

Appendix B: Provincial Case Definitions for Reportable Diseases

Disease: Transmissible Spongiform Encephalopathy, including:
i) Creutzfeldt-Jakob Disease, all types; ii) Gerstmann-Sträussler-Scheinker Syndrome; iii) Fatal Familial Insomnia, and iv) Kuru

Transmissible Spongiform Encephalopathy, including: i) Creutzfeldt-Jakob Disease, all types; ii) Gerstmann-Sträussler-Scheinker Syndrome; iii) Fatal Familial Insomnia, and iv) Kuru

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 / immunocytochemically confirmed: confirmation of protease-resistant prion protein (immunocytochemistry or Western Blot).

3.2 Probable Case

- Rapidly progressive dementia
AND
- At least two additional neurological manifestations (See Section 5.0 – Clinical Evidence)
AND
- Typical electroencephalography (EEG): generalized bilateral or unilateral triphasic periodic complexes at approximately one per second, lasting continuously for at least 10 seconds.

OR

- Suspect sporadic CJD
AND
Positive assay for 14-3-3 in cerebrospinal fluid (CSF)

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

4.0 Laboratory Evidence

4.1 Laboratory Confirmation

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

- Neuropathological confirmation of protease-resistant prion protein (immunocytochemistry *in situ* or *via* PET blot; or Western Blot).

4.2 Approved/Validated Tests

- Immunocytochemistry (*in situ* or PET blot variants) demonstrating prion protein immunoreactivity (plaque and/or diffuse synaptic and/or perivacuolar): confirmatory (if positive)
- PrP Western blot: confirmatory (if positive)
- Electron microscopy for scrapie-associated fibrils (SAF): 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)

4.3 Indications and Limitations

- Histopathologic evidence of spongiform change is no longer considered sufficient in itself for diagnostic confirmation of TSE.
- Demonstration of scrapie-associated fibrils (SAF) by electron microscopy, although historically important, is rarely undertaken for human diagnostic purposes.
- Absence of a known pathogenic mutation causative for genetic TSE 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 features
- Akinetic mutism

A clinical consultation is necessary for diagnosis

6.0 ICD Code (s)

ICD 10 Code A81.0

7.0 Comments

N/A

8.0 References

- Ministry of Health and Long-Term Care, Public Health Division. iPHIS manual. Toronto, ON: Queen's Printer for Ontario; 2005.
- Heymann D, editor. Control of communicable diseases manual. 18th ed. Washington: American Public Health Association; 2004.
- Nationally Notifiable Diseases Case Definitions with Canadian Public Health Laboratory Network (CPHLN) and Epidemiologic Group Draft Edits. March 2007. Based on case definitions as written in the: Health Canada. Case definitions for diseases under national surveillance. Can Commun Dis Rep. 2000; 26 Suppl 3:i-iv 1-122. Available from <http://www.phac-aspc.gc.ca/publicat/ccdr-rmtc/00pdf/cdr26s3e.pdf>.
- National CJD Surveillance Unit (NCJDSU).[Internet] National Creutzfeldt-Jakob Disease surveillance protocol. Diagnostic Criteria. University of Edinburgh. [cited 2009 Feb 1]. Available from <http://www.cjd.ed.ac.uk/criteria.htm>

Iatrogenic TSE (Accidentally transmitted TSE)

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 TSE similar to sporadic CJD, with a recognized iatrogenic factor. (See Section 7.0 - Comments for further details)

3.2 Probable Case

- Progressive predominant cerebellar syndrome in human pituitary hormone recipients
OR
- Probable TSE similar to sporadic CJD, with recognized iatrogenic risk factor (See Section 7.0 - Comments for further details)

4.0 Laboratory Evidence

4.1 Laboratory Confirmation

The following will constitute a confirmed case of Iatrogenic TSE

- Neuropathological confirmation of protease-resistant prion protein (immunocytochemistry *in situ* or *via* PET blot; or Western Blot).

