Ministry of Health and Long-Term Care

Infectious Diseases Protocol

Appendix B: Provincial Case Definitions for Diseases of Public Health Significance

Disease: Creutzfeldt-Jakob Disease, all types

Effective: February 2019

Ontario

Creutzfeldt-Jakob Disease, all types
Sporadic Creutzfeldt-Jakob Disease (sCJD)

1.0 Provincial Reporting

Confirmed, probable and suspect cases

2.0 Type of Surveillance

Case-by-case

3.0 Case Classification

3.1 Confirmed Case

Neuropathologically confirmed, with confirmation of protease-resistant prion protein (immunohistochemistry, PET blot, or Western Blot).

3.2 Probable Case

- Rapidly progressive dementia
  AND
- At least two additional neurological manifestations (See Section 5.0 – Clinical Evidence)
  AND
- One of three clinical tests:
  - Typical electroencephalography (EEG): generalized bilateral or unilateral triphasic periodic complexes at approximately one per second, lasting continuously for at least 10 seconds.
  - MRI with caudate nucleus and/or (anterior) putamen attenuation (preferred sequence DWI or FLAIR).
  - Positive assay for 14-3-3 protein in cerebrospinal fluid (CSF) **AND** total disease duration less than 24 months.

3.3 Suspect Case

- Rapidly progressive dementia
  AND
- At least two additional neurological manifestations (See Section 5.0 – Clinical Evidence)
  AND
- Duration of illness less than 2 years in the absence of a conclusive MRI and 14-3-3 protein assay.

4.0 Laboratory Evidence

4.1 Laboratory Confirmation

The following will constitute a confirmed case of sporadic Creutzfeldt-Jakob Disease:

- Confirmation of protease-resistant prion protein (immunohistochemistry, PET blot, or Western Blot), and when available, combined with routine neuropathological evidence of CJD (typical spongiosis). See also 4.3.

4.2 Approved/Validated Tests

- Immunohistochemistry (or PET blot) demonstrating prion protein immunoreactivity (plaque and/or diffuse synaptic and/or perivacuolar): confirmatory (if positive)
- Prion Protein (PrP) Western blot: confirmatory (if positive)
- Histopathology to demonstrate spongiform encephalopathy in cerebral and/or cerebellar cortex and/or subcortical grey matter: supportive (if positive)
- *PRNP* gene sequencing: supportive (if negative)
- CSF 14-3-3 Western blot: supportive (if positive).

The CJD Surveillance System (phone 1-888-489-2999) provides support for pathological evaluation (autopsies and biopsies), CSF testing, and genetic testing.

4.3 Indications and Limitations

- Histopathologic evidence of spongiform change is no longer considered sufficient in itself for diagnostic confirmation of CJD. However, the diagnostics in CJD/prion diseases on both a clinical and laboratory level are complex.
- Demonstration of scrapie-associated fibrils (SAF) by electron microscopy historically was part of the diagnostic criteria. Although historically important, this technique is no longer used for diagnostic purposes.
- Absence of a known pathogenic mutation causative for genetic CJD supports a diagnosis of sCJD.
- Because of limited diagnostic specificity, the CSF 14-3-3 assay is restricted to a supporting role in the diagnosis of probable sCJD.

5.0 Clinical Evidence

Additional neurological manifestations include:

- Myoclonus
- Visual or cerebellar disturbances such as ataxia
- Pyramidal or extrapyramidal symptoms
- Akinetic mutism

6.0 ICD 10 Code(s)

A81.0 Creutzfeldt-Jakob disease

7.0 References

Heymann DL, editor. Control of Communicable Diseases Manual. 20 ed. Washington, D.C: American Public Health Association; 2015.

National Creutzfeldt-Jakob Disease Research & Surveillance Unit. Surveillance: Diagnostic Criteria. Edinburgh, UK: The University of Edinburgh; 2017. Available from: http://www.cjd.ed.ac.uk/surveillance

Public Health Agency of Canada. Creutzfeldt-Jakob Disease, Classic and Variant. In: Case Definitions for Communicable Diseases under National Surveillance. Canada Communicable Disease Report. 2009;35S2.

