Case Report

BIOMEDICAL Journal of Scientific & Technical Research

ISSN: 2574 -1241

DOI: 10.26717/BJSTR.2024.58.009139

A Rapidly Fatal Case of Creutzfeldt-Jakob Disease

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ARTICLE INFO

Received: August 08, 2024

Published: August 22, 2024

Citation: T Patrick Jensen, Ashley Sentell and Olivia King. A Rapidly Fatal Case of Creutzfeldt-Jakob Disease. Biomed J Sci & Tech Res 58(2)-2024. BJSTR. MS.ID.009139.

ABSTRACT

This case details the events that occurred following an elderly woman who originally presented with altered mental status. She was admitted with acute metabolic encephalopathy secondary to a urinary tract infection and treated with antibiotics, but her mental status continued to deteriorate. Over the course of the next month, she experienced rapid neuropsychiatric decline, eventually resulting in death within 35 days. Through the collaborative efforts of the psychiatry and neurology services, the patient received an in-depth workup and accurate diagnosis. Based on her clinical picture in addition to neuroimaging results and cerebrospinal fluid testing, the patient was diagnosed with Creutzfeldt-Jakob disease. This case provides an opportunity to gain insight into an extremely rare but universally fatal prion disease. It is essential that medical professionals be aware of possible presenting symptoms so that a high level of suspicion is maintained. Although there is no current cure for this devastating disease, it is imperative that a swift diagnosis be reached in order to provide adequate supportive treatment, psychiatric care, and social services in the patient's remaining days.

Case Report

Initial Visit

A 65-year-old Caucasian female with a past medical history of diabetes, neuropathy, hypertension, hyperlipidemia, depression, paroxysmal atrial fibrillation, COPD and OSA presented to the emergency department with confusion and multiple recent falls. She had difficulty ambulating, dysphagia and word-finding difficulty. She also reported feeling depressed. In the emergency department she was noted to be"awake, alert, intermittently confused, and having difficulty answering questions." Her hemodynamics were stable. Laboratory evaluation was remarkable for the following: WBC 7300, hemoglobin 13.2, potassium 3.2, and glucose 122. Her urinalysis was consistent with urinary tract infection revealing positive leukocyte esterase and

greater than 50 wbc/hpf. CT of the head showed no evidence of acute intracranial hemorrhage and revealed age typical findings of cerebral volume loss and chronic microvascular ischemia. MRI was deemed not possible due to cardiac pacemaker. Initial physical exam demonstrated the following:

Physical Exam in the Emergency Department

Vital Signs: T: 36.8°C (Oral) HR: 72 (Peripheral) RR: 18 BP: 162/71 SpO2: 96%

Constitutional: Mild apparent distress, well appearing.

HEENT: Pupils are equally round, extraocular movements intact without nystagmus, clear conjunctiva, non-icteric sclera. normocephalic, atraumatic, moist mucous membranes, oropharynx clear without exudates

Neck: Nontender and supple with no nuchal rigidity, no lymphadenopathy, full range of motion.

Resp: Clear to auscultation without wheezes, rhonchi, or rales, normal excursion, no accessory muscle use and no stridor

CV: Regular rate, rhythm, normal S1 and S2. No appreciated murmurs. Strong radial pulses with intact distal perfusion

GI: normal bowel sounds, soft, non-tender, non-distended, no palpable masses, no rebound or guarding

Genitourinary: No costovertebral angle tenderness to palpation.

Lymphatics: No lymphadenopathy

Musculoskeletal: Extremities nontender to palpation and have no gross deformity or redness. No edema. Normal distal neurovascular exam in all extremities

Neurologic: a/o x 3, GCS 15, normal mentation and slight difficulty with speech. Moves all extremities x 4 without motor or sensory deficit. Cranial nerves 2-12 intact. No focal weakness or drift

Psychiatric: Depressed mood and affect, akathisia.

The patient was diagnosed with acute metabolic encephalopathy secondary to UTI, admitted to the hospital under the medical service, and was started on IV ceftriaxone. Over the next few days, her mental status improved with antibiotics and hydration. However, by day 4 of admission, she continued to show intermittent confusion and psychiatry was consulted. On psychiatric exam, she displayed a decreased level of consciousness and appeared very encephalopathic with depression and a blunted affect. It was reported that she has significant word-finding ability and difficulty answering assessment questions. She did admit to having occasional suicidal thoughts. With psychiatry's recommendation, she was transferred to the geriatric psychiatry unit. On day 11 after original admission, she was noted to be declining cognitively. She was disoriented, displaying dysarthria and responding to internal stimuli. The patient was initiated on Cymbalta 30 mg to combat her severe depression and peripheral neuropathy. Collateral information gathered from the patient's son revealed that she had been experiencing a slow cognitive decline over the past six years, but the past three weeks she displayed a rapid decline.

