Thinking Beyond Common Diagnoses: A Case Report of Creutzfeldt-Jakob Disease

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ABSTRACT

Introduction: Prion diseases are rare neurodegenerative disorders characterized by abnormal folding of prion proteins in the brain. Creutzfeldt-Jakob disease (CJD), is the most common prion disease in humans, typically presenting with neuropsychiatric manifestations, including dementia, behavioral abnormalities, and motor dysfunction. Diagnosis can be challenging because its nonspecific presentation overlaps with numerous other potential causes.

Case Presentation: A 60-year-old man presented with altered mental status and progressive neurologic decline. After an extensive diagnostic evaluation, he was diagnosed with probably CJD. Management was primarily supportive and focused on symptom relief and patient comfort. The patient died shortly after the diagnosis was confirmed.

Conclusions: This case highlights the challenges of diagnosing CJD and underscores the value of System 1 and System 2 reasoning in navigating a broad differential diagnosis in patients presenting with altered mental status and rapidly progressive neurologic symptoms.

INTRODUCTION

Prions are small pathogenic agents that induce abnormal folding of prion proteins naturally found in the brain. Creutzfeldt-Jakob disease (CJD) is the most common human prion disease. The average age at symptom onset is 62 years, following a long incubation period.[1] There is no sex predilection,[2] and 85% to 98% of cases occur sporadically, without known risk factors such as environmental exposure. The remaining 5% to 15% are genetically linked, and iatrogenic and variant CJD together comprise less than 1% of cases.[3]

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Early symptoms of CJD include impairments in attention, concentration, memory, and judgment. These neuropsychiatric findings rapidly progress to dementia, behavioral abnormalities, and aphasia and apraxia, reflecting deficits in higher cortical function.[4,5] Hypersomnia is frequently observed.[6] Mood disturbances such as depression and apathy are common, while anxiety, euphoria, and affective lability are less common.[7] Psychotic symptoms such as hallucinations also have been reported. On examination, signs of corticospinal tract involvement (eg, hyperreflexia, positive Babinski reflex, muscle spasticity) are present in 40% to 80% of cases. Extrapyramidal signs (eg, hypokinesia, bradykinesia, dystonia, muscle rigidity) are also seen.

Because CJD invariably progresses to death, with a median disease duration of 6 months, death records serve as a reliable measure of incidence. From 2003 through 2015, the age-adjusted mean annual incidence for CJD in the United States was 1.2 cases per million.[2]

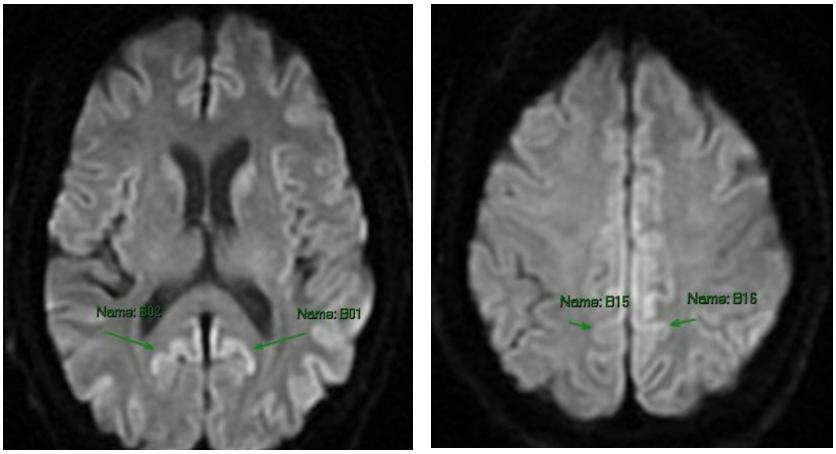
Management of CJD centers on supportive care to maximize patient comfort throughout disease progression.[8] Arriving at the diagnosis can be challenging, however, because of low clinical suspicion when a patient presents with altered mental status, which can arise from neurologic, infectious, systemic, or metabolic etiologies. The emotional and psychomotor disturbances that often accompany altered mental status can further complicate the diagnostic picture, especially in patients with a psychiatric history.[9]

This report describes the case of a middle-aged man with altered mental status and expressive aphasia who tested positive for CJD after the common, and even uncommon, diagnoses had been ruled out.

