dura mater graft.
2. Corneal graft in which the corneal donor has been classified as having a pathology-based diagnosis of human prion disease.
3. Neurosurgical exposure to instruments (including EEG depth electrodes) previously used on a patient classified as having a pathology-based diagnosis of human prion disease.

C. Genetic Prion Disease:

Definite Genetic Prion Disease:

- A pathology-based diagnosis of human prion disease PLUS pathogenic mutation in prion protein gene (*PRNP*) (the Canadian Creutzfeldt-Jakob Disease Surveillance System (1-888-489-2999 or cjdss@phac-aspc.gc.ca) may be consulted for the current list of *PRNP* mutations and strength of evidence for pathogenicity);

OR

- One or more pathological features seen in brain tissue (refer to section A, Table 1) PLUS definite or probable prion disease in a first-degree relative;

OR

- Probable sCJD (refer to section A) and a pathogenic mutation in *PRNP* (the Canadian Creutzfeldt-Jakob Disease Surveillance System (1-888-489-2999 or cjdss@phac-aspc.gc.ca) may be consulted for the current list of *PRNP* mutations and strength of evidence for pathogenicity);

OR

- Typical neuropathologic phenotype of Gerstmann-Sträussler-Scheinker disease (GSS)*(1).

*Presence of multicentric PrP-immunoreactive plaques in cerebral and/or cerebellar cortex, with neuron loss and spongiform change. Other large amorphous plaques or neurofibrillary tangles immunoreactive for PrP have been described in subsets of GSS, but these are associated with less-frequent *PRNP* mutations (A117V and F198S). Florid plaques or kuru plaques are not considered diagnostic for GSS (1).

Probable Genetic Prion Disease:

- Progressive neuropsychiatric disorder and definite or probable prion disease in a first degree relative

OR

- Progressive neuropsychiatric disorder and a pathogenic mutation in *PRNP* (the Canadian Creutzfeldt-Jakob Disease Surveillance System (1-888-489-2999 or cjdss@phac-aspc.gc.ca) may be consulted for the current list of *PRNP* mutations and strength of evidence for pathogenicity).

D. Variant Creutzfeldt-Jakob Disease:

Definite vCJD:

Progressive neuropsychiatric disorder AND neuropathologic confirmation (spongiform change, extensive PrP deposition, florid plaques throughout cerebrum and cerebellum) (1).

Probable vCJD:

1. Possible vCJD (refer to definition below);

AND

- Bilateral pulvinar high T2 signal OR restricted diffusion on MRI (relative to the signal intensity of other deep grey matter nuclei and cortical grey matter);

OR

2. Progressive neuropsychiatric disorder of < 6 months duration with no evidence of genetic prion disease or iatrogenic exposure to cCJD and routine investigation does not suggest an alternative diagnosis;

AND

- Tonsil biopsy positive for prion protein immunoreactivity: Note: Tonsil biopsy is not recommended routinely or in cases with EEG appearance typical of sporadic CJD, but may be useful in suspect cases in which the clinical features are compatible with vCJD and MRI does not show bilateral pulvinar high signal (1).

Possible vCJD:

- Progressive neuropsychiatric disorder of < 6 months duration with no evidence of genetic prion disease or iatrogenic exposure to cCJD and routine investigation does not suggest an alternative diagnosis;

AND

- At least 4 of the following:

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

IN THE ABSENCE OF

- The typical appearance of sCJD on EEG (i.e., either no generalized triphasic periodic complexes at ca. 1-2 Hz or EEG was not performed) in the early stages of the illness. Rarely, the typical appearance of sCJD may occur in the late stages of vCJD (1).

2. Reporting and Other Requirements

Creutzfeldt-Jakob disease is a designated disease under the Dead Bodies Regulation of *The Public Health Act* and this regulation should be referred to for the management of deceased individuals suspected or confirmed to have CJD <http://web2.gov.mb.ca/laws/regs/current/pdf-regs.php?reg=27/2009>.

Laboratory:

- All positive laboratory results from pathology, genetics, and cerebrospinal fluid (CSF) protein assays (e.g., positive QuIC, 14-3-3 protein >20,000 AU/mL, tau protein > 1,000 pg/mL) associated with classic and variant CJD are reportable to the Public Health Surveillance Unit by secure fax (204-948-3044).

Health Care Professional:

- Definite and probable cases of CJD (including sporadic CJD, iatrogenic CJD, genetic prion disease and vCJD) must be reported to the Public Health Surveillance

Unit by secure fax (204-948-3044) within 5 business days of being identified. The *Clinical Notification of Reportable Diseases and Conditions* form (<http://www.gov.mb.ca/health/publichealth/cdc/protocol/form13.pdf>) should be used.