Up until then, she was still driving short distances, dressing, bathing, cooking, and managing her own financial affairs. The patient was accepted to a senior behavioral unit on day 14. At this point, the patient remained confused with dysarthria and expressive aphasia. A CTA, EEG, and repeat CT were ordered. CT Angiogram was unimpressive revealing age-related changes with no arterial occlusions, significant stenosis, or acute intracranial findings. EEG was abnormal without seizure activity, but with diffuse symmetric mild theta delta background, suggesting encephalopathy or drowsy/sedated state. Repeat CT was unremarkable (Figure 1). By day 16, the patient continued to be delirious and required daily IM Zyprexa injections for agitation and confusion. Low dose Risperdal concentrate was initiated. The nursing staff reported frequent outbursts including trying to strike staff and hospitalists daily progress notes showed progressing language disturbances, persistent delirium and disrupted circadian rhythm. Based on the patient's complicated and worsening presentation, neurology was consulted for further evaluation.

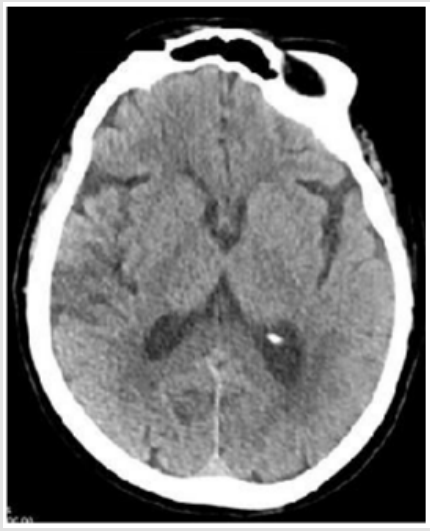

Figure 1: Repeat CT obtained on day 14 of admission revealing mild generalized cerebral volume loss with scattered white matter disease.

Initial neurology evaluation revealed left hemispheric dysfunction with aphasia, right hemiparesis, and right extensor plantar response. Upper extremity myoclonic jerks were also noted. It was documented on exam that she demonstrated difficulty tracking to the right, the inability to blink to threat of her peripheral vision, and no purposeful movement of her right upper or lower extremity. It was recommended to obtain an MRI after confirming that her pacemaker was MRI compatible. The psychiatry team also ordered a serum autoimmune encephalopathy panel, lumbar puncture, and a repeat EEG. MRI revealed subtle diffusion hyperintensity throughout the left hemispheric cortex which was the greatest within the left temporal lobe and left insula. Hyperintensity was also noted in the caudate and putamen bilaterally with subtle T2/FLAIR hyperintensity in left greater than right basal ganglia. This appearance was highly suggestive of

Creutzfeldt-Jakob disease. (Figure 2) Initial CSF panel displayed mildly increased glucose but was virtually unremarkable. (Table 1) Repeat EEG showed of diffuse polymorphic slow-wave patterns within the theta range of variable amplitude throughout the tracing along with bilateral periodic epileptiform discharges with sharp configuration. These findings, along with clinical and MRI correlation were highly suggestive of CJD.

