Sporadic Creutzfeldt-Jakob Disease Mimicking Variant Creutzfeldt-Jakob Disease

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**Background:** The determination of the form of prion disease and early diagnosis are important for prognostic, public health, and epidemiologic reasons.

**Objective:** To describe a patient with sporadic Creutzfeldt-Jakob disease (sCJD) who had a clinical history and initial electroencephalogram and magnetic resonance imaging findings consistent with variant CJD (vCJD).

**Results:** Results of a repeated electroencephalogram were suggestive of sCJD, and a subsequent brain biopsy confirmed this diagnosis.

**Conclusions:** This case cautions against relying solely on T2- and diffusion-weighted pulvinar hyperintensity and clinical features to differentiate between vCJD and sCJD, and further supports established diagnostic criteria for vCJD.

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**Protein Misfolding**

Protein misfolding diseases are universally fatal neurodegenerative disorders that occur in sporadic, familial, and iatrogenic forms, the most common of which is sporadic Creutzfeldt-Jakob disease (sCJD). In 1996, Will and colleagues described a new form of CJD, variant CJD (vCJD), with clinical, epidemiologic, and pathologic features distinctive from other human prion diseases. Variant CJD is characterized by a younger median age of onset than that of sCJD (26 vs 65 years) and a longer median disease duration (14 vs 4.5 months). The onset of vCJD almost uniformly exhibits a prodrome of a neuropsychiatric illness followed later by the development of dementia, chorea, ataxia, and persistent painful sensory symptoms, in contrast with the more variable presentation of sCJD. It has been emphasized that vCJD cases can be differentiated from sCJD and other rapidly progressive dementias by the characteristic magnetic resonance imaging (MRI) finding of the pulvinar sign. This consists of an increased bilateral pulvinar signal, best visualized with fluid-attenuated inversion recovery (FLAIR) and diffusion-weighted techniques. An increased signal in the medial thalami is commonly found with the pulvinar sign, giving the appearance of a “double hockey stick.” Neuropathologically, brain tissue in patients with vCJD shows florid amyloid plaques that differentiate this disorder from other human prion diseases.

Clinical recognition of vCJD is important because of its link to the consumption of infected beef and the possibility of a rising epidemic. For this reason, clinical criteria have been developed for probable vCJD. A probable diagnosis of vCJD requires fulfillment of the following criteria: a progressive neuropsychiatric disorder lasting at least 6 months, no history of iatrogenic exposure, an electroencephalogram (EEG) finding that is not indicative of sCJD, a bilateral pulvinar high signal on MRI, and at least 4 of the following 5 clinical features: early psychiatric symptoms, persistent painful sensory symptoms, ataxia, a movement disorder, and dementia. While some cases of sCJD with clinical and radiologic features typical of vCJD have been reported, they have only included patients closer in age to the mean of sCJD. We report a case that initially met all of the epidemiologic, clinical, and imaging features of vCJD, and was pathologically proven by brain biopsy to have sCJD.
A 36-year-old woman with an unremarkable medical history developed new-onset behavioral changes, including increased irritability and mild depression, in April 2000. One month later, she was seen by a psychiatrist, diagnosed as having depression, and treated with bupropion. In October 2000, she reported intense headaches. Between October and December 2000, she developed a progression of balance and gait problems as well as left leg weakness. In late December 2000, she developed short-term memory deficits and insomnia. Her social history was unremarkable except that she had traveled to the British Virgin Islands, Mexico, and Belize for 1 week every year for the prior 5 years.

As part of this patient’s evaluation at an outside institution, she received 2 sleep and waking EEGs, 3 MRIs, and urine, serum, and cerebrospinal fluid analyses. She was admitted to our institution, where she was evaluated with a neuroexamination, MRI, and an EEG, and underwent a brain biopsy for a pathologic diagnosis. The biopsy was performed in the right temporoparietal cortex. The specimen was treated with hematoxylin-eosin and periodic acid–Schiff stains. Immunohistochemical analysis for protease-resistant prion protein (PrPSc) was performed using the hydrolytic autoclaving technique and antibody 3F4. The histoblot technique, which is the most sensitive and specific immunohistochemical test for PrPSc in tissue sections, uses unfixed cryostat sections blotted onto nitrocellulose paper.