4.2 Approved/Validated Tests

- Immunocytochemistry (*in situ* or PET blot variants) demonstrating prion protein immunoreactivity (plaque and/or diffuse synaptic and/or perivacuolar): confirmatory (if positive)
- Electron microscopy for scrapie-associated fibrils (SAF): confirmatory (if positive)
- PrP-res 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)

4.3 Indications and Limitations

- Histopathologic evidence of spongiform change is no longer considered sufficient in itself for diagnostic confirmation of TSE.
- Demonstration of scrapie-associated fibrils (SAF) by electron microscopy, although historically important, is rarely undertaken for human diagnostic purposes.
- Absence of a known pathogenic mutation causative for genetic TSE supports a diagnosis of accidentally 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

A clinical consultation is necessary for diagnosis

6.0 ICD Code (s)

ICD 10 Code A81.0

7.0 Comments

Relevant exposure risks for classification as accidentally transmitted 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

- Ministry of Health and Long-Term Care, Public Health Division. iPHIS manual. Toronto, ON: Queen's Printer for Ontario; 2005.
 - Heymann D, editor. Control of communicable diseases manual. 18th ed. Washington: American Public Health Association; 2004.
 - Nationally Notifiable Diseases Case Definitions with Canadian Public Health Laboratory Network (CPHLN) and Epidemiologic Group Draft Edits. March 2007. Based on case definitions as written in the: Health Canada. Case definitions for diseases under national surveillance. Can Commun Dis Rep. 2000; 26 Suppl 3:i-iv 1-122. Available from <http://www.phac-aspc.gc.ca/publicat/ccdr-rmtc/00pdf/cdr26s3e.pdf>.
 - National CJD Surveillance Unit (NCJDSU).[Internet] National Creutzfeldt-Jakob Disease surveillance protocol. Diagnostic Criteria. University of Edinburgh. [cited 2009 Feb 1]. Available from <http://www.cjd.ed.ac.uk/criteria.htm>.
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Genetic TSE - includes genetic forms of CJD; Gerstmann-Sträussler-Scheinker syndrome (GSS); and Fatal Familial Insomnia (FFI)

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

OR

- Confirmed TSE
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 TSE 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 TSE:

- Confirmation of protease-resistant prion protein (immunocytochemistry *in situ* or *via* PET blot; or Western Blot).

4.2 Approved/Validated Tests

- Immunocytochemistry (*in situ* or PET blot variants): confirmatory (if positive)
- Electron microscopy for scrapie-associated fibrils (SAF): confirmatory (if positive)
- 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 positive)
- CSF 14-3-3 Western blot: supportive (if positive)

4.3 Indications and Limitations

- Histopathologic evidence of spongiform change is no longer considered sufficient in itself for diagnostic confirmation of TSE.

- Demonstration of scrapie-associated fibrils (SAF) by electron microscopy, although historically important, is rarely undertaken for human 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

A clinical consultation is necessary for diagnosis

6.0 ICD Code (s)

ICD 10 Code A81.0

7.0 Comments

7.1 Genetic Prion Disease

- PRNP* mutations associated with a neuropathologic phenotype of Creutzfeldt-Jakob disease (CJD): R148H; D178N on 129V allele; V180I; V180I + M232R; T183A; T188A; 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 a neuropathologic phenotype of Gerstmann-Sträussler-Scheinker disease (GSS; see note a above): P102L; P105L; A117V; G131V; F198S; D202N; Q212P; Q217R; M232T; octapeptide repeat insertion 192 bp
- PRNP* mutations associated with a neuropathologic phenotype of Familial Fatal Insomnia (FFI): D178N on 129M allele
- PRNP* mutations associated with other neuropathologic phenotypes: I138M; G142S; Y145Stop; Q160S; H187R; T188K; M232R; octapeptide repeat insertions 24 bp, 48 bp
- The pathology findings in genetic TSE are quite variable. However, presence of multicentric plaques by histopathology, PAS strain or prion protein immunocytochemistry in cerebral and/or cerebellar cortex, with neuron loss and spongiosis, is considered diagnostic of GSS. 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 or Kuru plaques are not considered diagnostic for GSS.

