Sporadic Creutzfeldt-Jakob disease with focal findings: caveats to current diagnostic criteria

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Abstract

The clinical diagnosis of Creutzfeldt-Jakob disease (CJD) is largely based on the 1998 World Health Organization diagnostic criteria. Unfortunately, rigid compliance with these criteria may result in failure to recognize sporadic CJD (sCJD), especially early in its course when focal findings predominate and traditional red flags are not yet present. A 61-year-old man presented with a 3-week history of epilepsia partialis continua (jerking of the left upper extremity) and a 2-week history of forgetfulness and left hemiparesis; left hemisensory neglect was also detected on admission. Repeated brain magnetic resonance imaging (MRI) showed areas of restricted diffusion in the cerebral cortex, initially on the right but later spreading to the left. Electroencephalography (EEG) on hospital days 7, 10, and 14 showed right-sided periodic lateralized epileptiform discharges. On day 20, the EEG showed periodic sharp wave complexes leading to a diagnosis of probable sCJD and subsequently to definite sCJD with brain biopsy. Neurological decline was relatively fast with generalized myoclonus and akinetic mutism developing within 7 weeks from the onset of illness. CJD was not immediately recognized because of the patient’s focal/lateralized manifestations. Focal/lateralized clinical, EEG, and MRI findings are not uncommon in sCJD and EEG/MRI results may not be diagnostic in the early stages of sCJD. Familiarity with these caveats and with the most current criteria for diagnosing probable sCJD (University of California San Francisco 2007, MRI-CJD Consortium 2009) will enhance the ability to recognize sCJD and implement early safety measures.

Introduction

Creutzfeldt-Jakob disease (CJD) belongs to a family of rare transmissible brain disorders (prion diseases) in which the causative agent (prion) induces abnormal folding of normal cellular proteins (prion proteins) leading to progressive spongiform degeneration and loss of brain neurons (spongiform encephalopathy). Sporadic CJD (sCJD) accounts for 85% of CJD cases; the remaining 15% are familial or iatrogenic. Clinically, sCJD is diagnosed based on criteria published by the World Health Organization (WHO) consultation group in 1998.1 These criteria were updated in 2007 by the University of California San Francisco (UCSF) group and in 2009 by the MRI-CJD Consortium (MCC).2,3 The definitive diagnosis of sCJD requires pathological studies of the brain.4

Table 1 outlines the WHO, UCSF, and MCC diagnostic criteria for probable/possible sCJD.1,3 Diagnosing probable sCJD requires the presence of clinical manifestations and at least one positive laboratory finding. Both WHO and UCSF criteria require the presence of unexplained cognitive decline, at least two other neurological disturbances, and at least one positive laboratory test finding. The MCC criteria require at least two neurological disturbances (cognitive decline may or may not be one of them) and at least one positive laboratory test finding. Based on WHO or MCC criteria, a diagnosis of possible sCJD is made if the patient has the clinical signs required to diagnose probable sCJD, but none of the laboratory signs are present. Possible sCJD is not a diagnostic entity in the UCSF criteria set.

In theory, replacing the WHO criteria with the UCSF/MCC criteria will improve diagnostic yield. Nevertheless, sCJD with prominent focal manifestations and/or non-diagnostic electroencephalography/magnetic resonance imaging (EEG/MRI) findings can still escape diagnosis no matter which criteria set is used. We present a case of sCJD that was not immediately suspected because of the focal/lateralized clinical, EEG, and MRI manifestations.

Case Report

A 61-year-old man presented with a 3-week history of left upper extremity jerking and a 2-week history of left hemiparesis, forgetfulness, and inattention. On admission, the patient was alert and oriented to self and place, but not to time; his vital signs were normal. He manifested left arm clonic movements consistent with epilepsia partialis continua (EPC); this was easily suppressed with lorazepam. The neurological exam revealed 3/5 strength in the distal left upper extremity muscles, 4/5 strength in the left lower extremity muscles, +3 reflexes on the left and +2 on the right, left Babinski sign, and left hemisensory neglect. Primary sensation, cranial nerves, and cerebellar function were intact. Because of the focal/lateralized findings and the patient’s history of hypertension, hyperlipidemia, myocardial infarction, and coronary artery bypass graft surgery, stroke was diagnosed on admission.

Brain MRI on hospital days 1, 7, and 20 showed restricted diffusion in the cerebral cortex; the cortical areas affected appeared hyperintense on diffusion-weighted imaging (DWI) and hypointense on apparent diffusion coefficient (ADC) (Figure 1). Some cortical lesions were also visible on fluid attenuation inversion recovery (FLAIR) sequences. At first limited to the right occipitoparietal, right posterior frontal, and bilateral mesial frontal cortices, the areas of restricted diffusion expanded and spread to the adjacent cortices in the right, and eventually, in the left hemisphere. Restricted diffusion was not present in the basal ganglia and thalamus.

Scalp EEG on hospital days 7, 10, and 14 showed right hemispheric periodic lateralized epileptiform discharges (PLEDs) in the form of sharp and slow waves with a right centropari-
Table 1. Clinical diagnostic criteria for sporadic Creutzfeldt-Jakob disease (sCJD). This table outlines the World Health Organization (1998), University of California San Francisco (2007), and MRI-CJD Consortium (2008) criteria for diagnosing probable sCJD and possible sCJD. Brain biopsy is required for premortem diagnosis of definite sCJD.