- In deaths resulting from definite or suspected CJD, the medical examiner must be notified (204-945-2088) under C.C.S.M. c. F52 *The Fatality Inquiries Act*; 7.9(v).
- The regional Medical Officer of Health and Infection Prevention and Control should be notified as soon as a probable or confirmed case definition for vCJD is met.
- CJD is a reportable disease requiring Public Health follow-up. The health care professional may be contacted for additional information as part of the investigation.

Regional Public Health/First Nations Inuit Health Branch (FNIHB):

- Once the case has been referred to Regional Public Health/FNIHB, the *Communicable Disease Control Investigation Form* (www.gov.mb.ca/health/publichealth/cdc/protocol/form2.pdf) should be completed and returned to the Public Health Surveillance Unit by secure fax (204-948-3044).

Reporting to Canadian Blood Services:

- If the case investigation indicates that a probable or confirmed case of vCJD was a blood donor or blood recipient, the Public Health Surveillance Unit will notify Canadian Blood Services.

3. Clinical Presentation/Natural History

Creutzfeldt-Jakob Disease (CJD) is a fatal neurodegenerative disease (5). Cases of classic CJD can be distinguished from cases of GSS, FFI (Fatal Familial Insomnia) and variant CJD on the basis of clinical and pathologic data. Refer to sections 3.1 and 3.2 below as well as Table 4. CJD must be differentiated from other forms of dementia (especially Alzheimer's disease and dementia with Lewy bodies), other neurological diseases (including encephalitis and vasculitis), and toxic endocrine, autoimmune, and metabolic encephalopathies (6-8).

3.1 Classic Creutzfeldt –Jakob Disease:

The classical diagnostic presentation of CJD is a rapid cognitive decline with visual, cerebellar, pyramidal or extrapyramidal signs, myoclonus, and abnormalities on EEG or diffusion-weighted MRI. The mean duration of illness is 4.5 months (9). The clinical features of CJD can sometimes be seen in mimics for CJD, including Alzheimer's disease (AD) and less commonly dementia with Lewy bodies (DLB) (7, 8, 10). Neither AD nor DLB have the EEG or MRI changes seen in CJD.

Sporadic CJD (sCJD) is the most common form of CJD, and is believed to result from the spontaneous transformation of prion protein from its normal form (PrP^C, referring to its normal Cellular form) into an abnormally shaped form called PrP^{Sc} (for Scrapie, referring to a prion disease of sheep) (11, 12). Disease progression is rapid compared to other neurodegenerative conditions such as Alzheimer's or Parkinson's disease (9). In many patients with sCJD, there is a prodromal phase of psychiatric disturbance (e.g., sleep disturbance, depression, anxiety) before the onset of neurological signs (9).

The clinical presentation of iatrogenic CJD (iCJD) is very similar to sCJD (9), with rapid progression,

myoclonus, periodic sharp waves in the EEG and a diffuse cortical distribution of the abnormal or pathologic prion protein (9).

Patients may develop CJD because of heritable mutations of the human prion protein gene *PRNP* (11, 13); however, not all patients with *PRNP* mutations have a family history of prion disease (13). Genetic prion diseases include familial CJD, Gerstmann-Straussler-Scheinker (GSS) syndrome and Fatal Familial Insomnia (FFI) (11). Genetic CJD often phenotypically resembles sCJD, but there are variations in clinical presentation, age at disease onset, duration of illness and neuropathological findings depending on the specific mutation (10).

3.2 Variant Creutzfeldt-Jakob Disease:

Variant CJD usually starts with non-specific psychiatric symptoms (10, 14). Common early psychiatric features include dysphoria, withdrawal, anxiety, irritability, insomnia and lack of interest (10). Less frequently, vCJD begins with sensory or other neurological disturbances (10). Nearly half of the patients hallucinate, and hallucinations tend to coincide with delusions (10). Clear neurological signs are generally not apparent for many months after disease onset (10). The disease then progresses over months with increasing ataxia, global cognitive impairment, and involuntary movements (10). The disease culminates in a state of incapacity and mutism (10). The most frequent conditions mimicking vCJD are sCJD, Alzheimer’s disease and cerebral vasculitis (10). Refer to Table 4 below for a comparison of classic CJD and variant CJD.

Characteristic	Classic CJD	Variant CJD
Median age at death	68 years	28 years
Median duration of illness	4-5 months	13-14 months
Clinical signs and symptoms	Dementia; early neurologic signs	Prominent psychiatric behavioural symptoms: painful dysesthesias; delayed neurological signs
Periodic sharp waves on electroencephalogram (EEG)	Often present	Absent
“Pulvinar sign” on magnetic resonance imaging (MRI)*	Not reported	Present in > 75% cases
Presence of “florid plaques” on neuropathology	Rare or absent	Present in large numbers
Immunohistochemical analysis of brain tissue	Variable accumulation of protease resistant prion protein	Marked accumulation of protease resistant prion protein
Presence of agent in lymphoid tissue	Not readily detected	Readily detected

Source: Centers for Disease Control and Prevention. Clinical and Pathologic Characteristics Distinguishing Classic CJD from variant CJD, February 11, 2015 <http://www.cdc.gov/prions/vcjd/clinical-pathologic-characteristics.html> .

