A Challenging Case of Creutzfeldt-Jakob Disease Presenting as Stroke

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ABSTRACT

Introduction: Early recognition of Creutzfeldt-Jakob disease relies on awareness of its clinical variability, particularly in patients with complex medical comorbidities.

Case Presentation: A 66-year-old woman presented with generalized weakness, tremor, double vision, and slurred speech. Initial imaging and laboratory studies were unremarkable, except for subtle magnetic resonance imaging findings suggestive of encephalitis. Despite treatment with methylprednisolone, her condition worsened. Repeat magnetic resonance imaging raised suspicion for Creutzfeldt-Jakob disease, which was confirmed by cerebrospinal fluid real-time quaking-induced conversion positivity and elevated total tau protein. She succumbed to the disease within a month.

Discussion: Creutzfeldt-Jakob disease is a rare, rapidly progressive prion disease that is often misdiagnosed due to nonspecific early symptoms. Extensive imaging and laboratory investigations may delay diagnosis, as seen in this case.

Conclusions: This case highlights the diagnostic challenges and rapid progression of Creutzfeldt-Jakob disease, emphasizing the need for early recognition and standardized intervention to improve patient care.

INTRODUCTION

Prion diseases are fatal, transmissible brain disorders that affect mammals and currently have no effective treatments.[1] These conditions are caused by an unusual mechanism in which the host's normal prion protein misfolds and aggregates into infectious structures known as prions, leading to progressive brain damage. This process, which can remain asymptomatic for years, is believed to underlie the most common human prion disorder, sporadic Creutzfeldt-Jakob disease (CJD).[2] CJD is clinically marked by rapidly worsening cognitive impairment and progression to akinetic mutinism, with pathologic features that include spongiform degeneration of the gray matter and accumulation of misfolded prion protein.[3] In humans, prion diseases are exceptionally rare, with an annual mortality rate estimated at 1 to 2 cases per million persons.[4] They can be categorized into 3 forms: sporadic, infection-acquired, and familial. Ongoing studies linking neurological symptoms to pathological findings, especially in atypical cases, are essential to improving our understanding of CJD pathogenesis.

CASE PRESENTATION

A 66-year-old woman presented to the emergency department (ED) with generalized weakness, tremor, diplopia, and slurred speech. Her medical history included multiple transient ischemic attacks (TIAs) in 2018 and 2023, hyperlipidemia, metabolic syndrome, anemia, benign paroxysmal positional vertigo, fibromyalgia, syringomyelia, degenerative disc disease, and depression. Following the TIA in 2018, she experienced mildly diminished sensation over the left side of her face and extremities, which resolved without permanent deficits. Previous TIAs had not resulted in lasting neurological symptoms.

Two months before this presentation, the patient had developed bilateral neuropathy in her hands and feet, which progressed proximally to her shoulders and buttocks. She also reported gait abnormalities characterized by a high-stepping pattern with intermittent crossing of the feet over the midline, as well as a slight right facial droop and increasing difficulty with balance and ambulation.

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On initial examination, she demonstrated abnormal finger-to-nose testing on the right, diminished right upper extremity strength, and slowed speech with intermittent stuttering. There was no resting tremor or distal sensory loss. Given concern for stroke, Neurology was consulted. Her National Institutes of Health Stroke Scale (NIHSS) score was 1 upon arrival and 0 during observation. Vital signs and the rest of the physical examination were stable. Initial workup, including complete blood cell count (CBC), basic metabolic panel (BMP), computed tomography (CT) of the head, and CT angiography (CTA) of the head and neck, was unremarkable. An electroencephalogram (EEG) revealed prominent slowing in the left cerebral hemisphere, prompting further investigation. Magnetic resonance imaging (MRI) of the brain showed mild signal changes in the right occipital lobe, left basal ganglia, and cingulate gyri, findings considered more suggestive of uncomplicated encephalitis or recent seizure activity rather than ischemia or prion disease (Figure 1). Given concern for an autoimmune etiology, the patient was started on a 5-day course of high-dose intravenous methylprednisolone.