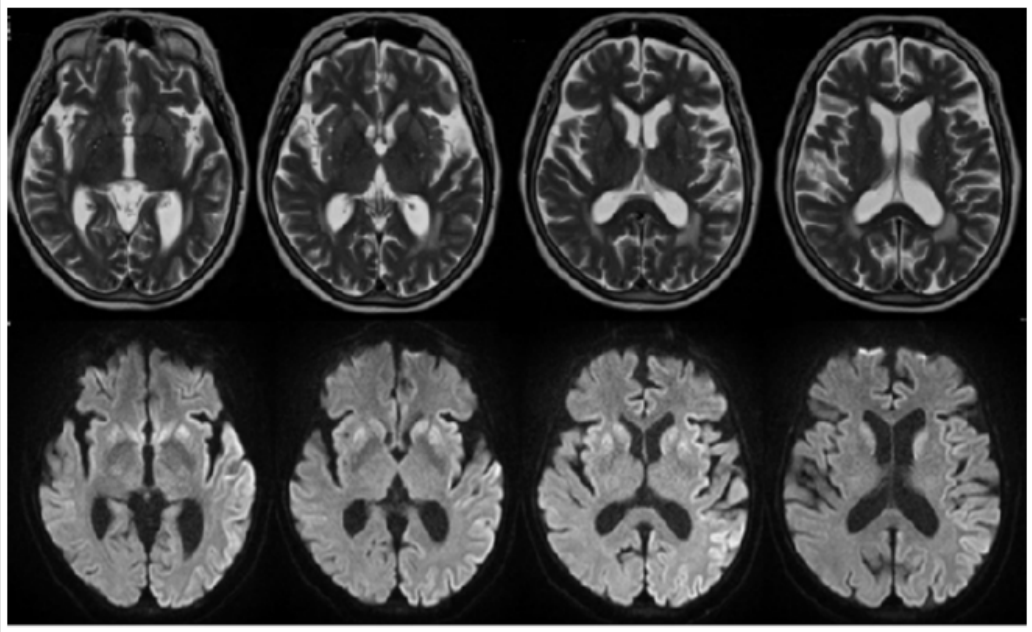

Figure 2: MRI demonstrating hyperintensity of the caudate and putamen and T2/FLAIR hyperintensity with subtle involvement of the basal ganglia.

Table 1: Cerebrospinal fluid analysis obtained from fluoroscopy guided lumbar puncture on day 18.

WBC CSF	0 cells/mcL
RBC CSF	0 cells/mcL
Color CSF	Colorless
Clarity CSF	Clear
Glucose CSF	95 mg/dL
Protein CSF	43.0 mg/dL
IgG Index CSF	0.55
IgG CSF	3 2 mg/dL
Albumin CSF	25.8 mg/dL
IgG/Albumin CSF	0.12
Synthesis Rate CSF	2.41 mg/24hr
IgG Serum	822 mg/dL
Albumin Serum	3800 mg/dL
IgG/Albumin Serum	0.22
Myelin Basic Protein CSF	< 2.0 mcg/L
Haem. Influenza	Not Detected
Lister. monocytogenes	Not Detected
Neis. meningitidies	Not Detected
Strep agalactiae	Not Detected
Strep pneumoniae	Not Detected
Varicella-zoster virus	Not Detected
HSV 1	Not Detected
HSV 2	Not Detected
HPeV	Not Detected
HHV-6	Not Detected
Cytomegalovirus	Not Detected
Enterovirus	Not Detected
Crypto neoform/gatti	Not Detected
E. Coli K1	Not Detected

On day 19, the patient was transferred from the Senior Behavioral Unit to the medical floor due to deterioration in her condition. By day 25, she was intermittently agitated, requiring wrist restraints, and noted to be confused, restless, agitated, and talking incomprehensibly with garbled speech. She was still displaying signs of weakness in her right upper extremity. A high dose steroid trial was initiated while other possible causes continue to be ruled out. Additional CSF studies including a sample sent to The National Prion Disease Pathology Surveillance Center were obtained. As the days continued, her condition continued to quickly deteriorate. She became increasingly lethargic and remained extremely encephalopathic. She opened her eyes with an unfocused gaze, mumbled incoherent phrases and did not respond to any commands. She did withdraw her extremities to noxious stimuli and exhibited a positive glabellar reflex with occasional tremors. The 5-day course of IV Solu-Medrol made no difference in her condition. Over the next several days, the patient remained in bed and opened her eyes only to voice. She did not respond to any questions or make any attempts to communicate. The palliative care team was consulted on day 26. By day 27, the patient was admitted to inpatient hospice. After an extensive workup and efforts made by medical staff, the patient eventually expired on day 35.

Cerebrospinal fluid results from the National Prion Disease Pathology Surveillance Center were returned after her expiration and displayed elevated 14-3-3 and tau proteins as well as positive PrPSc (Table 2).

Table 2: CSF results from the National Prion Disease Pathology Surveillance Center revealing a positive diagnosis of prion disease and Creutzfeldt-Jakob Disease.