*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.

4. Etiology

As mentioned above, CJD is believed to be caused by misfolding and self-propagation of the host-encoded prion protein (PrP^C) (6, 12). The abnormal prion protein (PrP^{Sc}) is resistant to proteases, accumulates in the brain (9), and by an incompletely understood mechanism causes nerve cells to die (12, 15).

The origin of sCJD remains unknown (16). Case-control studies of sCJD have not identified any consistent environmental risk factor (5). Genetic prion diseases are associated with one of various mutations in the prion protein gene (PRNP) located on chromosome 20 that encodes for the normal prion protein (6).

5. Epidemiology

5.1 Reservoir and Source:

Humans are the only species naturally affected by CJD prions, with the exception of vCJD which results from zoonotic spread of bovine spongiform encephalopathy (BSE) from its reservoir, domestic cattle (17). The consumption of food of bovine origin contaminated with the agent of BSE has been strongly linked to the occurrence of vCJD in humans (18). The causal link between vCJD and BSE is based on epidemiological, biochemical and transmission studies (16). Subclinical infection with the BSE prion appears to be present in exposed human populations, especially in the United Kingdom (6, 17). One large scale UK survey (based on detection of the PrP^{Sc} in archived appendix samples) observed a prevalence of 493 per million population (95% Confidence Interval: 282–801) (19). The magnitude of the risk from such infections is unknown but they may represent a potential reservoir of infection for secondary human-to-human spread by blood transfusion, organ transplantation, or surgery (6). Prions can remain infectious for years in a dried state and are partially resistant to routine sterilization and

disinfection procedures commonly used by health care facilities (20).

5.2 Transmission:

CJD is not known to be spread by person-to-person contact or by the airborne/respiratory route (20). There is no firm evidence that sCJD is an exogenously acquired disease (6). Sporadic CJD has no recognizable pattern of transmission (21). The self-replicating abnormally folded prion protein causing sCJD is believed to originate spontaneously (6). Iatrogenic transmission of CJD (including sCJD, vCJD and genetic prion diseases) has occurred following the use of contaminated cadaver-derived human pituitary hormone, dura mater grafts and corneal grafts, as well as EEG depth electrodes and neurosurgical instruments (6). Tissues which are most infectious for iatrogenic transmission of CJD include the brain, spinal cord, pituitary gland and some parts of the eye (18). The detection of small amounts of abnormal PrP in a tissue does not necessarily mean that the tissue would transmit disease in all circumstances (22). The presence of familial cases of CJD has been attributed to genetic factors, rather than from person-to-person spread of illness within a family (9). Person-to-person transmission of classic CJD by blood, milk, saliva, urine or feces has not been reported (5). CJD has not been reported in infants born to infected mothers (5).

Transmission of vCJD is not well understood (15). Compelling evidence indicates that vCJD is the result of bovine-to-human transmission of BSE (9). The mechanism of transmission of BSE from cattle to humans has not been established, but the favoured hypothesis is that humans are infected through dietary consumption of the BSE agent (6). Secondary transmission of vCJD has been reported via blood and blood products (23, 24). In vCJD, other tissues such as the tonsils and appendix have been found to be infective, in contrast with classical CJD (15). Therefore,

patients with vCJD may pose a greater risk of transmitting iatrogenic infections than those with sporadic infection (20). There is no evidence that vCJD can be spread through touching or kissing a person with the disease (25). Milk and milk products from cows are not believed to pose any risk for transmitting the BSE agent (26).

The working assumption in the field is that all prion diseases may be transmitted under the right circumstances. Conversely, no prion disease has convincingly been shown not to be transmissible.

5.3 Occurrence:

General: CJD is thought to occur worldwide, but as systematic surveillance has only been undertaken in a minority of countries, the incidence in most of the world is unknown (10). The reported incidence is generally between 1 and 2 cases per million persons per year (14). Globally, over 80% of cases of CJD occur as sporadic disease (sCJD) (16). Most sCJD cases occur in persons between the ages of 60 and 80 years with a median age at death of about 68 years (16).

Genetic, iatrogenic, and variant forms of CJD show much lower and more variable incidence in different countries (16). Genetic prion disease accounts for approximately 10-15% of all classical CJD cases and iatrogenic CJD accounts for less than 1% of all classical CJD cases (27). The first iCJD case was reported from the United States of America in 1974 in a patient that had received a corneal transplant (10). Most countries of the world no longer use human-derived growth hormone (hGH), hence it can be expected that hGH-associated CJD will disappear over time (10). A recent publication summarized the epidemiological characteristics of a total of 469 cases of iCJD from all transmission routes that had been reported by all affected countries as of 2012 (28).