Iatrogenic Creutzfeldt-Jakob Disease

1.0 Provincial Reporting

Confirmed and probable cases

2.0 Type of Surveillance

Case-by-case

3.0 Case Classification

3.1 Confirmed Case

- Confirmed CJD (see Confirmed Sporadic CJD section 3.1),
  AND
- A recognized iatrogenic factor (see Section 7.0 - Comments).

3.2 Probable Case

- Progressive predominant cerebellar syndrome in human pituitary hormone recipients.
  OR
- Probable CJD (see Probable Sporadic CJD section 3.2),
  AND
- A recognized iatrogenic risk factor (see Section 7.0 - Comments).

4.0 Laboratory Evidence

4.1 Laboratory Confirmation

The following will constitute a confirmed case of iatrogenic CJD in the presence of a recognized iatrogenic risk:

- Confirmation of protease-resistant prion protein (immunohistochemistry, PET blot, or Western Blot), and when available, combined with routine neuropathological evidence of CJD (typical spongiosis). See also 4.3. Findings need to be interpreted in the presence of a risk factor as described in Section 7.0 – Comments.

4.2 Approved/Validated Tests

- Histopathology to demonstrate spongiform encephalopathy in cerebral and/or cerebellar cortex and/or subcortical grey matter: supportive (if positive)
- Immunohistochemistry (or PET blot) demonstrating prion protein immunoreactivity (plaque and/or diffuse synaptic and/or perivacuolar): confirmatory
- PrP-res Western blot: confirmatory (if positive)
- *PRNP* gene sequencing: supportive (if negative)
- CSF 14-3-3 Western blot: supportive (if positive)

The CJD Surveillance System (phone 1-888-489-2999) provides support for pathological examination (autopsies and biopsies), CSF testing, and genetic testing.

4.3 Indications and Limitations

- Histopathologic evidence of spongiform change is no longer considered sufficient in itself for diagnostic confirmation of CJD. However, the diagnostics in CJD/prion diseases on both a clinical and laboratory level are complex.
- Demonstration of SAF by electron microscopy historically was part of the diagnostic criteria. Although historically important, this technique is no longer used for diagnostic purposes.
- Absence of a known pathogenic mutation causative for genetic CJD supports a diagnosis of iatrogenically transmitted CJD.
- Because of limited diagnostic specificity, the CSF 14-3-3 assay is restricted to a supporting role in the diagnosis of probable sporadic CJD.

5.0 Clinical Evidence

Neurological manifestations include:

- Rapidly progressive dementia
- Myoclonus
- Visual or cerebellar disturbances such as ataxia
- Pyramidal or extrapyramidal features
- Akinetic mutism

6.0 ICD 10 Code(s)

A81.0 Creutzfeldt-Jakob disease

7.0 Comments

Relevant exposure risks for classification as iatrogenic CJD:

- Treatment with human pituitary growth hormone, human pituitary gonadotrophin or human dura mater graft.
- Corneal graft in which the corneal donor has been classified as definite or probable human prion disease.
- Exposure to neurosurgical instruments previously used in a case of definite or probable human prion disease.

Note:

i. The relevance of any exposure to disease causation must take into account the timing of exposure in relation to disease onset.
ii. The above list is provisional as previously unrecognized mechanisms of human prion disease may occur.

8.0 References

Heymann DL, editor. Control of Communicable Diseases Manual. 20 ed. Washington, D.C: American Public Health Association; 2015.

National Creutzfeldt-Jakob Disease Research & Surveillance Unit. Surveillance: Diagnostic Criteria. Edinburgh, UK: The University of Edinburgh; 2017. Available from: http://www.cjd.ed.ac.uk/surveillance

Public Health Agency of Canada. Creutzfeldt-Jakob Disease, Classic and Variant. In: Case Definitions for Communicable Diseases under National Surveillance. Canada Communicable Disease Report. 2009;35S2.

