

## Clinical Communications

### CREUTZFELDT-JAKOB DISEASE: AN EMERGENCY DEPARTMENT PRESENTATION OF A RARE DISEASE

Louise A. Prince, MD, Deborah Mann, MD, and Tracey Reilly, MD

Department of Emergency Medicine, SUNY Upstate Medical University, Syracuse, New York

Reprint Address: Louise A. Prince, MD, Department of Emergency Medicine, SUNY Upstate Medical University, 750 E. Adams St.,  
Syracuse, NY 13210

□ **Abstract**—Creutzfeldt-Jakob Disease (CJD) is one of a group of neurodegenerative disorders causing spongiform encephalopathies. CJD is the most common human transmissible spongiform encephalopathy, or prion disease, but has an annual incidence of only 0.4–1.8 cases per million population worldwide. The prognosis for this disease is very poor and there is currently no cure. Patients typically present with non-specific neurological or psychiatric complaints and often have multiple physician visits before diagnosis, which requires histological examination of brain tissue. This patient had serial presentations to our Emergency Department, with progressive symptoms and multiple laboratory and radiological tests as well as consults, but her diagnosis remained unclear until her disease rapidly progressed and a brain biopsy was performed. With increasing concerns about prion diseases such as bovine spongiform encephalopathy (BSE)—or mad cow disease—and CJD, awareness of the symptoms and diagnostic challenges associated with these diseases will be helpful to emergency physicians. © 2006 Elsevier Inc.

□ **Keywords**—Creutzfeldt-Jakob Disease; CJD; prion diseases; spongiform encephalopathy, dementia

#### INTRODUCTION

Creutzfeldt-Jakob Disease (CJD) is the most common human transmissible spongiform encephalopathy but has an annual incidence of only 0.4–1.8 cases per million population worldwide (1). The disease occurs sporadi-

cally in up to 85% of cases with familial and acquired cases accounting for the remainder (2). The prognosis is dismal, with a mean of 8 months from onset to death. Due to the non-specific neurological and psychiatric complaints, the diagnosis is initially elusive. Recently, magnetic resonance imaging (MRI) has become a helpful adjunct in diagnosis; however, brain biopsy remains the definitive diagnostic test. This case report of a patient who presented to the Emergency Department (ED) on multiple occasions with progressive CJD details the symptoms, diagnostic testing, pathophysiology, and transmissibility of spongiform encephalopathies like bovine spongiform encephalopathy (BSE) and CJD.

#### CASE REPORT

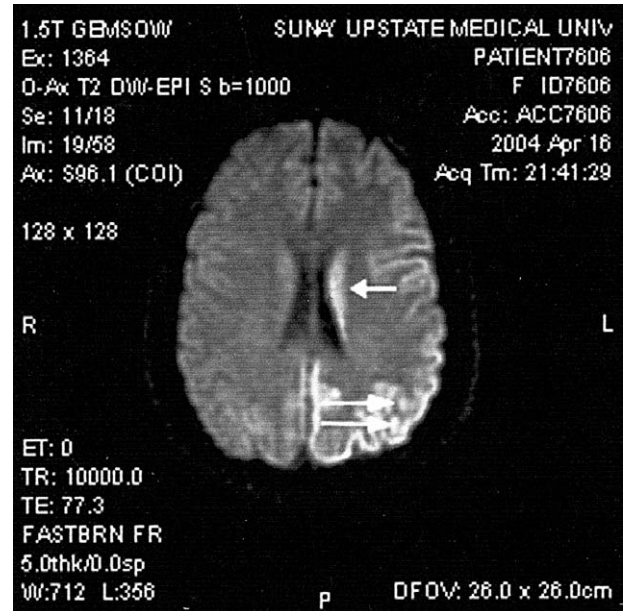
A 46-year-old right-handed woman with no significant past medical history first presented to the ED for evaluation of a possible stroke. The patient had become ill one day earlier while traveling home from Florida, experiencing a sensation of floating, gait imbalance, and a general feeling of not being well. She had a vague sensation of numbness of both sides of her face and both hands, which was intermittent. On the morning of presentation, she developed difficulty with forming complex thoughts and sentences and with expressing words. She denied slurring of speech, but stated that she felt at times she was unable to express the words she was thinking.