Worldwide, as of September 2016, 231 cases of vCJD have been reported, with a majority of them in the United Kingdom (178 cases) and France (27 cases). Variant CJD was first described in the United Kingdom in March 1996 (18). Compared to sCJD, vCJD is characterized by a younger age of onset and by longer illness duration (10). The incidence of vCJD cases is declining because of human dietary protection measures and changes in animal feeding and slaughtering practices (6). However, there is concern about iatrogenic transmission of vCJD by blood, surgery and dentistry (6).

Canada: Since 1998 when Health Canada created a national epidemiologic surveillance system for human prion diseases, the Canadian CJD Surveillance System (CJDSS), 1711 suspected CJD cases were referred to the CJDSS by November 30, 2016 (29). Of the 845 reported deaths due to definite and probable CJD for the same period, there were 776 sCJD, 34 familial CJD, 24 GSS, 5 FFI, 4 iCJD, and 2 vCJD (29). The two cases of vCJD were diagnosed in 2002 and 2011, and were believed to have been acquired outside of Canada (30, 31).

Manitoba: Eight cases of CJD, confirmed by autopsy, were reported to Manitoba Health, Seniors and Active Living from 2010 to 2015 inclusive. All cases appeared to be classic CJD.

5.4 Incubation Period: Incubation period is difficult to estimate, and may not be applicable, for the classic sporadic CJD and genetic prion disease subtypes as they are thought to arise endogenously (6). Iatrogenic CJD and vCJD in contrast are thought to be exogenously acquired and incubation periods could range from 15 months to over 30 years depending on the exposure route (6). In a 171-case cohort of UK vCJD patients reported to 2010, the estimated median incubation period after consuming BSE (bovine spongiform encephalopathy)-contaminated cattle products was 11.6 years (95%

Credible Interval: 10.9–12.2) from exposure to death (32). (Note that the upper boundary of the range of vCJD incubation periods may increase over time, although without substantial numbers of additional cases the median estimate is unlikely to change greatly).

5.5 Risk Groups: Individuals at greater risk of developing classic CJD are recipients of human dura mater graft, human cadaver-derived pituitary hormones (especially human cadaver-derived growth hormone), and cornea transplants; persons undergoing neurosurgery; and members of families with genetic prion disease (6). There is also significant variation in CJD mortality rates with age, which in Canada for example have been estimated at 0.05 per million per year and 7.1 per million per year in individuals < 50 and 70 -79 years of age respectively (33). Refer to section 8.1 for more detail.

Risk factors for the development of vCJD include young age (9), residence in the United Kingdom or other BSE-affected European countries, and methionine homozygosity at codon 129 of the prion protein gene (34).

5.6 Period of Communicability: The level of prion infectivity in the central nervous system (CNS) rises late in the incubation period, and high levels of infectivity occur in the CNS throughout symptomatic illness (6). Investigations of three recipients of blood contaminated with the vCJD agent indicate that the blood of asymptomatic, infected donors can contain infectivity 18 months to 3.5 years before the onset of vCJD (9).

6. Diagnosis

All forms of CJD are initially diagnosed based on clinical features, EEG and MRI findings (6). Early neurological consultation is strongly recommended.

Currently, definitive diagnosis of CJD requires an examination of the brain tissue of the patient

revealing PrP^{Sc} deposits and associated nerve cell loss resulting in the brain having a sponge-like appearance (4). Such specimens should be sent to the Winnipeg Health Sciences Centre Pathology Laboratory.

Where a reasonably high index of suspicion for CJD exists after consultation with a neurologist, cerebrospinal fluid (CSF) specimens should be submitted to Cadham Provincial Laboratory (CPL). Notification to CPL (204-945-6123) is preferred prior to specimen submission. At date of publication, the following protein tests are performed on submitted specimens that meet the minimum clinical criteria: a CSF Protein Marker test panel consisting of immunoassays for:

- 14-3-3 protein;
- tau protein;
- as well as detection of the disease associated form of the prion protein by the quaking induced conversion (QuIC) assay.

The sensitivity and specificity of the 14-3-3 protein varies by population tested and by laboratory but it has approximately 88% sensitivity and 72 – 87% specificity. The sensitivity and specificity of the Tau protein are approximately 86 -91% and 88 – 90% respectively.

The definitive test for genetic prion diseases is DNA sequence analysis of *PRNP* (the prion protein gene) for relevant mutations and it can be performed on a blood sample (35). *PRNP* mutations are found in all cases of CJD from families with a history of inherited prion disease, but have also been detected in individuals with no family history of dementia (up to one-third of prion disease cases with *PRNP* mutations) (9, 13). Genetic counselling and consultation with the CJDSS to obtain informed consent should occur prior to obtaining and submitting specimens for genetic testing. CPL should be called prior to submitting blood specimens for genetic testing

(204-945-6123). During regular business hours, the call should be directed to the Virus Section. After regular business hours, the on-call CPL physician (204- 787-2071) should be contacted.

