CREUTZFELDT-JACOB DISEASE

Disease Overview

Prion diseases are rare, fatal, degenerative brain disorders that are thought to occur worldwide in both humans and animals. They belong to the general category of brain diseases called proteinopathies. These diseases are believed to be caused by an abnormal isoform of a cellular glycoprotein known as the prion protein. There are several forms of human prion disease, the most common is Creutzfeldt-Jakob disease (CJD), which is a rapidly progressive and invariably fatal neurodegenerative disorder with characteristic clinical and diagnostic features. 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.

Creutzfeldt-Jacob Disease (CJD) includes the following forms:

Classic CJD (sporadic) occurs sporadically with no evidence of genetic or iatrogenic transmission and is believed to result from the spontaneous transformation of prion protein from its normal form into an abnormally shaped form. Disease progression is rapid compared to other neurodegenerative conditions.

Classic CJD (iatrogenic) occurs as a result recognized risk factor for iatrogenic transmission. Disease progression is similar to sporadic CJD.

Classic CJD (genetic) occurs because of inherited mutations of the prion protein gene, but not all patients with PRNP mutations have a family history of prion disease. Genetic prion diseases include familial CJD, Gerstmann-Straussler-Scheinker (GSS) syndrome and Fatal Familial Insomnia (FFI).

Variant CJD is a similar disease presentation except the agent responsible for disease in cattle, called bovine spongiform encephalopathy or 'mad cow' disease, is the same agent that may also cause illness in humans.

Symptoms

Variable symptoms occur early in the disease and include anxiety, depression, forgetfulness and progression to forgetfulness, memory impairment, dementia and eventual death within a year or two of symptom onset.

Reservoir

The infectious agent of prion diseases is thought to be an abnormal form of the prion protein (PrP). The normal form of PrP (PrP^c) is present in all healthy humans and animals. However, in prion disease somehow one or a few PrP^c molecules are converted to an abnormal infectious form, or prion (proteinaceous infectious particle). The abnormal molecules can then convert more of an individual human's or animal's PrP^c molecules to the abnormal form, eventually causing a neurological disease.

Under certain circumstances (such as invasive medical procedures, or exposure to BSE-contaminated food), prion diseases can therefore be transmitted, because in some circumstances contact with even tiny amounts of prion-contaminated material can initiate this process in a healthy individual.

Mode of Transmission

Most cases of CJD occur as sporadic disease, a smaller proportion of patients develop CJD associated with genetic mutations. Very rarely cases have been associated with brain surgeries involving contaminated instruments and other procedures.

The most likely source of variant CJD in humans is cattle infected with bovine spongiform encephalopathy. Although the exact route of spread is unknown, the consumption of infected brain and nerve tissue is thought to be the most likely.

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.

Iatrogenic CJD and vCJD are thought to be exogenously acquired and incubation periods could range from 15 months to over 30 years depending on the exposure route.

Period of Communicability

Direct person to person transmission does not occur.

Risk factors

The risk of classic CJD (sporadic) is higher in older persons.

The risk of classic CJD (iatrogenic) is higher in individuals who have received treatment with human cadaveric pituitary growth hormone, human pituitary gonadotrophin or human dura mater graft; individuals who have received a corneal graft in which the corneal donor has been classified as having a pathology-based diagnosis of human prion disease, and individuals who have had a neurosurgical exposure to instruments (including EEG depth electrodes) previously used on a patient classified as having a pathology-based diagnosis of human prion disease.

The risk of classic CJD (genetic) is higher in individuals who have a first-degree relative with a diagnosis of a definite or probable prion disease.

The risk of variant CJD has been strongly linked with the consumption of food of bovine origin contaminated with the agent of BSE (bovine spongiform encephalopathy).

Surveillance Case Definition

Nationally notifiable since 2000. This section describes the three etiologic subtypes of classic Creutzfeldt- Jakob disease (CJD) (sporadic CJD, iatrogenic CJD and genetic prion diseases) and variant CJD (vCJD)

A: Sporadic Creutzfeldt-Jakob Disease (sCJD) (definite, probable and possible cases)

Case Classification

Confirmed (or definite?) sCJD

- Neuropathologically and/or immunocytochemically and/or biochemically confirmed, through observation of one or more neuropathologic features (see Box 1) and no evidence of iatrogenic CJD or genetic human prion disease (see Sections B and C).

Probable sCJD

- Routine investigation should not suggest an alternative diagnosis
- Rapidly progressive dementia + at least two features of list I + II (see Box 2)

OR

- Possible CJD + cerebrospinal fluid positive for 14-3-3 by immunoblot + duration < 2 years

Possible sCJD

- Rapidly progressive dementia + two of list I (see Box 2) + duration < 2 years + no electroencephalography (EEG) or atypical EE

Box 1

- Spongiform encephalopathy in cerebral and/or cerebellar cortex and/or subcortical grey matter
- Encephalopathy with 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)
- Presence of scrapie-associated fibrils (SAF) by electron microscopy
- Presence of protease-resistant PrP by Western blot

Box 2

- Myoclonus
- Visual disturbances or cerebellar dysfunction (ataxia)
- Pyramidal or extrapyramidal features
- Akinetic mutism
- Typical EEG pattern: periodic sharp-wave complexes ca. 1 Hz

B: Iatrogenic CJD (iCJD) (definite and probable case)