Test	Result	Ref. Range
Specimen Condition	Clear	
RT QuIC	Positive	Negative
T-tau protein	>20000 pg/mL	0-1149 pg/mL
14 3 3 GAMMA	122463 AU/mL	0 1999 AU/mL
Likelihood of prion disease	>98%	

Discussion

Prion diseases, also known as spongiform encephalopathies, are a group of rare, rapidly progressing, and fatal diseases caused by the misfolding of proteins. The most widely recognized of these is Creutzfeldt-Jakob disease

(CJD). First described in 1920 by Hans Gerhard Creutzfeldt, it can be divided into three classifications: acquired (kuru, iatrogenic, etc.), sporadic, or familial, with sporadic far and away being the most common. CJD is a result of mutations in the PRNP gene encoding the human prion protein (PrP). It can be divided into six subtypes: MM1, MM2, MV1, MV2, VV1, and VV2, with the categorization being determined by the mutation present on the gene: Met/Met, Met/Val, and Val/Val with type 1 or type 2 being determined by the molecular weight of the unglycosylated gene product [1,2]. The typical presentation of CJD is a rapidly progressing neurological deterioration, classically divided into three stages. The first being changes of psychiatric symptoms, often with visual and memory impairment. The second being impressive cognitive impairment. This phase is also associated with myoclonus and the appearance of Periodic sharp-wave complexes on EEG. Lastly, the third stage presents with akinetic mutism, or the inability to initiate volunteer movement or to produce meaningful words [1]. Although this is the typical presentation of CJD, it is often seen mimicking other neurological insults or pathologies with similar findings, making the diagnosis that much more challenging.

Multiple case reports have documented the prion disease presenting as various pathologies including a stroke with right-sided weakness and language difficulties, autoimmune encephalitis with diffuse cognitive impairment and elevated thyroperoxidase antibodies, expressive aphasia with nonconvulsive status epilepticus, and finally blurred vision progressing to gait disturbances [2-5]. With these frequently documented atypical presentations of CJD, it is important to maintain and high index of suspicion to ensure patients are diagnosed accurately and in a timely manner. The diagnosis of Creutzfeldt-Jakob disease, however, is not straightforward. By the time a diagnosis can be made, patients are typically deep into the course of the disease or worse, already deceased. An autopsy with brain biopsy and neuropathologic examination is needed for definitive diagnosis. Even with a brain biopsy, results still may be inconclusive as the pathognomonic CJD findings may not be ubiquitously distributed throughout a patient's brain tissue [6]. A probable diagnosis can be made based on clinical features, imaging and lab results. In order for timely diagnosis, a high level of suspicion must be observed by clinicians.

It is unclear how long the patient described here was experiencing symptoms before seeking treatment, but she declined rapidly and death resulted in just 35 days. Rapid neuropsychiatric decline is often the common denominator within CJD patients and patients typically die within one year of symptom onset [7]. In order for diagnosis, one must display neuropsychiatric disorder and receive a positive real-time quaking-induced conversion (RT-QuIC) test to meet diagnostic criteria for CJD. Alternatively, progressive dementia plus two of the following: myoclonus, visual disturbance, cerebellar disturbance, extrapyramidal dysfunction, or akinetic mutism, must be present. For the alternative diagnostic route, a patient must also receive at least one supportive finding such as EEG, MRI, or characteristic CSF results [8]. Because of the rarity of the disease and its unique ability to mimic other disease processes, dementia from other causes, autoimmune encephalitis, paraneoplastic syndromes and psychiatric disorders must remain on the differential when examining patients. The patient in this case was originally admitted with altered mental status and depressive symptoms. She became progressively encephalopathic

and developed worsening aphasia, eventually displaying myoclonic jerking and hyperreflexia.

In addition to her clinical presentation, her EEG and MRI findings supported probable diagnosis of CJD. The patient's initial EEG imaging displayed nonspecific findings of symmetric mild theta delta background slowing consistent with possible encephalopathy. Later in the hospital course, her EEG displayed diffuse polymorphic theta slowing and frequent bilateral epileptiform discharges with intermittent sharp configuration recurring periodically. The finding of diffuse slowing and periodic discharges on EEG are characteristic for sporadic CJD (sCJD), which is the most common form [9]. Unfortunately, an MRI was not performed at initial admission to the hospital due to the presence of a pacemaker. It was not until later in the hospital course that MRI was eventually performed with assurance of pacemaker compatibility. MRI has become a crucial factor in the early diagnosis of sCJD, so it is imperative that clinicians discuss individual pacemaker compatibility with cardiology and radiology to determine if those patients would be eligible. Diffusion weighted MRI (DWI) and fluid attenuated inversion recovery (FLAIR) imaging in sCJD characteristically display intensification in striatal, cortical and thalamic regions of the brain, also referred to as 'cortical ribboning [10]. In this case, the patient's eventual MRI revealed diffusion hyperintensity throughout the left cortex and bilateral cingulate, caudate, and putamen regions. FLAIR imaging also revealed hyperintensity in the basal ganglia, all consistent with CJD.