In January 2001, sleep and waking EEG findings were normal, and an MRI of the brain showed a “questionable pituitary microadenoma” but was otherwise read as normal. Additional workup showed no microadenoma. In our later evaluation of this MRI, we noted abnormal hyperintensities in the basal ganglia on T2-weighted and FLAIR images (Figure 1). A second MRI of the brain in February 2001 showed hyperintensity in the caudate, putamen, and thalami bilaterally. Results of an EEG in March were abnormal due to the presence of triphasic waves and frontal intermittent rhythmic delta flowing. During spring 2001, she developed worsening confusion, slowed thinking, and visual hallucinations, and by July 2001, she was no longer ambulatory.

Brain MRI in June 2001 showed increased hyperintensity bilaterally in the caudate, putamen, and in the medial thalami; there was also gyrmiform hyperintensity on FLAIR and T2-weighted images involving the cortex through the right posterior temporal and parietal regions. Results of urine, serum, and cerebrospinal fluid analyses were all normal, and 14-3-3 protein testing was negative.

In August 2001, she was admitted to our institution for further evaluation. On admission, she had 1- or 2-word verbal output, was oriented to name only, recognized family members, and intermittently followed simple 1-step commands with minimal verbal expression. Motor system examination showed asymmetric (left much greater than right), increased tone in all extremities, bilateral planter extensor responses, and occasional myoclonic jerks in the extremities. She was unable to ambulate.
Brain MRI showed diffuse bilateral symmetric hyperintensities on T2, FLAIR, and diffusion-weighted imaging sequences involving the caudate, putamen, and posterior and medial thalami, as well as a gyriform pattern along the posterior (right greater than left) temporoparietal cortex. Areas of abnormal intense T2 prolongation were associated with reduced diffusion (Figure 1) on diffusion-weighted imaging and attenuated diffusion coefficient maps. These images were read as consistent with vCJD. A repeated EEG showed typical periodic epileptiform discharges consistent with sCJD. Because of the patient's young age, clinical history, and MRI findings, a brain biopsy was performed to determine the form of CJD.

The biopsy specimen from the patient's right temporoparietal cortex revealed numerous 5- to 20-µm vacuoles in the gray matter neuropil within neuronal layers 4, 5, and 6, detected by hematoxylin-eosin and periodic acid–Schiff stains. A, The periodic acid-Schiff (PAS)–stained section reveals multiple vacuoles, ranging in size from 5–20 µm, within the gray matter neuropil. Note the absence of PAS-positive amyloid plaques. B, Fine granular (synaptic) deposits and coarse deposits adjacent to some of the vacuoles are shown in this immunoperoxidase stain for protease-resistant prion protein (PrPSc) (Nomarski optics). C, The presence of multiple PAS-positive, Kuru-type amyloid plaques within vacuoles is characteristic of vCJD. D, The Kuru-type plaques in vCJD are often found in clusters and are strongly immunopositive for PrPSc (Nomarski optics). Bar=25 µm.

The histologic features of sporadic Creutzfeldt-Jakob disease (sCJD) (A and B) are different from those of variant CJD (vCJD) (C and D). A, The periodic acid-Schiff (PAS)–stained section reveals multiple vacuoles, ranging in size from 5–20 µm, within the gray matter neuropil. Note the absence of PAS-positive amyloid plaques. B, Fine granular (synaptic) deposits and coarse deposits adjacent to some of the vacuoles are shown in this immunoperoxidase stain for protease-resistant prion protein (PrPSc) (Nomarski optics). C, The presence of multiple PAS-positive, Kuru-type amyloid plaques within vacuoles is characteristic of vCJD. D, The Kuru-type plaques in vCJD are often found in clusters and are strongly immunopositive for PrPSc (Nomarski optics). Bar=25 µm.