CASE PRESENTATION

The patient was a relatively healthy 60-year-old man with a past medical history of major depressive disorder with compulsive behaviors controlled with bupropion, attention-deficit/hyperactivity disorder controlled with Adderall, obstructive sleep apnea, and alcohol use disorder in sustained remission for 30 years. His past surgical history was notable only for a cadaver bone graft 20 years prior following failed pin stabilization of a left foot fracture.

Figure. Magnetic Resonance Imaging Evidence of Cortical Ribboning



The patient was transferred to our facility for neurologic evaluation of worsening confusion, visual and auditory hallucinations, and gait instability over a 2-month period. Before transfer, he developed progressive expressive aphasia without evidence of acute stroke or other overt intracranial abnormalities on imaging.

Because of his inability to participate in an interview, the history was obtained primarily from his wife. Three months before admission, he developed ear pain and was diagnosed with bilateral acute otitis media. He was treated with antibiotics. Notably, he also reported headaches accompanying the ear pain, followed by the aforementioned neuropsychiatric symptoms in subsequent months. He exhibited paranoia related to his hallucinations.

The patient lived in a rural environment. He and his wife had recently become more active outdoors, often hiking in wooded areas near their home. For several years, he had been putting out food for a feral cat on his property but had no direct contact with the animal. He worked as a truck driver. He consumed a well-balanced diet without exposure to game or undercooked meats and typically packed meals from home for long truck routes. Despite heavy alcohol consumption in his 20s and early 30s, he had limited his drinking to holidays and special occasions for the past 3 decades.

Examination on the day of admission demonstrated bilateral upper- and lower-extremity hyperreflexia without clonus, as well as waxy flexibility, catalepsy, and repetitive handwaving and finger-tapping motions reminiscent of catatonia. Pupils were 3 mm and reactive without nystagmus. Speech comprehension appeared intact; he was able to provide 1- or 2-word responses to questions, perform simple calculations such as "2+2," and follow basic commands.

Based on his initial presentation, the differential diagnosis notably included indolent (eg, parasitic or fungal) meningitis, autoimmune (including Hashimoto) encephalitis, metabolic encephalitis, Wernicke encephalopathy, rapidly progressive dementia, catatonic state secondary to psychopharmacotherapy, and seizure disorder. High-dose thiamine and folate were initiated out of concern for Wernicke encephalopathy. Continuous electroencephalogram (EEG) was ordered to monitor for abnormal brain wave activity. A lumbar puncture was planned to evaluate for these potential pathologies.

Initial laboratory results were unrevealing: ethanol level 0mg/dL; negative results for COVID-19, influenza A and B, and respiratory syncytial virus; unremarkable complete blood cell count (CBC), with peripheral blood smear showing only mild absolute monocytosis; international normalized ratio of 1.0; urine drug screen positive for amphetamines consistent with prescribed medications; unremarkable comprehensive metabolic panel; ammonia level within normal limits; and vitamin B12 and folate levels within normal limits. Methylmalonic acid (MMA) levels were normal. Syphilis, HIV, and hepatitis C testing results were negative.

Subsequently, the patient's tick-borne panel, including testing for *Babesia*, *Ehrlichia*, *Anaplasma*, and Lyme disease, returned negative results. Testing for *Coccidioides*, *Histoplasma*, *Blastomyces*, and *Bartonella* was also negative. Antinuclear antibody, antineutrophil cytoplasmic antibody, myeloperoxidase, and proteinase 3 testing results were unremarkable.

Thyroid-stimulating hormone, thyroid peroxidase antibody, and thyroglobulin antibody levels were within normal limits. Paraneoplastic and autoimmune encephalopathy panels were negative for CV2 antibody; neuronal nuclear antibodies to Hu, Ri, Yo, and Tr antigens; amphiphysin antibody; contactin-associated protein 2 (CASPR2), leucine-rich glioma-inactivated protein 1 (LGI1) antibody, and γ-aminobutyric acid receptor type B (GABA-B) antibody. Interestingly, the patient's JC virus antibody test was positive despite no history of immunocompromise.