Genetic CJD

1.0 Provincial Reporting

Confirmed and probable cases

2.0 Type of Surveillance

Case-by-case

3.0 Case Classification

3.1 Confirmed Case

- Confirmed CJD
  AND
- Confirmed or probable CJD in a first-degree relative

OR

- Confirmed CJD
  AND
- Pathogenic *PRNP* mutation (see Section 7.0 – Comments for further discussion of *PRNP* mutations and their associated phenotypes)

3.2 Probable Case

- Progressive neuropsychiatric disorder
  AND
- Confirmed or probable CJD in a first-degree relative

OR

- Progressive neuropsychiatric disorder
  AND
- Pathogenic *PRNP* mutation (see Section 7.0 – Comments for further discussion of *PRNP* mutations and their associated phenotypes)

4.0 Laboratory Evidence

4.1 Laboratory Confirmation

The following will constitute a confirmed case of genetic CJD:

- Confirmation of protease-resistant prion protein (immunohistochemistry, PET blot, or Western Blot), and when available, combined with routine neuropathological evidence of CJD (typical spongiosis). This must be in combination with genetic or family history as described in 3.1. Please also see 4.3.

4.2 Approved/Validated Tests

- Histopathology to demonstrate spongiform encephalopathy in cerebral and/or cerebellar cortex and/or subcortical grey matter: supportive (if positive)

- Immunohistochemistry (or PET blot) demonstrating prion protein immunoreactivity (plaque and/or diffuse synaptic and/or perivascular): confirmatory (if positive)
- PrP Western blot: confirmatory (if positive)
- *PRNP* gene sequencing: supportive (if positive)
- CSF 14-3-3 Western blot: supportive (if positive)

The CJD Surveillance System (phone 1-888-489-2999) provides support for pathological examination (autopsies and biopsies), CSF testing, and genetic testing.

4.3 Indications and Limitations

- Histopathologic evidence of spongiform change is no longer considered sufficient in itself for diagnostic confirmation of CJD. However, the diagnostics in CJD/prion diseases on both a clinical and laboratory level are complex.
- Demonstration of SAF by electron microscopy historically was part of the diagnostic criteria. Although historically important, this technique is no longer used for diagnostic purposes.
- Because of problems with diagnostic specificity, the CSF 14-3-3 assay is restricted to a supporting role in the diagnosis of probable sporadic CJD.

5.0 Clinical Evidence

Neurological manifestations include:

- Rapidly progressive dementia
- Myoclonus
- Visual or cerebellar disturbances such as ataxia
- Pyramidal or extrapyramidal features
- Akinetic mutism

6.0 ICD 10 Code(s)

A81.0 Creutzfeldt-Jakob disease

7.0 Comments

Genetic CJD

- *PRNP* mutations associated with a neuropathologic phenotype of Creutzfeldt-Jakob disease (CJD): P105T; G114V; R148H; D178N on 129V allele; V180I; V180I + M232R; T183A; T188A; T193I; E196K; E200K; V203I; R208H; V210I; E211Q; M232R; octapeptide repeat insertions 96 bp, 120 bp, 144 bp, 168 bp and deletion 48 bp
- *PRNP* mutations associated with other neuropathologic phenotypes I138M, G142S, Q160Stop, T188K, T188R, P238S, M232R; octapeptide repeat insertions (various lengths)

8.0 References

Heymann DL, editor. Control of Communicable Diseases Manual. 20 ed. Washington, D.C: American Public Health Association; 2015.

National Creutzfeldt-Jakob Disease Research & Surveillance Unit. Surveillance: Diagnostic Criteria. Edinburgh, UK: The University of Edinburgh; 2017. Available from: http://www.cjd.ed.ac.uk/surveillance

Public Health Agency of Canada. Creutzfeldt-Jakob Disease, Classic and Variant. In: Case Definitions for Communicable Diseases under National Surveillance. Canada Communicable Disease Report. 2009;35S2.

