Creutzfeldt-Jakob Disease Surveillance in Texas 2000–2006

Abstract

Creutzfeldt-Jakob disease (CJD) is a rare neurodegenerative disease caused by prions. The disease is usually fatal within a year and there is currently no known treatment or cure. CJD has been a reportable condition in Texas since 1998. There are currently four known types: sporadic, familial, variant, and iatrogenic. Diagnosis is complex and direct examination of brain tissue is required for case confirmation and identification of the type of CJD. During 2000–2006, there were 181 cases of confirmed, probable, or possible CJD diagnosed among Texas residents, including 88 cases of sporadic CJD, 5 cases of familial CJD, and 1 case of variant CJD. Most case-patients were male (55%) and 55 years of age or older (78%). The Texas Department of State Health Services is available to assist health care professionals with arrangement of free diagnostic testing and to provide resources for family support.

Introduction

Creutzfeldt-Jakob disease (CJD), a neurodegenerative disease, is the most common form of transmissible spongiform encephalopathies (TSEs) to affect humans. The etiologic agents associated with this disease are prions (PrP), proteinaceous particles devoid of nucleic acid. The disease process involves the conversion of the prion protein from its normal cellular isoform (PrP^{C}) into the disease-causing misfolded form (PrP^{Sc}) resulting in an alpha-to-beta transition in the protein structure and holes in brain tissue.[1]

CJD is rare (about 1 per 1,000,000 population). The incubation period is difficult to determine and may span decades. There is no known cure or treatment and it is usually fatal within 12 months of disease onset, though 5%–10% of patients have been known to survive for more than 2 years.[2]

There are 4 known types of CJD. In the United States sporadic or classic CJD (sCJD) accounts for 80%–90% of cases. It occurs sporadically and has no known route of acquisition. Less common types of CJD include familial CJD (fCJD), iatrogenic CJD (iCJD), and variant CJD (vCJD). Familial CJD represents 5%–10% of United States cases and involves a hereditary route of transmission through an autosomal dominant genetic mutation. Two types of CJD known to be transmissible include vCJD and iCJD. Iatrogenic CJD, less than 1% of United States cases, results from accidental surgical transmission. Variant CJD (vCJD), also less than1% of United States cases, has been linked to bovine spongiform encephalopathy (BSE) or “mad cow disease” and the consumption of contaminated beef or beef products.

Clinical Course of CJD

Sporadic CJD typically occurs in adults 60 years of age and older. It is characterized by spontaneous onset of rapidly progressive dementia and other neurological signs such as myoclonus, visual disturbance, tremors, rigidity, spasticity, cerebellar disturbance (incoordination, ataxia), and akinetic mutism (inability to speak). Patients with sCJD may present with abnormal

electroencephalogram (EEG) readings (i.e., generalized slow-wave activity that progresses to periodic sharp waves produced against a slow background). The disease course is rapid and death typically occurs within 4 to 5 months after disease onset.

Symptom onset for persons with familial CJD typically occurs near 50 years of age and the duration of illness is 7 to 36 months, although in some cases, symptoms may persist for 18 years. Patients generally have symptoms characteristic of sporadic CJD, however, dementia usually comes later in the disease process.

Variant CJD differs from sCJD in a number of ways. Patients are usually younger (median age at death is 28 years) and the duration of illness is longer (median duration of 12 to 14 months). Furthermore, early in the course of the disease, patients may exhibit psychiatric or behavioral changes followed by early abnormal painful sensations, ataxia, myoclonus, dementia, and akinetic mutism. Upon magnetic resonance imaging (MRI) examination, a hyperintense signal may be reflected from the pulvinar region of the brain. This pulvinar sign is present in approximately 75%–80% of all vCJD cases.[3]

Iatrogenic transmission of CJD has been known to occur through contaminated surgical instruments, corneal transplants, dura mater grafts, depth electrodes, and use of human cadaver-derived pituitary hormone.[4] Variability in clinical presentation and incubation period in iCJD occurs depending upon the route of inoculation into the brain. Clinical presentation resulting from invasive neurosurgery or dura mater transplant has clinical features similar to sCJD. In contrast, the clinical presentation of iatrogenically-acquired CJD through use of pituitary growth hormone is distinct from sCJD and includes progressive cerebellar syndrome and late-stage onset of dementia. Incubation periods for iCJD have means ranging from 1.5 years (depth electrodes) to 15.5 years (corneal transplants).