Catatonic features became more prominent during the first 24 hours after admission. During that time, he was verbally unresponsive but appeared to understand conversations, signaling "yes" or "no" with finger movements or blinking. As he became

Table. Patient History Timeline

Prior to Admission
- History of heavy alcohol consumption in 20s-30s and cadaver bone graft for left foot fracture repair

1 year
- Patient moves from Oregon to rural Wisconsin

3 months
- Patient complains of ear pain with headaches ➔ diagnosed with bilateral acute otitis media, treated with antibiotics

2 months
- Patient experiences progressively worsening cognitive changes ➔ begins using walker due to gait instability

Day of Admission (Hospital Day 0)

Events
- Patient transferred for neurology evaluation; experiencing AMS and expressive aphasia; concern for parasite passed in urine

Exam findings
- Bilateral upper and lower extremity hyperreflexia without clonus; waxy flexibility, catalepsy, stupor, stereotypy, minimal speech; receptive language intact, able to follow simple commands; eye movements within normal limits

Imaging
- No acute findings on noncontrast CT head, CTA head/neck, MRI brain with and without contrast

Hospital Day 1

Laboratory results
- Ethanol level: 0; UDS: unremarkable; COVID-19, influenza A/B, RSV: neg; INR: 1.0; parasite exam: neg; syphilis: neg; HIV 1/2: neg; ammonia, CBC, CMP, B12, folate, MMA: within normal limits

Hospital Days 2–5

Events
- LP performed; patient initiated on Solu-Medrol 1 g daily x3 doses, valproate 500 daily x 3

Imaging
- Repeat MRI brain: restricted diffusion in cortex of occipital and parietal lobes bilaterally; patchy and ill-defined signal alteration in subcortical and deep white matter bilaterally; not significantly changed from prior MRI.

Laboratory results
- CSF chemistry: incl protein; CSF acid-fast bacilli, gram stain/culture, fungal culture: neg; TSH/FT4, TPO Ab, anti-thyroglobulin Ab: unremarkable; ANA titer: within normal limits; CSF meningitis panel:[a] neg

Hospital Days 6–7

Events
- AMS-induced oropharyngeal dysphasia ➔ diet status changed to nothing by mouth, first NG tube attempt; IVIG initiated for possible autoimmune encephalitis

Laboratory results
- *Blastomyces*, *Histoplasma*, *Coccidioides*: neg; *Bartonella*: neg; West Nile virus: neg; Lyme: neg; *Babesia*, *Ehrlichia*, *Anaplasma*: neg; ANCA, MPO/PR3 Ab, CASPR2 Ab, LGI1 Ab, GABA-B Ab: neg

Imaging
- CT chest/abd/pelvis: neg for occult malignancy

Hospital Day 9

Laboratory results
- CSF JC virus: pos

Hospital Day 12–13

Events
- Second NG tube attempt; PICC line placed

Laboratory results
- CV2 Ab, neuronal nuclear Abs, amphiphysin Ab: neg

Hospital Day 14

Events
- Third NG tube failure ➔ TPN initiated; concern for developing dysautonomia consistent with advancing prion disease

Hospital Day 16

Laboratory results
- CSF 14-3-3: pos; CSF RT-QuIC: pos; CSF T-tau protein: >20 000

Day of Discharge (Hospital Day 17)

Events
- Patient discharged with plan to transition to hospice ➔ succumbs to CJD the following day

[a]CSF meningitis panel included testing for *Escherichia coli*, *Haemophilus influenzae*, *Listeria monocytogenes*, *Neisseria meningitidis, Streptococcus agalactiae, Streptococcus pneumoniae*, cytomegalovirus, enterovirus, herpes simplex virus 1 and 2, human herpesvirus 6, human parechovirus, varicella-zoster virus, and *Cryptococcus neoformans*.