Figure 1. Initial Magnetic Resonance Imaging Demonstrating Nonspecific and Subtle Abnormalities in the Right Occipital Lobe, Left Basal Ganglia and Cingulate Gyri

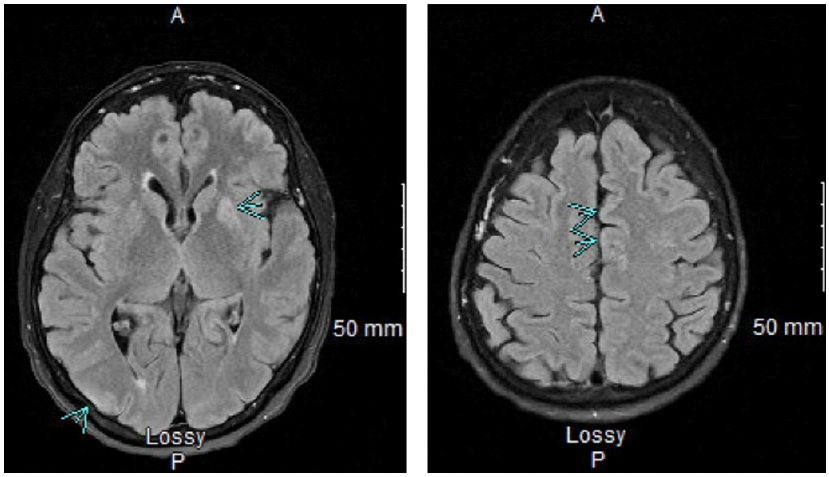
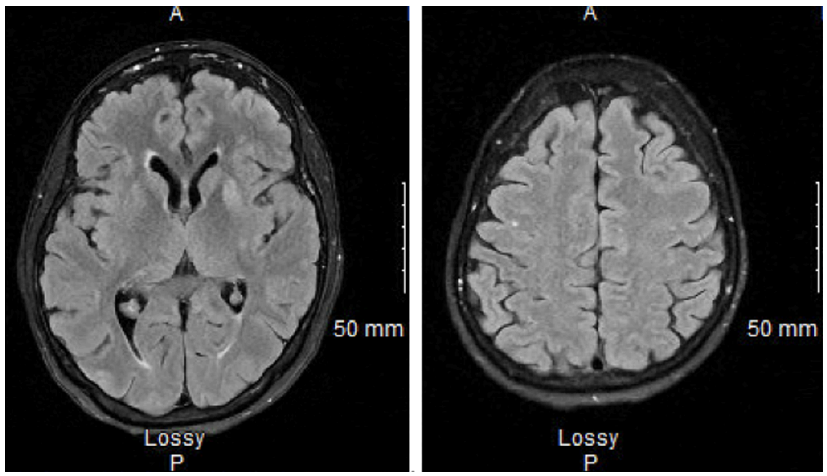


Figure 2. Repeat Magnetic Resonance Imaging Obtained Four Weeks Later Showing Progressive Cortical and Basal Ganglia Signal Abnormalities



Approximately 4 weeks later, her condition worsened despite treatment. She developed increasing ataxia, difficulty ambulating, and worsening balance issues. A repeat MRI demonstrated progressive signal abnormalities (Figure 2). Additional testing, including lumbar puncture, serum autoimmune/paraneoplastic panel, and cerebrospinal fluid (CSF) immunoglobulin G (IgG), returned unremarkable results. Due to the worsening clinical and radiological findings, suspicion for CJD increased, and further CSF testing for prion disease markers was ordered. At this point, the patient and her family elected to return home while awaiting results.

Subsequent CSF analysis revealed negative results for movement disorder markers; however, the real-time quaking-induced conversion (RT-QuIC) test was positive for prion disease, with a markedly elevated total tau protein level of 6422 pg/mL. These findings correspond to a greater than 98% likelihood of CJD. During a follow-up telemedicine visit 2 days after receipt of the tau protein results, the patient exhibited severe, rapidly progressive dementia, global ataxia, titubation of the head, and vocal tremor. Her condition continued to deteriorate, and she died 1 month after her initial ED presentation. The clinical presentation and diagnostic findings were consistent with a definitive diagnosis of sporadic CJD.

DISCUSSION

Creutzfeldt-Jakob disease (CJD) is a rare and uniformly fatal neurodegenerative disorder caused by prion proteins and characterized by rapid neurological decline. Early symptoms are often nonspecific or mimic other neurological conditions, frequently leading to misdiagnosis and delays in recognition. This report describes a case of sporadic CJD in a patient who initially presented with nonspecific, stroke-like neurological symptoms—including generalized weakness, tremor, diplopia, and slurred speech—that obscured the diagnosis and postponed appropriate management. This case

highlights the diagnostic challenges posed by atypical presentations when classical symptoms and imaging findings are absent and underscores the importance of early recognition of prion diseases for appropriate management.