Variant Creutzfeldt-Jakob Disease (vCJD)

1.0 Provincial Reporting

Confirmed, probable, and suspect cases

2.0 Type of Surveillance

Case-by-case

3.0 Case Classification

3.1 Confirmed Case

- Progressive neuropsychiatric disorder
  AND
- Neuropathological confirmation of vCJD: spongiform change and extensive PrP deposition with florid plaques, throughout the cerebrum and cerebellum

3.2 Probable Case

- Progressive neuropsychiatric disorder of duration >6 months, where routine investigations do not suggest an alternative diagnosis and there is no evidence of iatrogenic exposure or a genetic form of CJD
  AND
- Four out of five criteria from Section 5.0
  AND
- Electroencephalography (EEG) does not show typical appearance of sporadic CJD: generalized triphasic periodic complexes at approximately one per second; or no EEG performed
  AND
- MRI brain scan shows bilateral symmetrical pulvinar high signal, relative to the signal intensity of other deep gray-matter nuclei and cortical gray matter

OR

- Progressive neuropsychiatric disorder of duration >6 months, where routine investigations do not suggest an alternative diagnosis and there is no evidence of iatrogenic exposure or evidence of a genetic form of CJD
  AND
- Tonsil biopsy positive for prion protein immunoreactivity

3.3 Suspect Case

- Progressive neuropsychiatric disorder of duration >6 months, in the absence of a conclusive MRI or tonsil biopsy, where routine investigations do not suggest an

alternative diagnosis and there is no evidence of iatrogenic exposure or evidence of a genetic form of CJD
AND

- Four out of five criteria from Section 5.0
  AND
- Electroencephalography (EEG) does not show typical appearance of sporadic CJD: generalized triphasic periodic complexes at approximately one per second; or no EEG performed

4.0 Laboratory Evidence

4.1 Laboratory Confirmation

The following will constitute a confirmed case of vCJD:

- Spongiform change and extensive PrP deposition with florid plaques, throughout the cerebrum and cerebellum (see also 4.3 – Indications and Limitations), in a patient with progressive neuropsychiatric disorder.

4.2 Approved/Validated Tests

- Immunohistochemistry (or PET blot) of brain tissue demonstrating prion protein immunoreactivity (florid plaques, throughout the cerebrum and cerebellum): confirmatory (if positive)
- PrP Western blot of brain tissue: confirmatory (if positive)
- Histopathology to demonstrate spongiform encephalopathy in cerebral and/or cerebellar cortex and/or subcortical grey matter with florid plaques: supportive (if positive)
- Immunohistochemistry (or PET blot) of tonsil demonstrating prion protein immunoreactivity: supportive (if positive)
- PrP Western blot of tonsil: supportive (if positive)
- *PRNP* gene sequencing: supportive (if homozygous Met/Met at codon 129)
- CSF 14-3-3 Western blot: supportive (if positive)

The CJD Surveillance System (phone 1-888-489-2999) provides support for pathological examination (autopsies and biopsies), CSF testing, and genetic testing.

4.3 Indications and Limitations

- Histopathologic evidence of spongiform change is no longer considered sufficient in itself for diagnostic confirmation of CJD. However, the diagnostics in CJD/prion diseases on both a clinical and laboratory level are complex.
- Demonstration of SAF by electron microscopy historically was part of the diagnostic criteria. Although historically important, this technique is no longer used for diagnostic purposes.
- All known clinical cases of vCJD have been homozygous Met/Met at codon 129 of the *PRNP* gene.
- Because of problems with diagnostic sensitivity, the role of CSF 14-3-3 assay in diagnosis of vCJD has not yet been formalized.

- In late stages of the disease triphasic waves/periodic complexes have been described in the EEG, similar to sporadic CJD.
- In late stages of the disease signal attenuation in the neocortex and caudate nucleus/putamen have been described to be similar to the pulvinar/thalamus attenuation.

5.0 Clinical Evidence

Neurological manifestations include:

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

6.0 ICD 10 Code (s)

A81.0 Creutzfeldt-Jakob disease

7.0 References

Heymann DL, editor. Control of Communicable Diseases Manual. 20 ed. Washington, D.C: American Public Health Association; 2015.