Figure 2. The histologic features of sporadic Creutzfeldt-Jakob disease (sCJD) (A and B) are different from those of variant CJD (vCJD) (C and D). A, The periodic acid-Schiff (PAS)–stained section reveals multiple vacuoles, ranging in size from 5–20 µm, within the gray matter neuropil. Note the absence of PAS-positive amyloid plaques. B, Fine granular (synaptic) deposits and coarse deposits adjacent to some of the vacuoles are shown in this immunoperoxidase stain for protease-resistant prion protein (PrPSc) (Nomarski optics). C, The presence of multiple PAS-positive, Kuru-type amyloid plaques within vacuoles is characteristic of vCJD. D, The Kuru-type plaques in vCJD are often found in clusters and are strongly immunopositive for PrPSc (Nomarski optics). Bar=25 µm.

The biopsy specimen from the patient's right temporoparietal cortex revealed numerous 5- to 20-µm vacuoles in the gray matter neuropil within neuronal layers 4, 5, and 6, detected by hematoxylin-eosin and periodic acid–Schiff stains (Figure 2A). No Kuru-type amyloid plaques or other amyloid deposits were identified. Immunohistochemical analysis for protease-resistant prion protein (PrPSc) revealed fine granular (synaptic) deposits as well as coarse deposits of PrPSc adjacent to some of the vacuoles (Figure 2B). PrPSc was distributed in a diffuse pattern throughout the full thickness of the cerebral cortex in the histoblots (data not shown). The histologic features described above are characteristic of sCJD. In contrast, vCJD is characterized by large confluent vacuoles (50-100 µm in diameter) that contain 1 or more Kuru-type amyloid plaques. This complex is known as a “florid plaque” (Figure 2C). Florid plaques are PrPSc immunopositive (Figure 2D). The absence of florid plaques in the current case argues that it was not vCJD. The scrapie prion protein type was determined by Western blot to be type 2, and sequencing of the prion protein gene showed that codon 129 was heterozygous methionine/valine. Therefore, this was an M/V2 variant of sCJD.

Early in her course, our patient had the classic clinical and imaging findings of vCJD. Her early psychiatric symptoms of depression and behavioral changes were all consistent with a vCJD prodrome. Like many vCJD cases reported in the literature, this patient was first seen and treated by a psychiatrist for depression. Her young age...
at the onset of this disease was close to the median age of reported vCJD cases (age 26 years). Only 4.5% of cases of sCJD occur in the 30- to 40-year age bracket. Her relatively young age, long duration of illness, 6-month psychiatric/behavioral prodrome, progression to a movement disorder, and the “double-hockey stick” appearance on MRI were all highly suggestive of vCJD. Until her second EEG showed abnormalities typical of sCJD, this patient had met all of the diagnostic criteria for vCJD. Criteria based on the knowledge that the signature EEG findings in sCJD are absent in vCJD excluded her from a diagnosis of probable vCJD. Our case is similar to that of a 55-year-old patient with sCJD who was initially thought to have vCJD based on her psychiatric symptoms, double-hockey-stick appearance of the dorsomedial thalami, and the absence of EEG findings typical of sCJD. The young age of our patient made a diagnosis of vCJD even more suspect. The current age range for vCJD of 12 to 74 years overlaps with sCJD. In general, young age should not be used to rule out a diagnosis of sCJD. Although not well described in the literature, behavioral changes may occur in the earlier stages of sCJD as well.

The MRI findings in this patient, obtained at 4 different time points throughout the disease course, showed a bilateral signal intensity in the pulvinar and medial portions of the thalamus, giving a “double hockey stick” appearance. Specificity of the pulvinar sign was reported to be 100% when comparing 36 confirmed vCJD cases with 56 non-vCJD controls that were initially suspected as having vCJD. Our case suggests that the specificity is not 100%. The pulvinar sign allows a probable diagnosis of vCJD as long as other criteria are fulfilled. Furthermore, as several studies suggest, a higher relative hypointensity in the pulvinar as compared with the caudate and putamen may confer greater specificity in the appropriate clinical context.

In our patient, the change in EEG finding to one suggestive of sCJD would by established criteria have eliminated the diagnosis of vCJD. However, if the EEG had not been done or did not become suggestive of sCJD as occurs in a large minority of patients, the prebiopsy diagnosis would have remained vCJD. Because of the profound implications of diagnosing a patient as having vCJD, we cannot overstate the importance of thoroughly investigating every case with studies that include brain MRI, EEG, and when necessary, pathologic analysis, to obtain a diagnosis of the specific form of the disease.

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