Case Classification

Definite iCJD

- Definite CJD (see Section A, Box 1 for diagnostic criteria) with a recognized risk factor for iatrogenic transmission (see Box 3)

Probable iCJD

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

OR

- Probable CJD (see Section A.3.2 for diagnostic criteria) with a recognized risk factor for iatrogenic transmission (see Box 3)

Box 3

- *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.*
- Treatment with human cadaveric pituitary growth hormone, human pituitary gonadotrophin or human dura mater graft
- Corneal graft in which the corneal donor has been classified as having a definite or probable prion disease
- Neurosurgical exposure to instruments previously used on a patient classified as having definite or probable prion disease

C: Genetic Prion Diseases (definite and probable case)

Case Classification

Definite Genetic Human Prion Disease

- Definite (pathologically confirmed) prion disease + definite or probable prion disease in a first-degree relative

OR

- Definite prion disease + pathogenic mutation in prion protein gene (PRNP) (see Box 4)

OR

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

Probable Genetic Prion Disease

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

OR

- Progressive neuropsychiatric disorder + pathogenic mutation in PRNP (see Box 4)

Box 4

- PRNP mutations associated with a neuropathologic phenotype of CJD (see Section A, Box 1): P105T, G114V, R148H, D178N, V180I, V180I+M232R, T183A, T188A, T193I, E196K, E200K, V203I, R208H, V210I, E211Q, M232R; octapeptide repeat insertions (various lengths) and deletion (48 bp)
- PRNP mutations associated with a neuropathologic phenotype of GSS (see previous footnote above): P102L, P105L, A117V, G131V, A133V, Y145Stop, H187R, F198S, D202N, Q212P, Q217R, M232T; octapeptide repeat insertions (various lengths)
- *PRNP* mutations associated with a neuropathologic phenotype of Familial Fatal Insomnia (FFI): D178N

- PRNP mutations associated with other neuropathologic phenotypes: I138M, G142S, Q160Stop, T188K, T188R, P238S, M232R; octapeptide repeat insertions (various lengths)

*Presence of multicentric PrP-immunoreactive plaques in cerebral and/or cerebellar cortex, with neuron loss and spongiosis. Other large amorphic 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.

D: Variant Creutzfeldt-Jakob Disease(vCJD) (definite, probable and possible cases)

Case Classification

Definite vCJD

- IA (see Box 5) and neuropathologic confirmation as per pathologic features (see footnote a, Box 5)

Probable vCJD

- I + 4 or 5 criteria of II + IIIA + IIIB (see Box 5) OR
- I + IVA

Possible vCJD

- I + 4 or 5 criteria of II + IIIA (see Box 5)

Box 5

I. A. Progressive neuropsychiatric disorder
   B. Duration > 6 months
   C. Routine investigations do not suggest alternative diagnosis
   D. No history of potential iatrogenic exposure
   E. No evidence of genetic prion disease

II. A. Early psychiatric symptoms[b]
   B. Persistent painful sensory symptoms[c]
   C. Ataxia
   D. Myoclonus or chorea or dystonia
   E. Dementia

III. A. EEG does not show typical appearance of sporadic CJD[d] (or no EEG performed) in the early stages of the illness
   B. Bilateral pulvinar high signal on magnetic resonance imaging (MRI) scan[e]

IV. A. Tonsil biopsy positive for prion protein immunoreactivity[f]

a. Spongiform change, extensive PrP deposition, florid plaques throughout cerebrum and cerebellum
b. Depression, anxiety, apathy, withdrawal, delusions
c. Frank pain and/or dysaesthesia
d. Generalized triphasic periodic complexes at ca. 1 Hz. Rarely, these may occur in the

late stages of vCJD.

e. Relative to the signal intensity of other deep grey matter nuclei and cortical grey matter
f. 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.

Diagnosis and Laboratory Guidelines

Diagnosis is based on clinical symptoms and postmortem laboratory testing. Cases of classic CJD can be distinguished from cases of genetic CJD and variant CJD on the basis of clinical and pathologic data.

Detection of 14-3-3 ɣ protein is done using an ELISA test performed on CSF samples at the National Microbiology Laboratory in Winnipeg.

Reporting

Per Disease and Event Reporting section.

Regional PH is required to notify PHNB for all *Notifiable Diseases and Events Notification Forms* received from referring healthcare providers (suspect or confirmed case).

Case Management

For Creutzfeld-Jacob disease (classic and new variant), physicians and laboratories report such cases by following the routine reporting process for Creutzfeld-Jacob Disease as established by the national Creutzfeldt-Jakob Disease Surveillance System (CJDSS), including the required notification to Regional Public Health Office using the *Notifiable Diseases and Events Notification Form*.

Regional PH does not follow up on cases, unless directed by Regional Medical Officer of Health in collaboration and consultation with CJDSS. When CJD is suspected the following should be considered:

- 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
- Residence in Europe between January 1980 and December 31, 1996, mainly in the United Kingdom or France for a cumulative total of three months or more; or Saudi Arabia for six months or more.
- Residence in Western Europe between January 1980 and December 31, 2007 (outside the UK or France) for 5 years or more
- 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.

Education

Not applicable

Investigation

Not applicable

Exclusion/Social Distancing

Not applicable

Treatment

Not applicable

Immunization Not applicable.

Contact Management

Education

Not applicable

Investigation

Not applicable

Exclusion/Social Distancing

Not applicable

Prophylaxis

Not applicable

Outbreak Management

Activate the local outbreak plan when an outbreak is declared.