National Creutzfeldt-Jakob Disease Research & Surveillance Unit. Surveillance: Diagnostic Criteria. Edinburgh, UK: The University of Edinburgh; 2017. Available from: http://www.cjd.ed.ac.uk/surveillance

Public Health Agency of Canada. Creutzfeldt-Jakob Disease, Classic and Variant. In: Case Definitions for Communicable Diseases under National Surveillance. Canada Communicable Disease Report. 2009;35S2.

8.0 Document History

Table 1: History of Revisions

Revision Date	Document Section	Description of Revisions
March 2017	sCJD 3.1 Confirmed Case	Delete “immunocytochemically” Add “,”, delete “:”, and add “with” after “confirmed” Replace “immunocytochemistry” with : immunohistochemistry” and add “,PET blot,” after “immunohistochemistry”
March 2017	sCJD 3.2 Probable Case	Add “One of three clinical tests:” And include two new bullet points: “- MRI with caudate nucleus and/or (anterior) putamen attenuation (preferred sequence DWI or FLAIR). - Positive assay for 14-3-3 protein in cerebrospinal fluid (CSF) **AND** total disease duration less than 24 months.” Delete: “OR • Suspect sporadic CJD AND • Positive assay for 14-3-3 in cerebrospinal fluid (CSF)”
March 2017	sCJD 3.3 Suspect Case	Delete bullet marking from last point and Add “in the absence of a conclusive MRI and 14-3-3 protein assay” after “2 years”
March 2017	sCJD 4.0 Laboratory Evidence	Revision to the entire section
March 2017	sCJD 5.0 Clinical Evidence	Bullet 3: Replace “features” with “symptoms” Delete last sentence “A clinical consultation is necessary for diagnosis”

Revision Date	Document Section	Description of Revisions
March 2017	Iatrogenic CJD 3.1 Confirmed Case	Turn points to bulleted points (add “AND” in between bullets) Bullet 1: replace “similar to sporadic CJD” with “(see Confirmed Sporadic CJD section 3.1)” Delete “for further details” from bullet two
March 2017	Iatrogenic CJD 3.2 Probable Case	Format added to bullet points (add bullet 3) Bullet 2: replace “similar to sporadic CJD” with “(see Probable Sporadic CJD section 3.2)” and delete “with” Bullet 3: Delete “for further details”
March 2017	Iatrogenic CJD 4.0 Laboratory Evidence	Revision to the entire section
March 2017	Iatrogenic CJD 5.0 Clinical Evidence	Delete last sentence “A clinical consultation is necessary for diagnosis”
March 2017	Iatrogenic CJD 7.0 Comments	Replace “iatrogenically transmitted CJD” with “iatrogenic CJD”
March 2017	Genetic CJD 4.0 Laboratory Evidence	Revision to the entire section
March 2017	Genetic CJD 5.0 Clinical Evidence	Delete last sentence “A clinical consultation is necessary for diagnosis”
March 2017	Genetic CJD 7.0 Comments	Add new bullet: “PRNP mutations associated with other neuropathologic phenotypes I138M, G142S, Q160Stop, T188K, T188R, P238S, M232R; octapeptide repeat insertions (various lengths)”
March 2017	Variant CJD (vCJD) 3.2 Probable Case	Bullet 2: Add “criteria” after “five” and change “5.2” to “5.0” Last Bullet: Replace “Positive tonsil biopsy” with “Tonsil biopsy positive for prion protein immunoreactivity”

Revision Date	Document Section	Description of Revisions
March 2017	Variant CJD (vCJD) 3.3 Suspect Case	Bullet 1: Add “in the absence of a conclusive MRI or tonsil biopsy” after “>6 months,” Bullet 2: Add “criteria” after “five” and change “5.1” to “5.0”
March 2017	Variant CJD (vCJD) 4.0 Laboratory Evidence	Revision to the entire section
March 2017	Variant CJD (vCJD) 5.0 Clinical Evidence	Revision to the entire section
February 2019	General	Minor revisions were made to support the regulation change to Diseases of Public Health Significance.


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