

# Creutzfeldt-Jakob Disease Surveillance and Diagnosis

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(See article by Jara et al. on pages 829–33)

Creutzfeldt-Jakob disease (CJD) and other transmissible spongiform encephalopathies, also known as “prion diseases,” came to the world’s attention after the emergence of bovine spongiform encephalopathy (BSE) in Europe and the subsequent revelation of scientific evidence indicating that its transmission to humans causes a variant form of CJD [1]. Since BSE first emerged in the 1980s in the United Kingdom, the disease has been found in native cattle in 23 other countries, most of which are in Western Europe [2]. Half of these countries, including Canada, Israel, and Japan, reported their first cases of BSE during 2001–2003. In the United States, BSE was identified for the first time in 2003 in a cow imported into Washington state from Canada, where 3 additional BSE cases were reported in native cattle, 2 of them in January 2005 [1, 3]. In June 2005, BSE was reported in a cow born and raised in Texas.

Strong epidemiologic and laboratory evidence supported a causal link between BSE and variant CJD cases that were recognized initially in the United Kingdom but were later also reported in other coun-

tries [4]. As of July 2005, a total of 179 cases of variant CJD were reported worldwide, including 156 cases in the United Kingdom, 13 cases in France, 3 cases in Ireland, and 1 case in each of Canada, Italy, Japan, The Netherlands, Saudi Arabia, and the United States [1, 5, 6]. Cases of variant CJD in 1 of the patients in Ireland and in patients in Canada, Japan, and the United States were attributed to BSE exposure during each patient’s past residence in the United Kingdom. The Japanese patient with variant CJD spent ~24 days in the United Kingdom, indicating that long-term cumulative exposure to the BSE agent may not be necessary to contract the disease. In addition, some of the cases of variant CJD in France and the cases in The Netherlands and Saudi Arabia may have resulted from consumption of imported BSE-contaminated cattle products from the United Kingdom.

The classic form of CJD can be distinguished from variant CJD by the age distribution (median age at death, 68 and 28 years, respectively), clinical presentation and progression, and codon 129 polymorphism of the patients, and by the characteristic neuroimaging, neuropathologic analysis, and immunodiagnostic profiling (table 1) [3]. Patients with classic CJD commonly present with dementia, ataxia, behavioral changes, and/or visual deficits [7]. Other less prominent signs, such as involuntary movements, also may be noted at the time of clinical presentation. As the disease progresses, patients typically

develop a variety of neurologic deficits, including worsening dementia, cerebellar dysfunction, myoclonus, pyramidal and extrapyramidal signs, and akinetic mutism; death usually occurs at a median of 4–6 months after onset of illness. Most patients with CJD have a characteristic electroencephalogram (EEG) finding of periodic sharp waves. In some patients, abnormal findings of MRI, primarily in cortical regions of the brain and the basal ganglia, are believed to be suggestive of a CJD diagnosis [8, 9]. Elevated levels of 14-3-3 protein in the CSF may also aid in the diagnosis of CJD, particularly if patients manifest with the typical clinical signs and progression. Elevation of the 14-3-3 protein in the CSF is a marker for rapid neuronal death, and this marker can occur in other conditions associated with rapid cell death (e.g., intracerebral hemorrhages and encephalitis) [10]. The clinical manifestations of some of these conditions could mimic CJD and, thus, present a diagnostic challenge to clinicians.

A definitive diagnosis of CJD requires analysis of brain tissues obtained by either biopsy or autopsy. In this issue of *Clinical Infectious Diseases*, Jara et al. [11] report that a CSF 14-3-3 test was performed for less than one-half of patients with CJD identified during 1991–2001 in Massachusetts [11]. In contrast, all patients with CJD whose medical records were reviewed had an EEG assessment, and 84% of patients underwent MRI. The characteristic EEG findings were reported for 84% of

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**Table 1. Clinical and pathologic characteristics distinguishing variant Creutzfeldt-Jakob disease (CJD) in the United Kingdom from classic CJD in the United States, 1979–2001.**

Characteristic	Variant CJD in the United Kingdom	Classic CJD in the United States
Age at death, median years (range)	28 (14–74)	68 (23–97) <sup>a</sup>
Duration of illness, median months	13–14	4–5
Clinical presentation	Prominent psychiatric/behavioral symptoms, painful sensory symptoms, and delayed neurologic signs	Dementia and early neurologic signs
Periodic sharp waves on electroencephalogram	Often absent	Often present
“Pulvinar sign” on MRI <sup>b</sup>	Present in >75% of cases	Very rare or absent
Presence of “florid plaques” on neuropathologic sample	Present in great numbers	Rare or absent
Immunohistochemical analysis of brain tissue	Marked accumulation of PrP-res	Variable accumulation
Presence of agent in lymphoid tissue	Readily detected	Not readily detected
Increased glycoform ratio on Western blot analysis of PrP-res	Present	Not present
Genotype at codon 129 of prion protein	Methionine/methionine <sup>c</sup>	Polymorphic

**NOTE.** Table adapted from [3]. PrP-res, protease-resistant prion protein.

<sup>a</sup> US CJD surveillance data 1979–2001.