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<tr>
<td>Probable sCJD = A + at least 2 of B + at most 1 of C</td>
<td>MRI-CJD Consortium diagnostic criteria (2009)</td>
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<tr>
<td>Possible sCJD = A + at least 2 of B + duration &lt;2 years</td>
<td>Probable sCJD = at least 2 of A + at least 1 of B</td>
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A. Progressive dementia

B. Specific neurological manifestations
1. Myoclonus
2. Visual or cerebellar disturbance
3. Pyramidal or extrapyramidal dysfunction
4. Akinetic mutism

C. Laboratory tests
1. Positive EEG: periodic sharp wave complexes
2. Positive CSF: 14-3-3 protein

D. Routine investigations should not suggest an alternative diagnosis

Table 2. Recognizing sporadic Creutzfeldt-Jakob disease in its early stages: important caveats to current criteria.

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<th>Criteria</th>
<th>Probable sCJD = at least 2 of A + at least 1 of B</th>
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<td>Probable sCJD = A + at least 2 of B + duration &lt;2 years</td>
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A. Clinical signs
1. Dementia
2. Cerebellar or visual
3. Pyramidal or extrapyramidal
4. Akinetic mutism

B. Laboratory tests
1. Positive EEG: periodic sharp wave complexes
2. Positive CSF: 14-3-3 protein

C. Routine investigations do not suggest an alternative diagnosis

MRI: magnetic resonance imaging; ADC: apparent diffusion coefficient; DWI: diffusion-weighted imaging; FLAIR: fluid-attenuated inversion recovery.

**Discussion and Conclusions**

In the sCJD case presented, mild cognitive dysfunction was overshadowed by focal/lateralized findings, including EPC, left hemiparesis, left hemisensory neglect, and PLEDs. Such focal/lateralized findings steered the diagnosis.

sCJD, sporadic Creutzfeldt-Jakob disease; EEG, electroencephalography; CSF, cerebrospinal fluid; MRI, magnetic resonance imaging; DWI, diffusion-weighted imaging; ADC, apparent diffusion coefficient.
towards stroke and encephalitis. It was not until the twentieth hospital day that sCJD was suspected, when the EEG showed typical PSWCs.

Updated diagnostic criteria for sporadic Creutzfeldt-Jakob disease

The contemporary diagnosis of sCJD is largely based on the 1998 WHO criteria (Table 1).1 Using these criteria, a patient can be diagnosed with probable or possible sCJD. Unfortunately, strict reliance on WHO criteria may result in a failure to recognize sCJD because focal findings may predominate, cognitive dysfunction may be absent or subtle, and the classic red flag for CJD - PSWCs - may not yet be present in the EEG. Some of these diagnostic pitfalls can be avoided by being familiar with the most current UCSF and MCC criteria.

The UCSF criteria differ from the WHO criteria by taking into account specific higher cortical signs (e.g. neglect, aphasia, apraxia, agraphia), by removing CSF 14-3-3 protein as a criterion, by adding MRI subcortical/cortical hyperintensities as criteria, and by expanding the definition of positive EEG to include periodic epileptiform discharges other than PSWCs (e.g. PLEDs).2

The MCC criteria differ from the WHO and UCSF criteria by putting less emphasis on cognitive dysfunction, allowing one to diagnose probable sCJD in a cognitively intact person with visual/cerebellar disturbances, pyramidal/extrapyramidal signs, and at least one positive test result. The MCC criteria also differ from the other two sets by including EEG, CSF 14-3-3, and MRI findings as positive laboratory tests; however, it retains the original WHO definition of a positive EEG as one that shows typical PSWCs.3

Diagnosing sporadic Creutzfeldt-Jakob disease remains a challenge

The differential diagnosis of rapidly progressive dementia is broad.5 Myoclonus helps narrow down the differential diagnosis to some extent. However, cognitive dysfunction may be subtle and myoclonus may be absent in the early stages of sCJD. Furthermore, EPC is not typically viewed as myoclonus when, in fact, EPC is just another name for focal myoclonic status epilepticus.6 The lack of such awareness can delay the diagnosis of sCJD in a patient with EPC as an early manifestation.

A wide range of focal/lateralized manifestations have been reported in patients with sCJD. Examples of focal/lateralized neurological signs/symptoms in sCJD are: i) focal higher cortical deficits, such as aphasia,7 alexia without agraphia,8 and alien limb phenomenon;9 ii) movement disorders other than myoclonus,10 focal dystonia,11 and cerebellar ataxia;12 iii) visual abnormalities such as

Figure 1. Brain magnetic resonance imaging on hospital days 1, 7, and 20 showed areas of restricted diffusion in the cerebral cortex. The cortical areas affected appeared hyperintense on DWI (first column) and hypointense on ADC (second column). Each ADC map in the second column corresponds to the DWI image in the first column (b=1000). Restricted diffusion was not present in the basal ganglia and thalamus. Only a few of the cortical lesions were visible on FLAIR sequences (third column). Selected areas with clear-cut signal abnormalities are indicated by an arrow: yellow for DWI hyperintensities, red for FLAIR sCJD hyperintensities, and black for FLAIR chronic microvascular changes.

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Figure 2. Scalp EEG on hospital days 7, 10, and 14 showed right hemispheric PLEDs in the form of sharp and slow waves with a right centroparietal maximum and a discharge rate of about 1/second. Some sharp waves were time-locked to the patient’s myoclonic jerks. The background EEG was slow and attenuated on both sides. The PLEDs increased in amplitude and became broader in distribution. On day 20, the EEG showed bihemispheric PSWCs (right lower tracing) alerting the physicians to the possibility of sCJD. For all tracings: screen sensitivity = 5 µV/mm, timebase = 1 second/division. EEG tracings from the left side are in blue and tracings from the right side are in red.