Diagnosis of vCJD should be considered when patients with a history of residence in a BSE endemic area (e.g., United Kingdom, refer to section 7 below) develop a progressive neurodegenerative disease (9). After the onset of symptoms, bilateral pulvinar high T2 signal or restricted diffusion on MRI (relative to the signal intensity of other deep grey matter nuclei and cortical grey matter) or tonsil biopsy positive for prion protein immunoreactivity can establish a probable vCJD diagnosis. As soon as vCJD is suspected in a patient, the regional Medical Officer of Health should be contacted (after hours call the MOH on call 204-788-8666). Hospital Infection Prevention and Control should also be notified. The Virus Section of CPL (204-945-6123) should be contacted prior to submitting a tonsil biopsy specimen. After hours, the on-call CPL physician (204- 787-2071) should be contacted.

7. Key Investigations for Public Health Response

It is recommended that the following be considered in consultation with the Canadian Creutzfeldt-Jakob Disease Surveillance System (CJDSS) (1-888-489-2999 or cjdss@phac-aspc.gc.ca) when CJD is suspected in a patient.

- History of blood transfusion/donation.
- History of receiving or donating tissue/organs/hormones derived from human pituitary gland. In Canada, human growth hormone was used from 1965 until April 1985 (20).
- Residence between January 1980 and December 31, 1996 in

- The United Kingdom (UK) or France for a cumulative total of three months or more;
OR
- Saudi Arabia for six months or more.
- Residence in Western Europe (outside the UK or France) for 5 years or more extending from January 1980 to December 31, 2007 (36).
- Detailed history of surgery or invasive procedures the patient has undergone during the relevant lookback period for the type of CJD suspected or diagnosed.
- Family history of CJD.

8. Control

8.1 Definitions:

High-risk: Individuals considered to be at high-risk of transmitting CJD iatrogenically are those diagnosed, prospectively or retrospectively with:

- Definite, probable or possible classic CJD (refer to case definitions in section 1).
- Suspected CJD – undiagnosed, rapidly progressive dementia and CJD not ruled out.
- Asymptomatic carrier of genetic prion disease – a person who displays no symptoms or signs of prion disease, but meets one or more of the following criteria:
 - The person has been confirmed by genetic testing to carry a genetic mutation causative of familial CJD, GSS, or FFI;
 - The person has not been tested for a genetic mutation but has at least one first degree relative who has been confirmed by genetic testing to carry such a mutation, with or without pathologic confirmation of prion disease;
 - The person has not been tested for a genetic mutation but has two or more first degree relatives who have

been diagnosed with either confirmed or probable prion disease, with or without confirmation by genetic testing (22).

At-risk: At-risk individuals are defined as:

- Recipients of human tissue derived pituitary hormone treatment (either growth hormone or gonadotrophin).
- Recipients of a dura mater graft (until 1992 for Lyodura® grafts, until 1997 for Tutoplast Dura® grafts).
- Recipients of a corneal graft originating in a jurisdiction that does not require graft donors to be screened for neurological disease.
- Individuals who have been exposed, via contact with instruments, to high-infectivity tissue of a confirmed CJD patient (22).

8.2 Management of Cases:

Early consultation with the Canadian Creutzfeldt-Jakob Disease Surveillance System (CJDSS) (1-888-489-2999 or cjdss@phac-aspc.gc.ca) is recommended when CJD is suspected in a patient. CJDSS offers support to health professionals through assistance with laboratory investigations, logistic support and education for case management and public health decision-making.

- No treatment has been shown in humans to slow or stop the progressive neurodegeneration (5).
- Supportive therapy is necessary to manage dementia, spasticity, rigidity and seizures occurring during the course of the illness (5).
- Consultation with a neurologist is recommended.
- Psychological support may be helpful to affected families (5).

- The attending physician should notify the family of the clinical diagnosis and the histopathology results after death.
- Even if CJD is ruled out in the case, the family should be instructed to prevent organ/tissue/blood donation. The exception would be if there was a clear alternate diagnosis in the patient where it was certain that organ/tissue/blood donation would pose no risk to the recipient.

Infection Prevention and Control Measures:

The prions of CJD and other transmissible spongiform encephalopathies are not readily inactivated by standard disinfection and sterilization methods. Refer to appropriate guidelines.

- For cases in health care facilities, refer to page 87 of the Manitoba Health document *Routine Practices and Additional Precautions: Preventing the Transmission of Infection in Health Care* available at: <http://www.gov.mb.ca/health/publichealth/cdc/docs/ipc/rpap.pdf>.
- Public Health Agency of Canada's *Infection Control Guidelines for Classic Creutzfeldt-Jakob Disease in Canada Quick Reference Guide 2007* available at: <http://www.phac-aspc.gc.ca/nois-sinp/pdf/cjd-eng.pdf>.
- If a case of vCJD is clinically suspected or diagnosed, for specific infection prevention and control measures, the practitioner should consult with the Canadian Creutzfeldt-Jakob Disease Surveillance System at 1-888-489-2999.