<sup>b</sup> High signal in the posterior thalamus.

<sup>c</sup> A patient with preclinical variant CJD related to bloodborne transmission was heterozygous for methionine and valine.

patients with CJD. Brain biopsy or autopsy was performed for more than one-half of the patients with CJD whose medical records were reviewed by Jara et al. [11]. As expected, the proportion of patients with CJD for whom brain biopsy was performed was inversely related to the age of patients.

Because brain biopsy is an invasive procedure and its diagnostic value depends on successful sampling of a multifocal lesion, it is not routinely advised for patients with a reasonable clinical diagnosis of CJD. Brain biopsy is more useful for patients in whom an alternative, potentially manageable condition is suspected. Adequate CJD infection-control protocols should be in place in hospitals that perform brain biopsy for patients with suspected CJD. This might help to avoid inadvertent exposure of patients to inadequately sterilized neurosurgical instruments previously used on patients whose CJD diagnosis becomes apparent after their surgical procedure. Such episodes of exposure have been reported in many hospitals, resulting in ethical and legal dilemmas, such as whether exposed patients should be informed about any potential risk [1]. Neurosurgical instruments used on patients with suspected

CJD or on patients with no clear diagnosis at the time of craniotomy should be quarantined until the diagnosis is clarified, or they should be decontaminated by use of sterilization protocols recommended for reprocessing CJD-contaminated instruments [12].

In 1996–1997, the National Prion Disease Pathology Surveillance Center (NPDPS) was established by the Centers for Disease Control and Prevention (CDC) in collaboration with the American Association of Neuropathologists to facilitate prion disease surveillance. The NPDPS provides state-of-the-art prion disease diagnostic services to US physicians without charge. The diagnostic tests performed at the NPDPS include a CSF 14-3-3 immunoassay, routine histopathologic analysis, immunohistochemistry, and Western blot and prion protein gene analyses [13]. In 2002, the NPDPS confirmed a diagnosis of prion disease for approximately half of the annual number of expected new cases of CJD in the United States; since then, the number of confirmations per year may have increased, because more clinicians became aware of this service. As of April 2005, the NPDPS had confirmed prion disease in 1046 (60%) of 1747 suspected patients whose brain tissue

specimens were examined. Of the 1005 patients for whom data were available, 851 (84.7%) had sporadic CJD, 149 (14.8%) had familial prion disease, and 5 (0.5%) had iatrogenic CJD.

In addition, the CDC periodically reviews the national multiple cause-of-death data to monitor the trend of CJD-related deaths in the United States. An average annual age-adjusted CJD-related death rate of 0.97 deaths per million persons was reported for the years 1979–1998 [14]. During 1999–2002, the most recent period for which complete national mortality data are available, a total of 933 CJD-related deaths were identified (264 deaths in 1999, 223 in 2000, 233 in 2001, and 213 in 2002). The age-adjusted CJD-related death rate for 1999–2002 was 0.91 deaths per million persons. The death rate decreased from 1.05 deaths per million persons in 1999 to 0.82 deaths per million persons in 2002; the reason for this decrease is not known.

Efforts to increase the number of autopsies among patients suspected of having died of CJD should continue. Post-mortem examination of brain tissue specimens not only confirms a diagnosis of CJD, but also makes brain tissue available, which is crucial for furthering our

understanding of the various subtypes of CJD, for monitoring the occurrence of variant CJD, and for monitoring the possibility of animal-to-human transmission of chronic wasting disease, a prion disease endemic in North American deer and elk populations. Availability of brain tissues will also facilitate research of prion disease to better understand the biochemical characteristics of the etiologic agent and its pathogenesis and to help develop more-specific premortem diagnostic tools and disease-specific therapies. Unfortunately, the national trend of decreasing overall percentage of US decedents for whom autopsy is performed is not encouraging. The percentage decreased from 40%–50% of decedents in the 1960s to <6% in 1994 [15]. Neurologists and pathologists surveyed in California and New York cited cost of autopsy, family reluctance to give consent, and infection-control concerns by pathologists and hospitals as major barriers to performing autopsies for patients with suspected or clinically diagnosed CJD [16]. These barriers could potentially be surmounted by educating family members about the importance of autopsies, establishing a network of pathologists experienced and willing to perform CJD autopsies, and making available funds to cover the cost of performing autopsies. Such efforts might be most beneficial if they take into account the places where death occurred for patients with CJD. For example, Jara et al. [11] reported that ~39% of CJD-related deaths in their study occurred in a long-term care facility, 33% of deaths occurred in a hospital, and 28% of deaths

occurred at home or in hospice care. Health care workers providing care to terminally ill patients with CJD in these facilities should be encouraged to discuss possible options for autopsy with the attending physician and their local and state health departments. In addition, brain tissue specimens obtained by autopsy from patients with suspected or clinically diagnosed CJD should be submitted to the NPDPSA for further analysis. Detailed information about the NPDPSA is available at its Web site (<http://www.cjd-surveillance.com>).

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