Diagnostic Testing

A complicated and difficult disease to diagnose, CJD ultimately requires neuropathologic examination post mortem to confirm a diagnosis. Initially, physicians may rely on signs and symptoms to characterize a diagnosis or simply rule out other conditions. In the United States, the National Prion Disease Pathology Surveillance Center (Prion Center) at the Division of Neuropathology of Case Western University in Cleveland, Ohio, established by the Centers for Disease Control and Prevention (CDC), provides state-of-the-art prion disease diagnostic services free of charge. Testing services include cerebrospinal fluid (CSF) examination for 14-3-3 protein, DNA tests on blood or brain tissue for the presence of mutation, and confirmation and characterization of prion disease by microscopic examination following histological and immunohistochemical demonstration of the prion protein. In addition, the Prion Center offers arrangements for autopsy and shipping of tissue samples through their autopsy network.

Test results for examination of 14-3-3 protein in the CSF are reported as elevated, not elevated, or ambiguous. While an elevated level of 14-3-3 protein in the CSF is a good indication of a neurodegenerative disease, it is not considered a confirmatory test for CJD. Other conditions such as stroke, neoplasm, encephalitis and other encephalopathies can show elevated levels of 14-3-3 protein in the CSF. However, in the context of rapidly progressive dementia and other signs

and symptoms, CJD cannot be ruled out. Alternatively, a negative CSF 14-3-3 test result does not mean the patient does not have CJD. In most cases, 14-3-3 protein takes time to build up in the CSF; therefore, the level may not be elevated until later in the disease course. In the event the physician still suspects CJD and receives an ambiguous result, the Prion Center recommends repeating the test in 2 to 3 weeks.

Other tests used in a CJD workup include EEG and MRI. In most patients EEG shows a typical pattern of periodic sharp waves against a slow background for sCJD. A positive pulvinar sign (hyperintensity in the posterior thalamus) on MRI appears in approximately 75%–80% of vCJD cases. [3] Computed tomography (CT) scans can help to rule out other conditions, but do not show any abnormalities specific to CJD. Routine blood tests are usually normal in patients suspected of having CJD.

Neuropathological examination of brain tissue is the only way to confirm a diagnosis of CJD. Brain biopsy may detect CJD but should not be used to rule it out. False negatives can and do occur since tissues sampled during biopsy might not include affected brain tissue in which abnormal prions are present. Autopsy is required for confirmation of most types of CJD unless it has been previously confirmed by biopsy.

Infection Control

Prions are difficult to inactivate and can survive normal sterilization procedures. Therefore, exposure to prions during certain medical procedures is possible. Surgical instruments used in neurosurgery, especially during transplantation of neural tissue, pose the greatest risk for transmission. The CDC recommends precautions should be taken with any surgery done in contact with high-infectivity tissues (brain, spinal tissue and eyes). Instruments used during these types of procedures must first go through mechanical cleaning, followed by specific sterilization and decontamination processes to assure inactivation and removal of the prion. Normal social contact and basic nursing care do not pose a risk of exposure to nurses, family, or the community. Based on current knowledge, isolation precautions are not a necessary part of the care given to individuals with CJD. More information can be found at the CDC website (see resource page).

Global and Domestic Surveillance

In 1985–86, bovine spongiform encephalopathy (BSE) was first recognized in British cattle. [5] The origin of BSE is believed to result from meat-and-bone-meal (MBM), a dietary supplement derived mainly from the carcasses of fallen stock and other animal and poultry material, fed mainly to dairy calves. It was assumed that BSE and scrapie (prion disease in sheep) were similar and that there was no threat to humans through consumption of beef or beef products. However, in 1996, the first case of BSE in humans, now known as variant CJD, was recognized in the United Kingdom. As of August 2006, CDC reports 195 deaths occurring from variant CJD in 11 countries.[6] Only 3 cases have been classified as United States cases, and investigations concluded all of these individuals were likely exposed outside of the United States. As of September 2007, 4 cases of variant CJD infection have been associated with blood transfusions in case-patients living outside of the United States.[7]

Bovine meat and other bovine products were distributed across the world before the potential for exposure and spread were recognized. Consequently, little is

known about the extent of exposure to bovine products and spread of CJD. In response to this new epidemic, active CJD surveillance has become necessary worldwide. The United Kingdom developed the National Creutzfeldt-Jakob Disease Surveillance Unit in Scotland to monitor CJD cases. In the United States, the Prion Center conducts nationwide surveillance and offers assistance to clinicians in the diagnosis of prion diseases.