8.3 Management of Contacts of Cases and Other Potentially Exposed People:

- There is no screening test available for persons who may have been exposed to

CJD or vCJD to detect the infection before symptoms appear (15).

- Where appropriate, individuals who are known to be at-risk of developing CJD should be notified. The notified individuals should be asked to take public health precautions to reduce the risk of transmitting infection to other people (37).
- Possible testing of family members with genetic counseling both before and after testing is indicated when the case was diagnosed with genetic (familial) disease (5, 38).
- Available evidence indicates that even prolonged intimate contact with CJD patients has not resulted in transmission of disease (5).

8.4 Management of Clusters/Outbreaks:

An outbreak is defined generically as the occurrence of case(s) in a particular area and period of time in excess of the expected number of cases. Given the rarity of CJD cases in Manitoba, small variations in case numbers should be interpreted carefully as they may not represent a significant departure from what is expected. Where a common infectious exposure has been suspected on the basis of surveillance data, it should also be remembered that CJD is a disease with a long silent incubation period that is expected to vary in duration depending on intensity and route of infectious exposure, among other factors.

With the above caveats in mind, it is very important to remain alert to the occurrence of CJD cases (and potentially, case clusters) that may have originated through infectious transmission. In this light, individual cases of suspected iatrogenic or variant CJD require prompt public health attention in order to expedite diagnosis and investigate risk factors for exposure. In addition, ongoing close monitoring of CJD epidemiology is

recommended, in collaboration with the Public Health Agency of Canada's Canadian CJD Surveillance System (1-888-489-2999 or cjdss@phac-aspc.gc.ca).

8.5 Preventive Measures:

- There is no specific way to protect people from developing sporadic or familial CJD (39).

Prevention of Iatrogenic Transmission:

- The most effective, safe, and efficient means of preventing iatrogenic transmission of CJD is to identify high-risk individuals before an invasive procedure in order to implement the required infection prevention and control measures, and to have a system for instrument tracking (22).
- The number of instruments used for any procedure should be limited as much as possible. Disposable, rather than reusable instruments should be used whenever possible and especially when in contact with high-infectivity tissue (22). When reusable instruments must be used, whenever possible, instruments that can tolerate the rigors of CJD decontamination should be used (22). Prion-contaminated medical devices that are impossible or difficult to clean should be discarded. Destroying/discarding surgical instruments that have been used on certain tissues of people with CJD and not using their organs for transplant guards against iCJD (39). Refer to the Public Health Agency of Canada's *Infection Control Guidelines for Classic Creutzfeldt-Jakob Disease in Canada Quick Reference Guide 2007* available at: <http://www.phac-aspc.gc.ca/nois-sinp/pdf/cjd-eng.pdf> .
- Medical devices used on a CJD patient (e.g., cardiac catheters, pace-makers) should not be re-used on another patient.

- Persons with CJD or other forms of dementia should be excluded from donating organs, blood, tissue and hormones. Canadian Blood Services excludes individuals who have received a dura mater (brain covering) transplant from donating.
 - To ensure there is a large margin of safety in Canada's blood supply, Health Canada has recommended that people who are at-risk of developing iatrogenic CJD and blood relatives (parent, child, sibling) of people with familial CJD be deferred from donating blood or blood products (20).
 - Canadian Blood Services has developed blood donation deferral policies for individuals with risk factors for vCJD <https://www.blood.ca/en/blood/abcs-eligibility>.
 - The sale of human dura mater is no longer permitted in Canada (20).
 - As of 1985, the use of cadaver-extracted growth hormone has been replaced by recombinant growth hormone, which does not pose a risk of CJD (20).
- enters the slaughter system, the resulting meat and meat products should not contain those tissues known to contain the highest levels of BSE infectivity (40).
- As of 2007, SRM was also prohibited in all animal feeds, pet foods and fertilizers (40).
 - When domesticated animals are identified as having prion disease (e.g., BSE in cattle, scrapie in sheep, chronic wasting disease in deer or elk), appropriate farm management practices are followed (e.g., reporting, quarantine, disinfection, humane destruction).
 - Although the risk of transmission of chronic wasting disease (CWD, a prion disease of elk, deer and other cervids) to humans has not been fully characterized, to reduce the risk of exposure to CWD hunters should consult with appropriate wildlife agencies to identify areas where CWD occurs, and continue to follow advice provided by public health and wildlife agencies (41-43).