In addition to imaging, laboratory diagnosis is also used in the diagnosis of CJD. Cerebrospinal fluid can be analyzed for the presence of protein markers 14-3-3, tau, and misfolded prion protein Scrapie (PrPSc). The patient in this case displayed positive results for all three. RT-QuIC works through protein amplification and has been shown to have a sensitivity between 92-95 percent and a specificity between 98.5-100 percent [11]. The

protein amplification technique works due to the property of PrPSc to induce continuous conformational changes in recombinant prion proteins. This allows for small amounts of PrPSc found in a patient's CSF to be extracted and amplified into monitorable amounts of amyloid fibrils for laboratory detection via the quaking

technique [12]. This technique is currently only performed at the National Prion Disease Pathology Surveillance Center at Case Western University, so all samples must be sent off for testing, delaying the time of accurate diagnosis. In this case, the patient was already deceased by the time the results were obtained. 14-3-3 and tau can be used as adjunct evidence in addition to RT-QuIC. 14-3-3 is a regulatory protein involved in cell growth and signal transductionx.

Tau protein is a component of microtubules involved in the formation of neural tissue. Neither 14-3-3 or tau are directly linked to the pathogenesis of CJD, but damaged brain tissue leads to buildup of these markers in the CSF [13]. 14-3-3 was revealed by systematic review of data to have a 92 percent sensitivity and a specificity of 95 percent for CJD, resulting in many false positives [11]. Elevated tau protein (>1150 picogram/mL) has been proven to be superior to 14-3-3 in the ability to diagnosis of CJD [14]. Although many strides have been made in the diagnostic guidelines for CJD, effective treatments have yet to be established. The prognosis is grim, with a 100 percent mortality rate [6]. Death typically ensues within one year of diagnosis, but is often much more rapid, as displayed in this case [15]. Current treatment guidelines are centered around supportive care and may include social services and pharmacologic management of symptoms. Benzodiazepines and antiseizure medications may be used in the treatment of myoclonus. New research has focused on the use of drugs including flupirtine, pentosan polysulfate, quinacrine, doxycycline, and antibody therapies in CJD although they have not shown any significant efficacy increasing survival rates [15,16].

Because there is no current cure for this horrific and rapidly progressive disease, it is important to make an early diagnosis to ensure that patients can maximize the quality of their remaining life. Many studies have focused on supportively managing the physical symptoms, but most fail to take into account the immense mental toll of CJD. In one retrospective review performed on 126 cases of sCJD at the Mayo Clinic, the vast majority of patients displayed at least one psychiatric symptom over the course of their disease. In 26 percent of these patients, their presenting symptom was psychiatric in nature. The most prevalent mental health related symptoms reported were depression, psychotic symptoms, and sleep disturbances [17]. In all patients with suspected CJD, psychiatry should be consulted in order to correctly identify and manage these symptoms in the form of medication, psychotherapy, and education.

Conclusion

In conclusion, our patient was accurately diagnosed with Creutzfeldt-Jakob disease based on her clinical picture in addition to neuroimaging and lab results. She presented with altered mental status, confusion, aphasia and difficulty ambulating. She was admitted with acute metabolic encephalopathy secondary to a urinary tract infection and treated with antibiotics with no improvement of mental status. Over the course of the next month, she was treated supportively as she experienced rapid neuropsychiatric deterioration including severe encephalopathy, depressive symptoms, myoclonic jerking and hyperreflexia. Psychiatry and neurology services were consulted and aided in the work-up and diagnosis. Over the duration of the hospital course, characteristic findings for CJD were revealed in both EEG and MRI results. CSF samples were sent to the National Prion Disease Pathology Surveillance Center, and she was positive for elevated 14-3-3 and tau proteins as well as PrPSc determined by the RTQuIC technique. Although this case resulted in an unfortunate death, it can be used to gain insight into an extremely rare and rapidly fatal prion disease. Despite the rarity of CJD, it is imperative that a high level of suspicion be maintained by all clinicians when patients present with

neuropsychiatric symptoms. With collaborative efforts and proper education, a swift diagnosis can be obtained. The faster the diagnosis can be obtained, the faster the patient can receive adequate supportive care for their physical and mental decline to maintain the highest possible quality of life in their remaining days.

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ISSN: 2574-1241

DOI: 10.26717/BJSTR.2024.58.009139

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