Texas Surveillance

CJD has been a reportable condition in Texas since 1998. The majority of CJD cases are reported to the Texas Department of State Health Services (DSHS) by test or autopsy reports received from the Prion Center. A few cases are discovered by routine death certificate review and some cases are reported by a local or regional health department, health care provider, or family member. Copies of results from all CJD-related testing performed by the Prion Center are sent to DSHS as a part of routine surveillance procedures. DSHS reviews test results and investigates all cases with positive test results including those with elevated CSF 14-3-3 protein levels. **Table 1** summarizes the number of cases for all types of CJD in Texas (2000–2006). Each year in Texas, the total number of confirmed, probable, or possible sporadic CJD cases has remained somewhat constant (mean=13; range= 6–15). In addition, on average, one case of familial CJD was diagnosed each year in Texas during 2000–2006, all from separate families. Only 1 case of variant CJD has ever been diagnosed in Texas. The patient was a former resident of the United Kingdom, where the exposure was likely to have occurred. Texas has a population of 23 million, and since the national rate of sporadic CJD is about 1 per million, it is expected that approximately 23 cases of CJD would occur each year in the state. Therefore, it is believed that CJD is currently under-reported in Texas. **Table 2** describes sporadic and familial CJD cases in Texas according to gender and age. Of the patients diagnosed with CJD during 2000–2006, 58% were male and 79% were 55 years of age or older. **Figure 1** depicts the number of CJD cases per county for the years 2000–2006. Note that higher numbers of cases are located in counties with higher populations.

CJD should be suspected and reported to DSHS in individuals who meet the following criteria:

1) Dementia of early onset (younger than 55 years of age) **or**
2) Rapidly progressive dementia **and** one of more of the following:
   - Movement disorder
   - Painful sensory symptoms
   - Visual disturbances **or**
3) Diagnosed by a physician as having CJD

Case Classification

The World Health Organization (WHO) established recommended standards for all types of CJD surveillance in 1997 (**Table 3**). The United States, including Texas, has adopted these surveillance standards to determine case classification for sCJD, fCJD and iCJD. For vCJD, CDC has developed diagnostic case criteria for use in the United States (**Table 3**). Direct examination of brain tissue through either biopsy or autopsy is highly recommended for all types of CJD and is required for confirmation of sporadic CJD and variant CJD. A sCJD case is determined to be 'probable' if there is enough diagnostic testing to suggest CJD but no autopsy has been performed. Patients considered for

Table 1. Cases of Creutzfeldt-Jakob disease in Texas[*§]

Type	2000	2001	2002	2003	2004	2005	2006	Total
Sporadic								
Confirmed	9	8	4	6	7	8	5	47
Probable	2	4	1	5	5	6	3	26
Possible	3	1	1	4	1	0	0	10
Subtotal	14	13	6	15	13	14	8	83
Familial	0	1	1	1	0	1	1	5
Iatrogenic	0	0	0	0	0	0	0	0
Variant	0	0	0	0	0	0	1[†]	1
Total	14	14	7	16	13	15	10	89

[*] Based on data as of June 15, 2007.
[†] Confirmed in United Kingdom and reported to Texas Department of State Health Services through Centers for Disease Control and Prevention.
[§] Based on year of death.

Table 2. Creutzfeldt-Jakob disease cases[*] in Texas by gender and age 2000–2006[†§]

Characteristics	2000	2001	2002	2003	2004	2005	2006	Total
Gender								
Male	10	8	3	6	10	7	7	51
Female	4	6	4	10	3	8	2	37
Age (years)								
<55	3	0	3	4	3	4	2	20
≥55	11	14	4	12	10	11	7	68

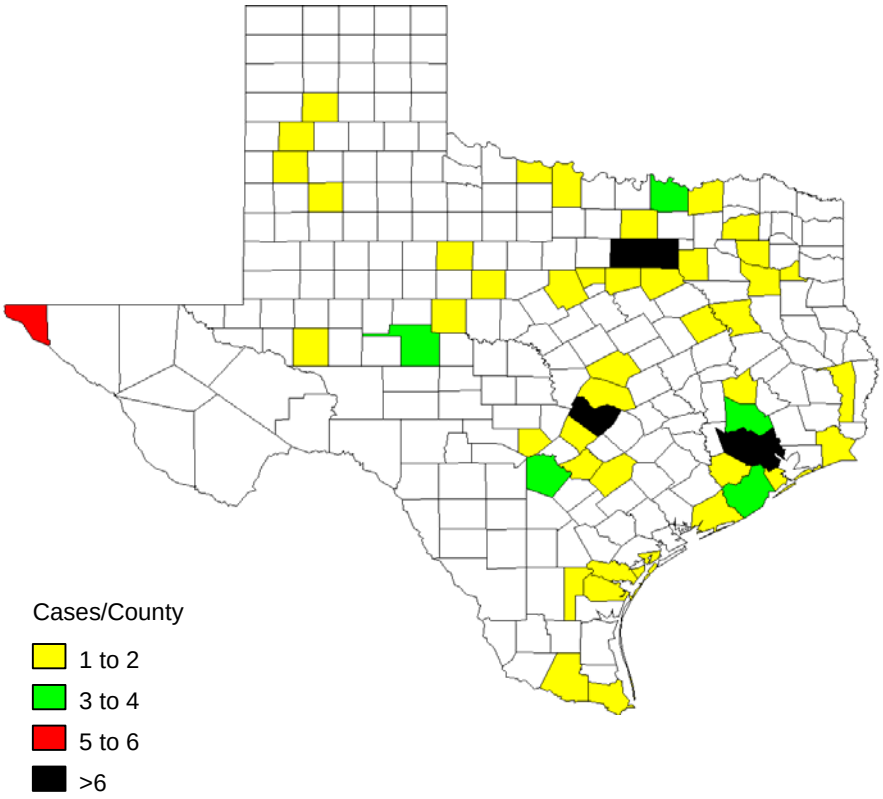
[*] Based on data as of June 15, 2007.
[†] Includes cases of possible, probable and confirmed sporadic CJD and confirmed familial CJD.
[§] Based on year of death.