The patient was married with children and her family had been with her that day. They did not notice a significant change in the patient's speech. She denied headache, vision changes, or weakness in the extremities, but did admit to a sense of being off balance. Her physical examination revealed a moderately obese woman with normal vital signs. The majority of her neurological examination—including orientation, short-term memory, cranial nerve testing (including facial sensation), strength, general sensation, cerebellar function testing, and gait—was normal. She did not clearly have expressive aphasia but was slow to name objects, could not subtract serial 7s from 100 backward, or spell the word "world" backward. Laboratory evaluation, electrocardiogram (EKG), and a head computed tomography (CT) scan did not reveal any significant findings. After consultation, the neurology service admitted the patient for further evaluation.

During her hospital admission, an MRI as well as a magnetic resonance angiogram (MRA) of the head and neck did not reveal any significant findings. A lumbar puncture was performed with completely normal results. Further laboratory evaluation revealed a TSH of 40.87 uU/mL (normal 0.350–5.500 uU/mL) and a free T4 of 0.85 ng/dL (normal 0.6–1.76 ng/dL). The patient was started on levothyroxine and aspirin and was discharged with referral for neurological and primary care follow-up.

The patient returned to the ED for three more visits within the next month. On the following visits she complained of increasing difficulty with thought formulation and verbal expression. She demonstrated mild expressive aphasia, but had periods of completely normal speech. Otherwise, she remained alert and oriented and her neurological examination continued to be normal, including short- and long-term memory. A repeat head CT scan was unremarkable. Repeated neurological consultations did not produce any further recommendations. The patient grew increasingly anxious about her symptoms and was ultimately seen by psychiatry. The preliminary diagnosis on the first psychiatry consultation was possible conversion disorder with complicating hypothyroidism.

On the fourth ED visit the patient complained of altered mentation and lethargy. She had intermittent slow speech and increased difficulty formulating thoughts and expressing them. Her family had noticed a definite change in behavior, diminished walking, increased time in bed, and lack of attention to activities of daily living. She had a dull affect and seemed to become lost in thought mid-sentence. The remainder of her neurological and physical examination was normal. She was awake, alert, and oriented, however, at times seemed lost in thought. All laboratory evaluations were unremarkable.



**Figure 1.** MRI of the brain with diffusion weighted images shows increased signal intensity predominantly in the left parietal cerebral cortex (double arrows) and left caudate nucleus (single arrow).

Her TSH was 4.725 uU/mL and her T4 was 1.69 ng/dL, both within normal limits. After another neurological consultation, the patient was again referred to—and this time admitted by—the psychiatry service.

While admitted, she began having increasing short- and long-term memory loss along with progressive ataxia with a wide-based gait. She was noted to have psychomotor retardation, abnormal wrist posturing, staring spells, and one episode of screaming along with jerking motions that resolved with lorazepam and haloperidol. Before this episode she had been on lorazepam and haloperidol on an as-needed basis for agitation but no other psychiatric medications. An electroencephalogram (EEG) showed persistent rhythmic triphasic sharp wave activity prominent in the left frontal and temporal regions but present bilaterally as well, and she was transferred to the neurological service for possible seizures. On examination by the neurologists, she was noted to have slow fragmented speech, ataxia, and abnormal dystonic posturing of both hands, right greater than left. An MRI of the brain with diffusion weighted images showed progression of increased intensity in the left temporal, occipital and parietal regions (Figure 1). A repeat cerebrospinal (CSF) examination was normal, including viral culture and other evaluations for possible encephalitic causes. The CSF protein analysis did not reveal any oligoclonal bands and the myelin basic protein level returned at < 2.0 UG/L (normal range 0–4.0 ug/L). A

cerebral angiogram revealed no evidence of vasculitis. Ultimately, a brain biopsy was recommended. The biopsy specimens revealed a spongiform encephalopathy. Specimens sent to the National Prion Disease Surveillance Center provided the diagnosis of a prion disease, likely CJD, however, the specific form of CJD was not identified. For the calendar year of her presentation, the National Prion Disease Surveillance Center had thus far reported 103 cases of sporadic CJD and no cases of variant CJD in the United States (3). The patient continued to decline clinically and expired one and one-half months after her first onset of symptoms. At this point, no source has been identified; however, the patient did travel to the United Kingdom in the 1980s.

