Prion Diseases

Organism: Prion diseases (PDs) or transmissible spongiform encephalopathies (TSEs)

- Family of rare progressive neurodegenerative disorders that affect both humans and animals with long incubation periods and pathologically characteristic spongiform changes associated with neuronal loss and absence of inflammatory response.
- Causative agent believed to be a prion – abnormal, transmissible agent able to induce abnormal folding of normal cellular prion proteins in brain, leading to brain damage and signs and symptoms of the disease.
- PDs are invariably fatal.

Incubation period: Highly variable, may be decades.

Infectious period: Not well characterized. See Table 1 for reports of transfusion-associated transmission from donors who were apparently well at the time of donation, but subsequently diagnosed with vCJD years later.

Transmission route: See Table 1.

Treatment: Always fatal; death usually occurs within a year without onset of illness. Treatment is supportive and not specific.

Information Needed for the Investigation

Verify the Diagnosis

Clinical picture: otherwise unexplained subacute progressive dementia and at least one of the following neurologic features – myoclonus, visual or cerebellar signs, pyramidal/extrapyramidal signs, or akinetic mutism. In variant cases: behavioral changes (psychosis, depression), painful sensory symptoms, and delayed neurological signs. Signs and symptoms may vary depending on the PD.

Differential Diagnosis: Alzheimer's disease, Dementia with Lewy bodies, Frontotemporal dementia, Corticobasal degeneration, Progressive supranuclear palsy, neoplasm, viral encephalitis, metal toxicity.

Laboratory results: Confirmatory testing requires pathologic examination of brain tissue. Gold standard for diagnosis is pathological and cerebrospinal fluid testing of brain tissue at autopsy.

Case definitions:

- CDC sporadic, familial, and iatrogenic CJD diagnostic criteria: https://www.cdc.gov/prions/cjd/diagnostic-criteria.html (February 2015).
- CDC Variant CJD: https://www.cdc.gov/prions/vcjd/diagnostic-criteria.html (February 2015).

- WA DOH: http://www.doh.wa.gov/Portals/1/Documents/5100/420-069-Guideline-Prion.pdf (August 2016).

Determine the Extent of Illness

- Confirmed cases will be rare; Alaska should have <1 case/year. [US rate is ~1/million, increases to 3-4/million if looking at older age groups.] However, if several different reports are received in a seemingly short period of time, consult with CDC about the need for a cluster-type analysis.
- For different scenarios, follow steps in Table 2 below.
- Use WA DOH's case report form: http://www.doh.wa.gov/Portals/1/Documents/5100/420-003-ReportForm-Prion.pdf

Public Health Investigation

- Collect information on clinical presentation and test results.
- Determine receipt of human-derived pituitary hormones, dura mater or corneal grafts, neurosurgery, or if related to a person with inheritable prion disease.
- If still alive encourage provider to discuss autopsy for diagnosis confirmation with the patient's family an autopsy consent form is available on NPDPSC website.
    - All autopsy (not funeral) arrangements and expenses are covered by the NPDPSC.
- If the patient is deceased, determine date of death and whether postmortem samples of brain tissue were collected. Include pathology reports with the case report form. Determine if prion disease was included in the causes of death.

Laboratory Specimens

- Consult with the National Prion Disease Pathology and Surveillance Center (NPDPSC) for assistance in obtaining an autopsy (see Table 3).
- Recommend clinicians consult with CDC/experts if they are looking for specific details on interpreting diagnostics or patient status.

Hospital Considerations

- Use Standard Precautions for patient; however additional precautions may be indicated for special procedures (i.e., brain biopsies, neurosurgery, etc.) http://www.cdc.gov/hicpac/2007IP/2007isolationPrecautions.html
- CDC Infection Control guidelines: http://www.cdc.gov/prions/cjd/infection-control.html
- World Health Organization (WHO) Infection control guidelines for Transmissible Spongiform Encephalopathies: http://www.who.int/csr/resources/publications/bse/WHO_CDS_CSR_APH_2000_3/en/

Contact and Control Measures

- Information for Funeral and Crematory Practitioners
    - http://www.cdc.gov/prions/cjd/funeral-directors.html

- Some of these cases have caused media inquiries and community concern; consider the need for educational materials.

Reporting Requirements

- FTR: write up cluster investigations
- AK STARS: enter all *confirmed* and *probable* cases.