Prevention of Foodborne Transmission:

- Consumption of central nervous system tissue from all mammals should be avoided.
- The risk of exposure to the BSE agent through the food supply has been reduced by requiring that tissues that have been demonstrated to have a higher potential for infectivity of BSE (specified risk material) (SRM) be removed at the time of slaughter and diverted away from the food supply. Refer to Health Canada Food Directorate Policy on Specified Risk Material http://www.hc-sc.gc.ca/fn-an/securit/animal/bse-esb/policy_srm-politique_mrs-eng.php. Removing SRM means that even if an infected animal

References

1. Public Health Agency of Canada. Case Definitions for Communicable Diseases under National Surveillance. *Canada Communicable Disease Report CDR* 2009; 35S2: 1-123.
2. Manix M, Kalakoti P, Henry M et al. Creutzfeldt-Jakob disease: updated diagnostic criteria, treatment algorithm, and the utility of brain biopsy. *Neurosurgical Focus* 39(5): E2, 2015.
3. University of California, San Francisco. CJD Diagnostic Criteria. Available at: <http://memory.ucsf.edu/cjd/medical/criteria>.
4. Godal D, Simon SL, Cheng K and Knox JD. A new diagnostic test for Creutzfeldt Jakob

disease (CJD): Real-Time Quaking Induced Conversion (RT-QuIC). *CCDR* 2015; 41(8): 192-195. Available at: http://www.phac-aspc.gc.ca/publicat/ccdr-rmtc/15vol41/dr-rm41-08/assets/pdf/15vol41_08-eng.pdf .

5. American Academy of Pediatrics. Prion Diseases: Transmissible Spongiform Encephalopathies. In: Pickering LK ed. *Redbook 2012 Report of the Committee on Infectious Diseases 29th ed.* Elk Grove Village, IL: American Academy of Pediatrics, 2012; 595-598.

6. Heymann David L. Prion Diseases. In: *Control of Communicable Diseases Manual 20th ed*, American Public Health Association, Washington, 2014; 484-490.

7. Coulthart MB, Jansen GH, Olsen E et al. Diagnostic accuracy of cerebrospinal fluid protein markers for sporadic Creutzfeldt-Jakob disease in Canada: a 6-year prospective study. *BMC Neurology* 2011; 11: 133.

8. Murray Katherine. Creutzfeldt-Jacob disease mimics, or how to sort out the subacute encephalopathy patient. *Postgrad Med J* 2011; 87:369-378.

9. Bosque PJ and Tyler KL. Prions and Prion Diseases of the Central Nervous System (Transmissible Neurodegenerative Diseases). In: Bennett JE, Dolin R and Blaser MJ eds. *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases 8th ed.* Elsevier, Philadelphia, 2015.

10. World Health Organization. WHO manual for surveillance of human transmissible spongiform encephalopathies including variant Creutzfeldt – Jakob disease, 2003.

11. Center for Disease Control and Prevention. Occurrence and Transmission, 2015. Available at:

<http://www.cdc.gov/prions/cjd/occurrence-transmission.html> .

12. Prusiner Stanley B. Prions. *Proc. Natl. Acad. Sci. USA* 1998; 95:13363-13383.

13. Kovács GG, Puopolo M, Ladogana A et al. Genetic prion disease: the EURO-CJD experience. *Hum Genet* 2005; 118: 166-174.

14. Heath CA, Cooper SA, Murray K et al. Validation of Diagnostic Criteria for Variant Creutzfeldt-Jakob Disease. *Annals of Neurology* 2010; 67(6):761-770.

15. Public Health Agency of Canada. Frequently Asked Questions about Variant Creutzfeldt-Jakob Disease (Variant CJD) May 2003. Available at: <http://www.phac-aspc.gc.ca/cjd-mcj/vcjd-faq-03-eng.php> .

16. World Health Organization. WHO Guidelines on Tissue Infectivity Distribution in Transmissible Spongiform Encephalopathies, 2006. Available at: <http://www.who.int/bloodproducts/cs/TSEPUBLISHEDREPORT.pdf?ua=1> .

17. Diack AB, Head MW, McCutcheon S et al. Variant CJD – 18 years of research and surveillance. *Prion* 2014; 8(4): 286-295.

18. World Health Organization. Variant Creutzfeldt-Jakob disease. Fact Sheet N° 180, February 2012. Available at: <http://www.who.int/mediacentre/factsheets/fs180/en/> .

19. Gill ON, Spencer Y, Richard-Loendt A et al. Prevalent abnormal prion protein in human appendixes after bovine spongiform encephalopathy epizootic: large scale survey. *BMJ* 2013; 347.

20. Health Canada. *Classic Creutzfeldt-Jakob Disease in Canada*. An infection control guideline. *CCDR* 2002; 28S5: 1-84.