## DISCUSSION

CJD is a universally fatal neurodegenerative disorder caused by prions (4). Prions are pathologically conformed proteins that are a product of partial physiologic proteolysis of cell membrane proteins. Abnormal isoforms of prions accumulate within neurons of the brain causing spongiform degeneration and disruption of function (5). Five human prion diseases have been described to date: kuru (a disease formerly transmitted through ritual cannibalism), Gerstmann-Straussler-Scheinker syndrome (a hereditary disorder), fatal insomnia (also inherited), atypical prion disease (a heritable trait in a few families), and Creutzfeldt-Jakob disease (6).

CJD is classified as sporadic, familial, and acquired, which includes iatrogenic and variant CJD (3). In the mid 1980s, the transmission of BSE to humans through contaminated beef along with the emergence of a new form of CJD, variant CJD (vCJD), focused attention on prion diseases (8). The continued occurrence of vCJD cases only in persons who have lived in BSE-endemic areas and several animal and molecular laboratory studies provide strong evidence that vCJD is causally linked with BSE (7,8). This case demonstrates that CJD, although rare, can present in the Emergency Medicine setting.

Clinically, patients with sCJD present with rapidly progressive dementia, ataxia, and myoclonus. The median age at onset is 65 years. In contrast, patients with vCJD present at a younger age (median 26 years), with a prodrome of neuropsychiatric illness followed by dementia, ataxia, chorea, and persistent dysesthesias and paresthesias (7–9). The diagnosis of CJD is difficult. The differential diagnosis for patients presenting with this constellation of symptoms would include central nervous system infections, other forms of encephalitis, central nervous system vasculitis or ischemic diseases, seizure disorder, cerebellar disorders, delirium, dementia, toxins,

endocrine and electrolyte abnormalities, and finally, psychiatric illness after all medical causes are ruled out. The clinical diagnosis of sCJD is supported by a characteristic EEG with bilateral synchronous periodic sharp waves and elevated levels of protein 14-3-3 in the CSF (2). However, both of these tests may be negative in vCJD patients; in this instance an MRI may be useful. In patients with sCJD, diffusion-weighted and fluid-attenuated inversion recovery (FLAIR) MRI sequences have shown hyperintense signals to be present in the neostriatum (the caudate nucleus and putamen); in vCJD patients, signal hyperintensity has been found in pulvinar thalami, known as the “pulvinar sign” (2,5). Emergency physicians can begin the evaluation by looking for causes of altered mental status that can be medically treated. Neuroimaging with computed tomography and ultimately MRI would be warranted. Neurological consultation and admission are necessary to continue the evaluation for atypical diseases, especially those that require advanced laboratory evaluation and EEG monitoring. Ultimately, definitive diagnosis requires a confirmatory brain biopsy.

Currently, there is no cure for CJD and once symptoms appear the course is rapidly progressive, causing dementia, disability and ultimately, death. Early on, antipsychotics and sedatives may be helpful in controlling aggressive behavior, but institutional care will likely be needed. Despite the bleak prognosis, diagnosing CJD is critical to assuring appropriate neurological care, reducing multiple unresolved medical evaluations, and avoiding unnecessary or inappropriate psychiatric admissions. It also provides the opportunity for counseling and for the patient to address end-of-life decisions. Although one would hope the constellation of signs and symptoms would be recognized and identified through referral to neurological services, many patients with many different health issues are not compliant with referrals for follow-up and continue to re-present to the ED. In such cases, it may be the emergency physician who is in the best position to recognize the continuing progression of the symptoms without diagnosis, and to raise the possibility of CJD in the differential diagnosis.

CJD is not known to be transmitted by droplet, airborne, or direct person-to-person contact, and there is no evidence of the occupational transmission of CJD to health care workers. Health care workers should use standard precautions when caring for patients with CJD (10). Iatrogenic spread of CJD has resulted after the use of contaminated medical equipment. Transmission also has been reported after the use of extracted pituitary hormones, and after the implantation of contaminated grafts of human dura mater and corneas (10,11). Conventional steam sterilization and most routinely used disinfectants are not adequate methods to inactivate the

CJD prion protein. Both the Centers for Disease Control and Prevention and the World Health Organization have published specific guidelines for the processing of CJD-contaminated medical equipment (12). Brain (including dura mater), spinal cord, and eye tissue are the only tissues considered highly infectious for CJD (10). There is a theoretical risk of transmission by tonometry, however, no cases have been reported (13,14). To eliminate the risk of transmission by tonometry, single-use tonometer prism tips or a sterile disposable cover for the tip of the tonometer should be used. If prisms must be reused, extensive decontamination is recommended (13,15). Other ophthalmic instruments, such as corneal burrs, should not be reused because the grooved surface is too difficult to clean fully (13). Finally, to date there is no definitive evidence that CJD can be transmitted by transfusion of human blood products (16). To protect the blood supply from the theoretical risk of contamination by prion disease, the United States has instituted strict donor screening criteria (17).