Table 1. Type of Prion Diseases

Sporadic	**Sporadic Creutzfeldt-Jakob Disease (sCJD)**	• Most common of the human prion diseases, ~85% of all cases. • Five distinct types that differ clinically (observable physical and subjective symptoms) and neuropathologically (tissue changes in brain). • Molecular features of types also vary, e.g., genotype at codon 129 of prion protein gene, length of the scrapie prion protein.
	Sporadic Fatal Insomnia (sFI)	• Clinical and histopathological features indistinguishable from those of FFI but does not have mutation on the prion gene that characterizes FFI.
Familial	**Familial CJD (fCJD)**	• Second most common type of CJD, ~10-15% of cases worldwide. • Caused by genetic mutation in the prion protein gene, which causes a change in the amino acid sequence of the normal prion protein; change believed to cause mutated prion protein to take on scrapie prion protein conformation. • DNA extracted from blood or brain tissue obtained at biopsy or autopsy may be used to test for mutations in persons with suspected fCJD. • Currently, 55+ mutations of the prion gene are known to cause fCJD and other familial prion diseases in humans, including FFI and GSS.
	Fatal Familial Insomnia (FFI)	
	Gerstmann -Sträussler-Scheinker disease (GSS)	
Iatrogenic	**Iatrogenic CJD (iCJD)**	• Form of acquired CJD, <1% of cases. • Both lab/clinical research determined that human-to-human transmission can occur as the result of tissue implant, use of contaminated neurosurgical instruments, or administration of human hormones extracted from cadavers. • Although blood transmission of CJD reported only in vCJD, American Red Cross currently defers donors with a history of permanence in certain foreign countries or family history of CJD.
	Variant CJD (vCJD)	• In 1996, the first cases reported in the UK; total cases worldwide ~200. • Strong evidence that vCJD was acquired from consuming cattle affected by bovine spongiform encephalopathy, or "mad cow" disease, which occurred with epidemic proportions in the UK in the 1980s. • Cases in nations with no documented BSE have had exposures elsewhere (e.g., two US cases grew up outside the US). • vCJD has well defined and consistent clinical and pathological features that make it relatively easy to identify and distinguish from sCJD. vCJD is only type of PD in which definitive dx can be made with a biopsy of the tonsils. • Two vCJD cases acquired via blood transfusion reported in the UK; blood was extracted from persons with vCJD prior to their diagnosis.
	Kuru	• Acquired PD that is virtually extinct. • Originally described in members of a native tribe in New Guinea known to practice cannibalism; epidemics probably originated from the consumption of infected meat from a member of the tribe affected by sporadic CJD. • Clinically and pathologically, Kuru is fairly different from vCJD.

Table 2: Scenarios that might occur

Scenario	Investigation needed	Recommendations
Health care provider (HCP) from outside AK treating an AK patient reports a suspected or confirmed PD case	• If dx is confirmed, complete case report form based on medical record and clinician interview. • Alert PHNs of cases in their region.	• Assume that proper diagnostics are being performed and that HCP is looped into NPDPSC. • Coordinate with the state DOH where the patient is receiving care.
HCP inside AK reports a suspected case	• If dx is confirmed, complete case report form based on medical record and clinician interview. • Alert PHNs of cases in their region.	• Body should be referred for an autopsy. • Call NPDPSC to facilitate this; or have the HCP call directly.
PD case has been diagnosed; facility is calling because PD precautions may not have been followed	• Consult with CDC about the appropriate follow-up. Facility staff (IP, risk managers, etc.) will need to make the final decisions about notification of patients, but CDC and/or SOE can be part of those discussions.	
PD suspect has a POSITIVE 14-3-3 or tau protein result	• In general, NPDPSC staff conducts the follow-up on these test results to determine if a PD is still a likely diagnosis. If so, NPDPSC will contact SOE.	• If PDs are suspected, NPDPSC will work to ensure that an autopsy is obtained.
Unusual PD suspected	• Work with CDC to determine the need for additional questionnaire, diagnostics, follow-up, etc.	

Table 3. Contacts

Name	Affiliation	Phone Number	Email address
Ermias Belay, MD	CDC	404-639-4655	ebelay@cdc.gov
Ryan Maddox	CDC	404-639-1170	rmaddox@cdc.gov
Andrea Webb (manager)	NPDPSC	216-368-0587	cjdsurveillance@case.edu
Natalie Linton, MPH	WA DOH	206-418-5500/5594	natalie.linton@doh.wa.gov

Resources

1. NPDSPC: http://case.edu/medicine/pathology/divisions/prion-center/
2. CDC: http://www.cdc.gov/prions/index.html
3. WA DOH: http://www.doh.wa.gov/Portals/1/Documents/5100/420-069-Guideline-Prion.pdf
4. CJD Foundation: www.cjdfoundation.org