probable sCJD must exhibit progressive dementia and have a typical EEG and/or elevated CSF 14-3-3 protein. In addition they must display at least 2 of 4 clinical features: myoclonus, visual or cerebellar disturbance, akinetic mutism, and/or pyramidal/extrapyramidal dysfunction. For a case to be listed as 'possible', the patient must have progressive dementia and at least 2 of the listed clinical features, disease duration of less than 2 years and either no EEG testing or EEG atypical for CJD. Iatrogenic CJD must have a known risk factor, e.g., high risk surgery or cadaver-derived pituitary hormone. Familial CJD is considered confirmed in a patient with a neuropsychiatric disorder if a first degree relative had confirmed or probable CJD or a disease-specific prion protein gene mutation has been identified. **Table 3** describes the case classification for each type of CJD.

Conclusions

CJD is an emerging disease that may be misdiagnosed and appears to be under-reported in Texas. As with other emerging diseases, the partnership of the medical community and public health epidemiologists provides a framework to share information and expertise among local, state, federal and international colleagues and to detect and respond to

Figure 1. Number of CJD (confirmed and probable) cases per county for 1998—2006



diseases that are rapidly fatal, difficult to diagnose, and rare. Enhanced surveillance will provide a better understanding of the epidemiology of this disease and its impact and opportunities for mitigation.

Recognition of possible CJD and reporting by health professionals is an integral part of CJD surveillance in Texas. CJD is a reportable disease in Texas. All suspected cases should be reported within one week to the Texas Department of State Health Services, Infectious Disease Control Unit. Confirmation and typing of the disease requires neuropathological confirmation by direct examination of brain tissue, usually postmortem, by the Prion Center. It is important to establish the precise type of CJD to help monitor disease occurrence especially for variant CJD. Physicians should strongly consider arranging for autopsies of suspected or clinically-diagnosed CJD patients. The Texas Department of State Health Services can assist health professionals by arranging free diagnostic testing and providing resources for family support.

References

1. Prusiner SB, editor. Prion biology and diseases. Cold Spring Harbor, NY: Cold Spring Harbor Laboratory Press; 2004:1–631.
2. Brown P, Rodgers-Johnson P, Cathala F, et al. Creutzfeldt - Jakob disease of long duration: clinicopathological characteristics, transmissibility, and differential diagnosis. Ann Neurol 1984; 16:295–304.

3. Collie DA, Summers DM, Sellar RJ, et al. Diagnosing variant Creutzfeldt-Jakob disease with the pulvinar sign: MR imaging findings in 86 neuropathologically confirmed cases. Am J Neuroradiol 24:1560–1569.
4. Will, RG. Acquired prion disease: iatrogenic CJD, variant CJD, Kuru. British Medical Bulletin 2003; 66: 255-265.
5. Bradley, R, Collee, JG, and Liberski, PP. Variant CJD (vCJD) and bovine spongiform encephalopathy (BSE): 10 and 20 years on: part 1. Folia Neuropahtolgica *2006;* 44(2).
6. Centers for Disease Control and Prevention, Atlanta, Georgia. Available at: http://www.cdc.gov/ncidod/dvrd/vcjd/factsheet_nvcjd.htm. Accessed on August 30, 2007.
7. Health Protection Agency. Variant CJD and blood products. Available at: http://www.hpa.nhs.uk/infections/topics_az/cjd/blood_products.htm. Accessed on August 30, 2007.