In summary, our patient presented with symptoms of a very rare disease. Despite repeated Emergency Department visits, her diagnosis remained elusive—due in part to her age, normal neurological examination, and initial nondiagnostic neuroimaging—until her condition deteriorated precipitously. This case illustrates the potential for emergency physicians to encounter, and the prospect for them to play a role in diagnosing CJD and other spongiform encephalopathies that present in a similar fashion. Although CJD is rare and BSE has been mostly confined to Europe, both have been reported inside the United States. It may be helpful for emergency physicians to be aware of the symptoms and diagnostic challenges associated with these diseases when treating patients with serial presentations of progressing neuropsychiatric symptoms without a clear cause or diagnosis.

## REFERENCES

1. Glatzel M, Ott PM, Linder T, et al. Human prion diseases: epidemiology and integrated risk assessment. *Lancet Neurol* 2003;2:757–63.
2. Tyler KL. Creutzfeldt-Jakob Disease. *N Engl J Med* 2003;348:681–2.
3. National Prion Disease Pathology Surveillance Center. Available at <http://www.cjdsurveillance.com/prion.html>.
4. Summers D, Collie D, Zeidler M, Will R. The pulvinar sign in variant Creutzfeldt-Jakob Disease. *Arch Neurol* 2004;61:446–7.
5. Collinge J, Brandner S, Kennedy A, et al. A 38-year-old man with a 9 month history of neurological and cognitive impairment. *Lancet Neurol* 2003;2:189–94.
6. Kretzschmar HA, Ironside JW, DeArmond SJ, Tateishi J. Diagnostic criteria for sporadic Creutzfeldt-Jakob disease. *Arch Neurol* 1996;53:913–20.
7. Martindale J, Geschwind M, De Armond S, et al. Sporadic Creutzfeldt-Jakob disease mimicking variant Creutzfeldt-Jakob disease. *Arch Neurol* 2003;60:767–70.
8. Belay E, Maddox R, Gambetti P, Schonberger L. Monitoring the occurrence of emerging forms of Creutzfeldt-Jakob disease in the United States. *Neurology* 2003;60:176–81.
9. Allroggen H, Dennis G, Abbott R, Pye I. New variant Creutzfeldt-Jakob disease: three case reports from Leicestershire. *J Neurol Neurosurg Psychiatry* 2003;68:375–8.
10. Weber DJ, Rutat WA. Managing the risk of nosocomial transmission of prion diseases. *Curr Opin Infect Dis* 2002;15:421–5.
11. Hammersmith KM, Cohen EJ, Rapuano CJ, Laibson PR. Creutzfeldt-Jakob disease following corneal transplantation. *Cornea* 2004;23:406–8.
12. WHO Infection Control Guidelines for Transmissible Spongiform Encephalopathies. Report of a WHO Consultation, Geneva, Switzerland, 23–26 March 1999. Available at <http://www.who.int/emc-documents/tse/whoedscsraph2003c.html>.
13. Lim R, Dhillon B, Kurian KM, et al. Retention of corneal epithelial cells following Goldmann tonometry: implications for CJD risk. *Br J Ophthalmol* 2003;87:583–6.
14. Mehta JS, Osborne RJ, Bloom PA. Variant CJD and tonometry. *Br J Ophthalmol* 2004;88:597–8.
15. Amin SZ, Smith L, Luthert PJ, Cheetham ME, Buckley RJ. Minimising the risk of prion transmission by contact tonometry. *Br J Ophthalmol* 2003;87:1360–2.
16. Wilson K, Code C, Ricketts MN. Risk of acquiring Creutzfeldt-Jakob disease from blood transfusions: systematic review of case-control studies. *BMJ* 2000;321:17–9.
17. Pomper GJ, Wu Y, Snyder EL. Risks of transfusion-transmitted infections: 2003. *Curr Opin Hematol* 2003;10:412–8.