This case demonstrates that CJD can present initially with features mimicking a cerebrovascular event, even though most patients present with ataxia and myoclonus, observed in approximately 90% of cases.[5] A review of the literature reveals only a limited number of reports describing CJD with this presentation (Table), emphasizing the importance of recognizing clinical presentations.

Table. Additional Case Reports Demonstrating Atypical Presentations Leading to Diagnostic Delays

Author Year	Patient Age	Presentation	MRI Findings	Diagnostic Modality
Kwon GT, et al[11] 2019	70	Rapid cognitive decline, aphasia, ataxia	Cortical ribboning on DWI without cerebral atrophy	CSF 14-3-3 protein; postmortem brain autopsy confirmed sCJD
Prodi, et al[12] 2020	59	Anomia, dyscalculia	Cortical diffuse restriction	RT-QuIC
Huang, et al[13] 2024	54	Severe and violent agitation	Restricted diffusion	14-3-3 and RT-QuIC; postmortem autopsy and Western blot

Abbreviations: MRI, magnetic resonance imaging; DWI, diffusion-weighted imaging; CSF, cerebrospinal fluid; sCJD, sporadic Creutzfeldt-Jakob disease; RT-QuIC, real-time quaking-induced conversion.

MRI remains the gold standard for in vivo diagnosis of CJD, with characteristic hyperintense lesions on diffusion-weighted imaging (DWI) and fluid-attenuated inversion recovery (FLAIR) sequences, primarily affecting the corpus callosum, caudate nucleus, and superior parietal lobe.[6] However, this patient's initial MRI demonstrated only subtle and nonspecific alterations, none of which were diagnostic for CJD. Initial MRI findings may be subtle or absent; normal imaging does not exclude CJD. This underscores the need for clinical vigilance despite inconclusive imaging.

The diagnostic delay in this case series raises important considerations regarding current standards of care when CJD is included in the differential diagnosis. Early suspicion may prompt more aggressive diagnostic approaches, including CSF analysis. RT-QuIC, the most specific and sensitive test for prion disease, was positive in this case and, together with markedly elevated total tau protein levels, confirmed the diagnosis. RT-QuIC and other CSF biomarkers, including 14-3-3 protein and neurofilament light chain, are critical tools in cases where imaging findings are inconclusive.[7]

The clinical course of CJD is invariably rapid and fatal, with a median survival of 4 to 6 months after symptom onset.[8] In this case, the patient experienced rapid deterioration, progressing to severe dementia with global ataxia and titubation within weeks and ultimately dying 1 month after presentation. This course underscores the aggressive nature of prion diseases and the importance of timely diagnosis to support patient and family counseling and initiate palliative care. Palliative management focuses on symptom relief and quality of life. For example, myoclonus, a common symptom in CJD, can be managed with clonazepam or valproic acid.[9] Anxiety, agitation, and insomnia are common and may be managed with benzodiazepines or antipsychotic agents, depending on patient tolerance and symptoms.[10] Pain control is also essential and may require opioids, particularly in advanced stages of the disease. Nonpharmacological interventions, including physical therapy and assistive devices, may help reduce fall risk and maintain mobility early in the disease course.

A high index of suspicion should be maintained for any patient with rapidly progressive neurological decline. Our literature review identified several cases of CJD presenting with atypical symptoms, including manifesting resembling psychiatric illness (Table). These reports highlight the broad clinical spectrum of CJD and the potential for atypical symptoms to delay diagnosis and appropriate management.[11,12] Further research is needed to support earlier diagnosis and improved care for this fatal condition.

Although no interventions currently slow the progression of CJD, ongoing investigations into neuroprotective agents and antiprion therapies remain promising. Until effective treatments become available, early recognition and palliative care remain the cornerstone of CJD management. This report aims to raise awareness of an uncommon presentation of CJD and emphasizes the need for clinicians to consider prion disease in patients with rapidly progressive neurological or psychiatric symptoms.

CONCLUSIONS

This case emphasizes the diagnostic challenges associated with atypical presentations of CJD, particularly when symptoms mimic common conditions such as stroke. Early and accurate diagnosis is critical not only to facilitate appropriate patient and family counseling but also to avoid unnecessary and potentially harmful interventions. The diagnostic delay observed in this case highlights the importance of maintaining a high index of suspicion for CJD in patients with rapidly progressive neurological symptoms, even when initial imaging findings are nonspecific. Timely recognition allows patients and families to avoid prolonged diagnostic uncertainty and focus on palliative measures during the limited disease course.

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