

# Pearls and Oy-sters: Typical Atypical Creutzfeld-Jakob Disease: A Case Presenting as a Rapidly Progressive Corticobasal Syndrome Without Dementia

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Creutzfeld-Jakob disease (CJD) is a rare disease but a common cause of rapidly progressive neurodegeneration. Although the “classic” presentation involves early dementia or behavioral changes, there are well-described atypical variants with less prominent cognitive symptoms at onset. One such variant is corticobasal syndrome (CBS), which may be seen with other underlying neurodegenerative processes; however when CBS is due to prion disease pathology, it typically involves a much more rapid progression and certain characteristic imaging findings. This report includes a case presenting with CBS without cognitive or behavioral changes at onset, which rapidly progressed and was determined ultimately to be due to underlying CJD. This case illustrates the need for a high index of suspicion for CJD to drive appropriate diagnostic testing and careful review of imaging and EEG findings, which may be subtle in early disease.

## Pearls

- Corticobasal syndrome (CBS), a phenotype with unilateral motor and secondary sensory deficits without significant cognitive impairment or dementia, is a well-described “atypical” presentation of Creutzfeld-Jakob disease (CJD).
- Although CBS is most associated with neurodegenerative tauopathies, characteristic imaging findings of restricted diffusion along with rapid progression to akinetic mutism or death are strong indicators for prion disease pathology.
- MRI abnormalities in early CJD can be subtle and easily missed. Awareness of atypical phenotypes of CJD presentations can increase clinical suspicion and better interpretation of subtle neuroimaging and neurophysiologic studies such as EEG.

## Oy-sters

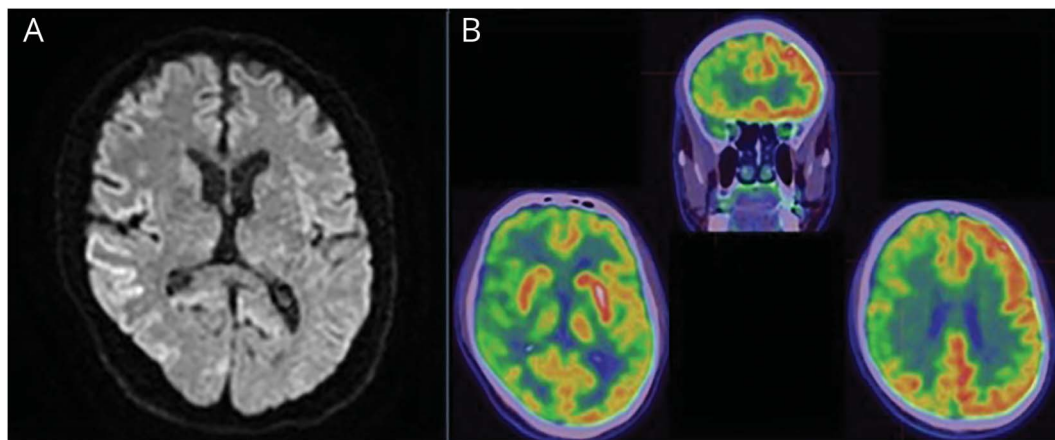
- EEG findings in early CJD may not show the classic diagnostic features of periodic synchronous discharges and should not be used alone to rule out the diagnosis.
- CSF 14-3-3 testing has low specificity and can be positive in other neurodegenerative diseases; results should be interpreted in the context of clinical suspicion for CJD.
- Although rapidly progressive dementia is included as a criterion for both “probable” and “possible” CJD diagnosis, atypical presentations of CJD without cognitive symptoms are well described. The absence of dementia should not dissuade from further targeted diagnostics.

## Case Report

A 58-year-old right hand–dominant man presented to the neurology clinic with a 4-month history of episodic left-sided weakness and lateral pulsion lasting several hours. Five months after initial presentation, he developed progressive, continuous left-sided symptoms, including pain, unsteady gait, and myoclonic jerks of his left arm and leg. He also reported “restricted” movement and abnormal tactile sensations, for example, he had difficulty setting his left foot down with certainty and reported that objects held in his left hand felt foreign to him. He had no

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(A) Diffusion-weighted MRI showing cortical ribboning predominantly in the right hemisphere. (B) Brain PET scan showing hypometabolism in the right hemisphere with some involvement of the deep structures (basal ganglia and thalamus).