21. Centers for Disease Control and Prevention. About CJD, 2015. Available at: <http://www.cdc.gov/prions/cjd/about.html> .
22. Public Health Agency of Canada. Infection Control Guidelines Classic Creutzfeldt-Jakob Disease in Canada. Quick Reference Guide 2007. Available at: <http://www.phac-aspc.gc.ca/nois-sinp/pdf/cjd-eng.pdf> .
23. The National CJD Research & Surveillance Unit (NCJDRSU), University of Edinburgh. The Different Types of Human Prion Disease (Including CJD); 2012. Available at: <http://www.cjd.ed.ac.uk/documents/cjdtype.pdf> .
24. Dodd RY. Current risk for transfusion transmitted infections. *Current Opinion in Hematology* 2007; 14(6):671-676.
25. Public Health Agency of Canada. First Canadian Case of Variant Creutzfeldt-Jakob Disease (Variant CJD). Available at: <http://www.phac-aspc.gc.ca/cjd-mcj/vcjd-ca-eng.php> .
26. Centers for Disease Control and Prevention. Risk for Travelers, 2015. Available at: <http://www.cdc.gov/prions/vcjd/risk-travelers.html> .
27. Public Health Agency of Canada. Classical Creutzfeldt –Jakob Disease, May 2003. Available at: <http://www.phac-aspc.gc.ca/cjd-mcj/cjd-eng.php> .
28. Brown P, Brandel J-P, Sato T et al. Iatrogenic Creutzfeldt-Jako Disease, Final Assessment. *Emerging Infectious Diseases* 2012; 18(6):901-907.
29. Public Health Agency of Canada. Creutzfeldt-Jakob Disease CJD-Surveillance System. Referrals of Suspected CJD Reported by CJDSS, 1997-2016 as of November 30, 2016. Available at: <http://www.phac-aspc.gc.ca/hcai-iamss/cjd-mcj/cjdss-ssmcj/stats-eng.php> .
30. Jansen GH, Voll CL, Gervais R et al. First Case of Variant Creutzfeldt-Jakob Disease in Canada. *CCDR* 2003; 29(13):117-120.
31. Canadian Creutzfeldt-Jakob Disease Surveillance System, National Microbiology Laboratory, Public Health Agency of Canada. Variant Creutzfeldt-Jakob Disease in a Canadian resident. *Infectious Diseases New Brief* – March 11, 2011 Issue 10.
32. Garske T and Ghani AC. Uncertainty in the Tail of the Variant Creutzfeldt-Jakob Disease Epidemic in the UK. *PLoS ONE* 2010; 5(2): e15626.
33. Coulthart MB, Jansen GH, Connolly T et al. Creutzfeldt-Jakob disease mortality in Canada, 1998-2013. *CCDR* 2015; 41(8):182-191.
34. The National CJD Research & Surveillance Unit (NCJDRSU), University of Edinburgh. 22nd Annual Report 2013 Creutzfeldt-Jakob Disease Surveillance in the UK. Available at: <http://www.cjd.ed.ac.uk/documents/report22.pdf> .
35. The National CJD Research & Surveillance Unit (NCJDRSU), University of Edinburgh. Investigations Undertaken in Possible Cases of Human Prion Disease; 2012. Available at: <http://www.cjd.ed.ac.uk/documents/investigations.pdf> .

36. Canadian Blood Services. The ABCs of Eligibility. Available at:

<https://www.blood.ca/en/blood/abcs-eligibility> .

[-animals/diseases/reportable/cwd/fact-sheet/eng/1330189947852/1330190096558](https://www.inspection.gc.ca/animals/diseases/reportable/cwd/fact-sheet/eng/1330189947852/1330190096558) .

37. Public Health England, Health Protection Scotland. Public Health Action Following A Report Of A New Case Of CJD Or A Person at Increased Risk of CJD January 2014.

Available at:

<https://www.gov.uk/government/publications/cjd-public-health-action-following-report-of-new-case-or-person-at-increased-risk> .

38. Public Health Agency of Canada. Winter 2012 CJD in Canada Healthcare Provider Edition.

39 Public Health Agency of Canada. Frequently asked questions about CJD, 2008.

Available at: <http://www.phac-aspc.gc.ca/hcai-iamss/cjd-mcj/faq-qfp-eng.php> .

40. Canadian Food Inspection Agency. Overview of Canada’s BSE Safeguards 2013.

Available at:

<http://www.inspection.gc.ca/animals/terrestrial-animals/diseases/reportable/bse/safeguards/eng/1363896195473/1363896681768>

41. Race B, Meade-White KD, Phillips K et al. Chronic Wasting Disease Agents in Nonhuman Primates. *Emerging Infectious Diseases* 2014; 20(5): 833-837.

42. Belay ED, Maddox RA, Williams ES et al. Chronic Wasting Disease and Potential Transmission to Humans. *Emerging Infectious Diseases* 2004; 10(6): 977-984.

43. Canadian Food Inspection Agency. Chronic Wasting Disease (CWD) –Fact Sheet 2012.

<http://www.inspection.gc.ca/animals/terrestrial>