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Resources for Health Professionals and Families

Texas Department of State Health Services

- Report suspected cases within one week
  http://www.dshs.state.tx.us/idcu/disease/creutzfeldt-jakob/reporting/
  Fax: (512) 458-7616
- Karen Moody, CJD Surveillance Coordinator
  Infectious Disease Surveillance and Epidemiology Branch
  Mailcode 1960
  PO Box 149347
  Austin, TX 78714-9347
  Email: karen.moody@dshs.state.tx.us
  Phone: (512) 458-7111, ext. 6338

The National Prion Disease Pathology Surveillance Center
Case Western University—Division of Neuropathology
Cleveland, Ohio

- Arrange autopsy for suspected CJD through their national autopsy network, free of charge
- Determine the precise type of prion disease from pathologic studies of brain tissue
- Provide CSF testing for 14-3-3 protein free of charge
- Provide DNA testing on blood and brain tissue free of charge
- http://www.cjdsurveillance.com
- (216)368-0587

The CJD Foundation
Akron, Ohio

- Provide support to families by monitoring a 24 hour help line (800) 659-1991
- Promote research to improve treatment options and to find a cure for CJD
- Provide education to communities and families about caring for individuals with CJD
- http://www.cjdfoundation.org

Centers for Disease Control and Prevention (CDC)

- http://www.cdc.gov/ncidod/dvrd/cjd/index.htm
- Infection Control:
  http://www.cdc.gov/ncidod/dvrd/cjd/qa_cjd_infection_control.htm

Table 3. Case classification (CDC and WHO)	
CJD TYPE	**DIAGNOSIS**
SPORADIC	**CONFIRMED:** Autopsy or biopsy confirmation
	PROBABLE : Progressive dementia **And** at least 2 of the following 4 clinical features: • Myoclonus • Visual or cerebellar disturbance • Pyramidal/extrapyramidal dysfunction • Akinetic mutism **And** • A typical EEG during an illness of any duration **and/or** a positive 14-3-3 CSF assay and a clinical duration to death of <2 years • Routine investigations should not suggest an alternative diagnosis
	POSSIBLE: Progressive dementia **And** at least 2 out of the following 4 clinical features: • Myoclonus • Visual or cerebellar disturbance • Pyramidal/extrapyramidal dysfunction • Akinetic mutism **And** • No EEG or atypical EEG and duration <2 years
VARIANT	**CONFIRMED:** Neuropathologic examination of brain tissue is required to confirm a diagnosis of variant CJD. The following confirmatory features should be present a) Numerous widespread kuru-type amyloid plaques surrounded by vacuoles in both the cerebellum and cerebrum (florid plaques). b) Spongiform change and extensive prion protein deposition shown by immunohistochemistry throughout the cerebellum and cerebrum.

Table 3. Case classification (CDC and WHO)

	SUSPECT: a) Current age at death <55 years (a brain autopsy is recommended, however, for all physician-diagnosed CJD cases, regardless of age). b) Psychiatric symptoms at illness onset and/or persistent painful sensory symptoms (frank pain and/or dysesthesia). c) Dementia, and development ≥4 months after illness onset of at least two of the following five neurological signs. • Poor coordination • Chorea • Hyperreflexia • Myoclonus • Visual signs (If persistent painful sensory symptoms exist, ≥4 months delay in the development of the neurologic signs is not required). d) A normal or an abnormal EEG, but not the diagnostic changes often seen in sporadic CJD. e) Duration of illness over 6 months. f) Routine investigations of the patient do not suggest an alternative, non-CJD diagnosis. g) No history of receipt of cadaveric human pituitary growth hormone or a dura mater graft. h) No history of CJD in a first degree relative or prion protein gene mutation in the patient.
	NOTE If a patient has the typical bilateral pulvinar high signal on MRI scan, a suspected diagnosis of variant CJD requires the presence of a progressive neuropsychiatric disorder, d, e, f and g of the above criteria and four of the following five criteria • Early psychiatric symptoms (anxiety, apathy, delusions, depression, withdrawal) • Persistent painful sensory symptoms (frank pain and/or dysesthesia) • Ataxia • Myoclonus or chorea or dystonia • Dementia
IATROGENIC	Progressive cerebellar syndrome in a recipient of human cadaveric-derived pituitary hormone **Or**

Table 3. Case classification (CDC and WHO)	
	Sporadic CJD with a recognized exposure risk, e.g. antecedent neurosurgery with dura mater implantation
FAMILIAL	Confirmed or probable CJD **plus** confirmed or probable CJD in a first degree relative **And/or** Neuropsychiatric disorder **plus** disease-specific prion protein (PrP) gene mutation