cognitive complaints, and his wife confirmed no changes in his behavior or personality. Examination showed preserved cognitive functions as tested using the Montreal Cognitive Assessment with a score of 26/30. Strength and primary sensory modalities were normal. He had continuous myoclonic jerks throughout his left upper and lower extremities, mild apraxia in the left upper extremity, and an upward drift of his left hand (parietal lift). Testing of secondary sensory modalities showed agraphesthesia bilaterally (worse on the left) and left-sided extinction. His deep tendon reflexes were +2 throughout; however, he had an exaggerated startle response. His gait was wide, with uncoordinated movements on the left with abnormal posturing of his left arm while walking. A brain MRI demonstrated diffusion restriction in the right temporal, parietal, and occipital cortices (Figure 1A) with apparent diffusion coefficient correlation but no significant T2 FLAIR changes. Retrospective review of his previous brain MRIs conducted during the episodic phase of his disease showed subtle diffusion restriction on diffusion-weighted imaging (DWI) in the same regions, not appreciated in the original neuroradiology review. An EEG finding showed lateralized complex delta slowing of the background over the right hemisphere. A second EEG finding 12 days later showed worsening asymmetric right hemispheric and left fronto-central complex delta with right hemispheric periodic discharges with triphasic morphology (Figure 2). A PET scan showed hypometabolism in the entire right cerebral hemisphere to include (to a lesser degree) the right basal ganglia and thalamus (Figure 1B). CSF studies showed normal white blood cell count and protein, and a rapid PCR meningitis/encephalitis panel was negative. CSF paraneoplastic and autoimmune dementia panels were negative. CSF neuron-specific enolase was elevated (45 ng/mL, normal 0–30 ng/mL), as was total tau protein (4,853 pg/mL, normal < 0–1,149 pg/mL). CSF 14-3-3 and RT-QuIC both returned positive. Myoclonus was symptomatically treated with levetiracetam. He continued to decline rapidly, eventually developing akinetic mutism. He died 1 month after his CSF results returned and 4 months after development of persistent motor symptoms.

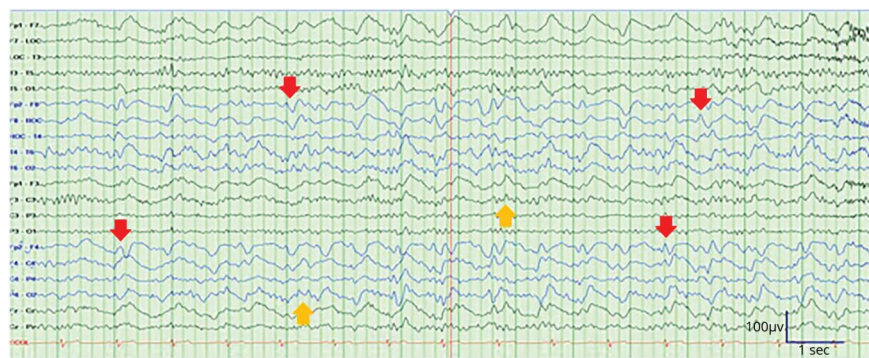
Given lack of family history or exposures to iatrogenic or dietary sources of prion disease, he was presumed to have sporadic Creutzfeldt-Jakob disease (CJD), which was later confirmed by autopsy. The results showed positive Western blot and immunohistochemical analyses for abnormal prion protein, without evidence of a deleterious gene mutation in the *PRNP* gene.

## Discussion

Patients with CJD show a variable combination of clinical symptoms, resulting in heterogeneous phenotypes of presentation. Although CJD is the most common cause of rapidly progressive dementia, misdiagnosis or delays of diagnosis can occur with atypical presentations, especially when cognitive deficits are mild or absent or when the presentation mimics another neurodegenerative disease.<sup>1,2</sup>

For example, Corticobasal Syndrome is an asymmetric movement disorder with lateralized higher cortical features. Motor signs show some combination of apraxia, rigidity, bradykinesia, myoclonus, dystonia, or alien limb. Cortical sensory features of neglect and agraphesthesia can accompany the motor signs.<sup>3</sup> The underlying disease causing corticobasal syndrome (CBS) can vary, and it is commonly associated with the tauopathies of corticobasal degeneration (CBD), progressive supranuclear palsy, and frontotemporal dementia. However, CBS can also present as an atypical manifestation of CJD, which should be considered in all cases presenting with CBS.<sup>4-7</sup> Cases of CBS misattributed to tauopathies have been previously described in the literature. One reported case was initially pathologically attributed to CBD and only on postmortem testing was confirmed to be caused by underlying sporadic CJD (sCJD).<sup>5</sup> A review of 19 cases of CBS due to confirmed CJD showed that the rapidity of progression and DWI abnormalities (such as cortical ribboning) were key discriminators—clues—which aid in the differentiation of sCJD-CBS and CBD-CBS. Length of

**Figure 2** EEG Findings of Creutzfeldt-Jakob Disease



EEG using a 10–20 system in longitudinal bipolar montage (double banana), demonstrating frequent unilateral right hemispheric 1- to 1.5-Hz periodic discharges with triphasic morphology (red arrows) and asymmetric complex delta slowing over the right hemisphere and left fronto-central regions (orange arrows).

disease course from diagnosis to death was a median of 5 months on average for sCJD vs 48–68 months in CBD-CBS.<sup>4,7</sup> This was similar in our patient, and along with imaging findings, his rapid decline helped prompt the appropriate diagnostic workup.