Abbreviations: Ab, antibody; AMS, altered mental status; ANA, antinuclear antibody; ANCA, antineutrophil cytoplasmic antibody; CBC, complete blood count; CASPR2, contactin-associated protein 2; CJD, Creutzfeldt-Jakob disease; CMP, comprehensive metabolic panel; CSF, cerebrospinal fluid; CT, computed tomography; CTA, computed tomography angiography; FT4, free thyroxine; GABA-B, γ-aminobutyric acid receptor type B; INR, international normalized ratio; IVIG, intravenous immune globulin; LGI1, leucine-rich glioma-inactivated protein 1; LP, lumbar puncture; MMA, methylmalonic acid; MPO, myeloperoxidase; MRI, magnetic resonance imaging; neg, negative; NG, nasogastric; PICC, peripherally inserted central catheter; pos, positive; PR3, proteinase 3; RSV, respiratory syncytial virus; RT-QuIC, real-time quaking-induced conversion; TPN, total parenteral nutrition; TPO, thyroid peroxidase; TSH, thyroid-stimulating hormone; UDS, urine drug screen.

increasingly lethargic, EEG demonstrated triphasic waves in the 1.0- to 1.5-Hz range within the left hemisphere. Repeat magnetic resonance imaging (MRI) of the brain with and without contrast demonstrated cortical ribboning that had not been observed on outside imaging studies (Figures 1 and 2). Lumbar puncture was completed without clear evidence of infection, with negative bacterial and viral meningitis panels (see Table for pathogens tested). Cerebrospinal fluid (CSF) analysis demonstrated only mild abnormalities in glucose (74 mg/dL; reference range, 50-70 mg/dL) and protein (82 mg/dL; reference range, 15-45 mg/dL), findings consistent with an encephalitic process.

The official EEG interpretation reported "generalized background abnormalities indicative of diffuse encephalopathy, periodic discharges diffuse with left hemispheric predominance typically seen in the setting of acute neuronal injury indicative of cortical excitability and can also be noted in chronic focal epilepsy."

The official repeat MRI interpretation reported "mildly restricted diffusion in the cortex of the occipital and parietal lobes bilaterally, which is greatest medially. Primary differential considerations include encephalitis, status epilepticus, Wernicke's encephalopathy, and metabolic encephalopathy. Hypoxic-ischemic encephalopathy is relatively less likely in this clinical context… patchy and ill-defined signal alteration in the subcor-

tical and deep white matter bilaterally not significantly changed, with radiological interpretation suggesting small-vessel disease chronic in nature, migraine headaches, and nonspecific gliosis."

In response to the severity of the patient's neurologic findings, empiric treatment was with methylprednisolone (Solu-Medrol) 1 g daily for 3 days and valproate (Depakote) 500 mg 3 times daily was initiated. Prion testing was ordered in light of EEG and MRI abnormalities and nondiagnostic lumbar puncture results.

By hospital day 6, the patient was deemed unable to safely swallow following speech-language pathology evaluation. He repeatedly self-dislodged multiple nasogastric (NG) tubes, and, because he did not improve with steroid and valproate therapy, so intravenous immune globulin was initiated while awaiting prion test results.

On hospital day 10, an abdominal x-ray obtained because of abdominal distension suggested moderate ileus formation. An NG tube was placed again for suction, and the patient was transitioned to total parenteral nutrition. Unstable blood pressure, heart rate, and respiratory rate raised concern of dysautonomia.

On hospital day 15, he developed Cheyne-Stokes breathing patterns and intermittent episodes of various arrhythmias on telemetry.

On hospital day 16, CSF prion test results returned positive 14-3-3 protein and real-time quaking-induced conversion (RT-QuIC) assay results, with CSF total tau protein >20 000pg/mL (reference range, 0-1149 pg/mL), indicating probable CJD. At his wife's request, he was transitioned to hospice care and died within 72 hours of the diagnosis.

DISCUSSION

Per the Centers for Disease Control and Prevention diagnostic criteria,[10] definite sporadic CJD is diagnosed by standard neuropathological techniques, immunocytochemical methods, Western blot confirmation of protease-resistant prion protein (PrP), or identification of scrapie-associated fibrils. Probable sporadic CJD is diagnosed by (1) the presence of a neuropsychiatric disorder plus a positive RT-QuIC assay in CSF or other tissues, or (2) rapidly progressive dementia plus at least 2 of following clinical features: myoclonus, visual or cerebellar signs, pyramidal or extrapyramidal signs, or akinetic mutism, together with at least 1 supportive test result, including periodic sharp-wave complexes on EEG, a positive CSF 14-3-3 assay in patients with disease duration of less than 2 years, or characteristic MRI abnormalities involving the caudette nucleus, putamen, or at least 2 cortical regions (temporal, parietal, or occipital) on diffusion-weighted imaging or fluid-attenuated inversion recovery sequences.