8.0 References

- Ministry of Health and Long-Term Care, Public Health Division. iPHIS manual. Toronto, ON: Queen's Printer for Ontario; 2005.
- Heymann D, editor. Control of communicable diseases manual. 18th ed. Washington: American Public Health Association; 2004.
- Nationally Notifiable Diseases Case Definitions with Canadian Public Health Laboratory Network (CPHLN) and Epidemiologic Group Draft Edits. March 2007. Based on case definitions as written in the: Health Canada. Case definitions for diseases under national surveillance. Can Commun Dis Rep. 2000; 26 Suppl 3:i-

iv 1-122. Available from <http://www.phac-aspc.gc.ca/publicat/ccdr-rmtc/00pdf/cdr26s3e.pdf>.

- National CJD Surveillance Unit (NCJDSU).[Internet] National Creutzfeldt-Jakob Disease surveillance protocol. Diagnostic Criteria. University of Edinburgh. [cited 2009 Feb 1]. Available from <http://www.cjd.ed.ac.uk/criteria.htm>.

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 prion protein (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 TSE
AND
- Four out of five from Section 5.2
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 TSE
AND
- Positive tonsil biopsy

3.3 Suspect 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 evidence of a genetic form of TSE
AND
- Four out of five from Section 5.2
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 Variant Creutzfeldt-Jakob disease:

- Spongiform change and extensive prion protein (PrP) deposition with florid plaques, throughout the cerebrum and cerebellum

4.2 Approved/Validated Tests

- Immunocytochemistry (*in situ* or PET blot variants): confirmatory (if positive)
- Electron microscopy for scrapie-associated fibrils (SAF): confirmatory (if positive)
- 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 homozygous Met/Met at codon 129)
- CSF 14-3-3 Western blot: supportive (if positive)

4.3 Indications and Limitations

- Histopathologic evidence of spongiform change is no longer considered sufficient for diagnostic confirmation of TSE.
- 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.
- The EEG has been described as “typical” in a small number (fewer than 1%) of vCJD cases.

5.0 Clinical Evidence

5.1 A Progressive neuropsychiatric disorder

- B Duration of illness > 6 months
- C Routine investigations do not suggest an alternative diagnosis
- D No history of potential iatrogenic exposure
- E No evidence of a familial form of TSE

5.2 A Early psychiatric symptoms (e.g., depression, anxiety, apathy, withdrawal, delusions)

- B Persistent painful sensory symptoms. This includes frank pain and/or dysaesthesia
- C Ataxia
- D Myoclonus or chorea or dystonia
- E Dementia

5.3 A EEG does not show the typical appearance of sporadic CJD: generalized bilateral or unilateral triphasic periodic complexes at approximately one per second, lasting] continuously for at least 10 seconds; or no EEG performed

- B MRI brain scan shows bilateral symmetrical pulvinar high signal - relative to the signal intensity of other deep gray-matter nuclei and cortical gray matter

5.4 A Positive tonsil biopsy

A clinical consultation is necessary for diagnosis

6.0 ICD Code (s)

ICD 10 Code A81.0

7.0 Comments

8.0 References

- Ministry of Health and Long-Term Care, Public Health Division. iPHIS manual. Toronto, ON: Queen's Printer for Ontario; 2005.
- Heymann D, editor. Control of communicable diseases manual. 18th ed. Washington: American Public Health Association; 2004.
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- National CJD Surveillance Unit (NCJDSU).[Internet] National Creutzfeldt-Jakob Disease surveillance protocol. Diagnostic Criteria. University of Edinburgh. [cited 2009 Feb 1]. Available from <http://www.cjd.ed.ac.uk/criteria.htm>.

Kuru

While most neurologic features correspond to those of CJD with plaques, Kuru should be diagnosed only in members of the Fore population in Papua New Guinea.

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