Atypical presentations of sCJD can also be missed because published criteria for the diagnosis of sCJD are incomplete and may not account for less common phenotypes. Although the definitive diagnosis of CJD is made histopathologically,<sup>1</sup> several organizations have published criteria aimed at making the diagnosis less invasively. The World Health Organization (WHO) created the original diagnostic criteria for CJD in 1998. Updates in 2007 by the University of California San Francisco (UCSF) group and again in 2009 by the MRI-CJD Consortium (MCC) improved diagnostic accuracy.<sup>8</sup> The Centers for Disease Control (CDC) have their own criteria adopted from the WHO criteria in 2018.<sup>9</sup> All the aforementioned criteria depend on clinical presentation supported by a combination of radiographic, electrographic, and laboratory findings. However, there are several diagnostic pitfalls in these criteria, and the current diagnostic schemes may miss atypical presentations of the disease, resulting in either a false-negative diagnosis or a truncated workup.

For example, only the MCC criteria do not require rapidly progressive dementia or neuropsychiatric symptoms as a feature of the patient presentation. This may have led to a missed diagnosis in our patient because he did not display any cognitive symptoms at onset. Along with sCJD-CBS, other known atypical variants present with prominent noncognitive symptoms, such as gait ataxia (Oppenheimer-Brownell) or purely visuospatial deficits (Heidenhain).<sup>2</sup> There are other cases described in the literature, with patients presenting initially with motor symptoms but without prominent dementia, although even cases presenting atypically eventually progress to dementia at the time of death.<sup>10</sup>

Neuroimaging, neurophysiologic studies, and laboratory studies are important diagnostic tools for evaluating CJD, and

recent advances have improved diagnostic specificity. The later updates to the WHO criteria added MRI changes as a means of diagnosis. Brain MRI may have sensitivity and specificity of 90% for probable CJD and may be more accurate than CSF studies in diagnosis.<sup>1,6</sup> However, these findings can be subtle or mistaken for artifact; in our patient, cortical ribboning was present on imaging before the development of motor symptoms but only identified on retrospective review. This illustrates well that neurologists should carefully review the imaging themselves if CJD is suspected. All the criteria include epileptiform discharges or, more specifically, periodic sharp wave complexes as diagnostic EEG findings. However, there are multiple reports showing that initial EEGs may show nonspecific background slowing or frontal intermittent rhythmic delta activity.<sup>1,8,10</sup> Finally, most criteria rely on 14-3-3 protein detected in the CSF, which, by some reports, varies in both specificity and sensitivity within a range of 80%–90% and can be positive in other neurodegenerative diseases.<sup>6</sup> Given imperfect specificity, 14-3-3 is more helpful as supportive in cases with high suspicion for CJD rather than independently diagnostic. The more recently developed real-time quaking-induced conversion (RT-QuIC) test demonstrates a similar sensitivity (90.3%) with much better specificity (98.5%).<sup>1,6,11</sup> However, only the CDC criteria are recent enough to include this test at this point.<sup>9</sup>

Neurologists should be familiar with atypical presentations, such as Corticobasal Syndrome, which do not seem to meet all current clinical criteria, especially as findings such as MRI and EEG changes may evolve as the disease progresses. Although CJD is a rare disease, it is a common cause of rapidly progressive neurodegeneration, and a high clinical suspicion is required to make the diagnosis. Use of the CSF real-time quaking-induced conversion diagnostic test has important clinical implications as a noninvasive test with both good sensitivity and specificity for the disease process.<sup>11</sup>

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## Appendix Authors

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<b>Zoe Olga Marinides, MD</b>	Department of Neurology, Walter Reed National Military Medical Center, Bethesda, MD	Drafting/revision of the article for content, including medical writing for content; major role in the acquisition of data; and analysis or interpretation of data
<b>Timothy R. Malone, MD</b>	Department of Neurology, Walter Reed National Military Medical Center, Bethesda, MD	Drafting/revision of the article for content, including medical writing for content, and analysis or interpretation of data.
<b>Yitao Ma, MD</b>	Department of Neurology, Walter Reed National Military Medical Center, Bethesda, MD	Drafting/revision of the article for content, including medical writing for content, and analysis or interpretation of data.

## Appendix (continued)

Name	Location	Contribution
<b>Jason Hawley, MD</b>	Department of Neurology, Walter Reed National Military Medical Center, Bethesda, MD	Drafting/revision of the article for content, including medical writing for content; major role in the acquisition of data; and analysis or interpretation of data.

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