Our patient met criteria for probable sporadic CJD based on his rapidly progressive dementia, positive CSF RT-QuIC result, and positive CSF 14-3-3 assay. At the start of his diagnostic journey, however, he presented as a patient with altered mental status and a focal neurologic deficit, a common presentation in the hospital setting. The evolution of his presentation illustrates how Systems 1 and System 2 reasoning can be used to prioritize high-mortality and high-morbidity conditions before proceeding through the differential diagnosis in a stepwise manner based on clinical likelihood.

System 1 thinking describes fast, intuitive, and reflexive decision-making.[11] In medicine, it often manifests as pattern recognition in the acute setting to quickly identify conditions requiring urgent or emergent intervention and thereby prevent substantial morbidity or death. In our patient, System 1 thinking guided our initial evaluation for stroke and other acute intracranial abnormalities using noncontrast computed tomography (CT) of the head, MRI of the brain with and without contrast, and CT angiography of the head and neck. It also informed the initial laboratory and bedside evaluation of rapidly reversible or time-sensitive causes of altered mental status, including electrolyte abnormalities, substance intoxication or withdrawal, Wernicke encephalopathy, and hypoglycemia. Comprehensive metabolic panel, complete blood cell count with differential, ethanol level, urine drug screening and point-of-care glucose testing were obtained as part of this evaluation. Following exclusion of vitamin B12 deficiency, hyperammonemia, tick-borne disease, and sexually transmitted infections through normal B12 and MMA levels, normal ammonia level and arterial blood gas results, negative Lyme and tick-borne disease testing, and negative syphilis and HIV serologic results, the differential diagnosis expanded to include less common conditions. This shift marked a transition from System 1 thinking to the slower, more deliberate, and methodical process of System 2 thinking.

System 2 reasoning built upon the initial impressions generated by System 1 thinking as patient's symptoms evolved. Although features of catatonia were observed early in the hospitalization, the progression from aphasia to an increasingly comatose state over a matter of days made a primary psychiatric etiology less likely. Similarly, despite his rural residence and propensity for the outdoors, CSF studies demonstrating an isolated protein elevation diminished concern for fungal or parasitic meningitis. Instead, these CSF findings, together with the formal EEG and repeat MRI interpretations, shifted the leading diagnostic considerations toward encephalopathy and focal seizure activity.

In hindsight, the triphasic waves identified on EEG prompt the question of why this characteristic finding of CJD[1,3,10] did not immediately raise suspicion for the diagnosis. One possible explanation is anchoring bias. Because the EEG was obtained primarily to evaluate altered mental status rather than a suspected prion disease, the interpretation may have been influenced by the more common causes of altered mental status encountered in the hospital setting. Similarly, the MRI report did not emphasize the hyperintense corticol signal abnormalities along the gyri, a characteristic feature of CJD known as the cortical ribbon sign.[3] This observation may likewise reflect anchoring bias, whereby interpretation remained focused on more common diagnostic considerations.

This case highlights the role of dual-process reasoning and potential cognitive biases that can occur in a complex diagnostic scenario. It also illustrates the significance of clinical context in diagnostic interpretation. Diagnostic studies are only as informative as the context in which they are interpreted. Ultimately, neurologic consultation and reconsideration of the patient's evolving symptoms were instrumental in establishing the diagnosis of probable sporadic CJD. Although earlier recognition would not have altered management or outcome, more detailed communication of the clinical concern to radiology (eg, altered mental status with concern of meningitis as well as irregular EEG containing triphasic spikes) may have facilitated earlier recognition of imaging and EEG findings suggestive of CJD.

Of note, our patient underwent cadaveric bone grafting during ankle reconstruction 20 years before his CJD diagnosis. Cadaveric dura mater grafts have been implicated in cases of iatrogenic CJD.[1,12] However, given the nature of the patient's prior procedure and the rarity of iatrogenic CJD, a sporadic etiology is considerably more likely, although the absence of definitive confirmatory testing precludes complete exclusion of an iatrogenic origin.

Another noteworthy aspect of this case was the diagnosis of acute otitis media 3 months before hospitalization. Whether this represented an unrelated condition or an early manifestation of the patient's evolving neurologic disease remains uncertain. Given the nonspecific nature of early CJD symptoms and the retrospective nature of this observation, any association should be interpreted cautiously.

CONCLUSIONS

Prion diseases, particularly Creutzfeldt-Jakob disease (CJD), are fatal neurodegenerative disorders that pose complex diagnostic challenges. This case of a 60-year-old man highlights the importance of maintaining a broad differential diagnosis and pursuing comprehensive evaluation in patients with rapidly progressive neurologic decline. The rapid progression and uniformly fatal nature of CJD underscore the need for heightened clinical awareness, timely recognition, and appropriate supportive care in managing this rare condition.

This case also highlights the potential influence of cognitive bias on diagnostic decision-making and emphasizes the value of careful clinical contextualization when interpreting diagnostic studies. Although the patient's prior history of cadaveric bone grafting raises a theoretical question regarding disease transmission, the available evidence supports a diagnosis of probable sporadic CJD. Further investigation into rare transmissible causes of prion disease remains warranted as understanding of these disorders continues to evolve.

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REFERENCES

1. Haywood AM. Transmissible spongiform encephalopathies. *N Engl J Med*. 1997;337(25):1821-1828. doi:10.1056/NEJM199712183372508

2. Maddox RA, Person MK, Blevins JE, et al. Prion disease incidence in the United States: 2003-2015. *Neurology*. 2020;94(2):e153-e157. doi:10.1212/WNL.0000000000008680

3. Belay ED, Holman RC, Schonberger LB. Creutzfeldt-Jakob disease surveillance and diagnosis. *Clin Infect Dis*. 2005;41(6):834-836. doi:10.1086/432726

4. Krasnianski A, Bohling GT, Heinemann U, et al. Neuropsychological symptoms in sporadic Creutzfeldt-Jakob disease patients in Germany. *J Alzheimers Dis*. 2017;59(1):329-337. doi:10.3233/JAD-161129

5. Rabinovici GD, Wang PN, Levin J, et al. First symptom in sporadic Creutzfeldt-Jakob disease. *Neurology*. 2006;66(2):286-287. doi:10.1212/01.wnl.0000196440.00297.67

6. Landolt HP, Glatzel M, Blättler T, et al. Sleep-wake disturbances in sporadic Creutzfeldt-Jakob disease. *Neurology*. 2006;66(9):1418-1424. doi:10.1212/01.wnl.0000210445.16135.56

7. Krasnianski A, Bohling GT, Harden M, Zerr I. Psychiatric symptoms in patients with sporadic Creutzfeldt-Jakob disease in Germany. *J Clin Psychiatry*. 2015;76(9):1209-1215. doi:10.4088/JCP.13m08915

8. Appleby BS, Yobs DR. Symptomatic treatment, care, and support of CJD patients. *Handb Clin Neurol.* 2018;153:399-408. doi:10.1016/B978-0-444-63945-5.00021-0

9. Veauthier B, Hornecker JR, Thrasher T. Recent-onset altered mental status: evaluation and management. *Am Fam Physician*. 2021;104(5):461-470.

10. Clinical overview of Creutzfeldt-Jakob disease. Centers for Disease Control and Prevention. Accessed January 2025. https://www.cdc.gov/creutzfeldt-jakob/hcp/clinical-overview/diagnosis.html

11. Kahneman, D. *Thinking, Fast and Slow.* 1st ed. Farrar, Straus and Giroux; 2011.

12. Centers for Disease Control (CDC). Rapidly progressive dementia in a patient who received a cadaveric dura mater graft. *MMWR Morb Mortal Wkly Rep*. 1987;36(4):49-55.

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