A Case of Rapidly Progressive Dementia

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Abstract
Creutzfeldt-Jakob disease (CJD) is a very rare neurodegenerative disorder that usually presents as rapidly progressive dementia with an extremely poor prognosis. The diagnosis of CJD can be extremely challenging due to its rarity, manifestation with non-specific neurological symptoms, associated broad differentials, and a need for extensive workup. Awareness of disease-specific biomarkers, radiological signs, and diagnostic criteria are crucial for timely diagnosis. Here, we report a case of CJD, which presented as an atypical movement disorder that progressed to dementia and failure to thrive within a few weeks of presentation.

Introduction
Creutzfeldt-Jakob disease (CJD), also known as subacute spongiform encephalopathy, is a rare, life-threatening neurodegenerative disorder. CJD is caused by the pathological misfolding and aggregation of the prion protein (PrP), a cellular glycoprotein [1]. The majority of the CJD are sporadic (approximately 85% patients) with no recognizable transmission pattern. Still, they can be due to inherited mutations of the PrP gene in a smaller proportion of patients (5% to 15%) [2]. CJD can present clinically as rapidly progressive dementia. Once transmitted to individuals, the pathologic PrP misfolds the normal PrP resulting in progressive disease. Initial manifestations include impaired memory, behavioral disturbances, visual disturbances, and poor coordination. As the disease advances, patients develop symptoms of dementia, involuntary movements, loss of vision, weakness, and coma.

Case Presentation
A 70-year-old female presented to the emergency room with complaints of involuntary movements of the left upper extremity of 10 days duration. Medical history is notable for Stanford type-A aortic dissection status post aortic repair and bioprosthetic aortic valve replacement 18 months ago. According to the patient, involuntary movements of the left upper extremity lasted several minutes, often waking her from sleep, and resolved spontaneously. She denied any fever, chills, or headache. She was seen by a neurologist three days prior. At the neurology clinic, laboratory studies were remarkable for mild thrombocytopenia with platelets 127,000. Erythrocyte sedimentation rate (ESR) was 2, and C-reactive protein (CRP) was 0.16. Electroencephalogram (EEG) was negative for seizure activity but due to clinical suspicion for atypical seizures, she was started on Levetiracetam 1,000 mg twice daily and Divalproex sodium 500 mg twice daily. However, she developed left upper extremity weakness and presented to the hospital. Imaging studies on admission as in Table 1.

| Imaging studies on admission | 
| --- | 
| Computerized Tomography (CT) scan of the brain | No acute changes |
| Magnetic Resonance Imaging (MRI) scan of the brain with and without contrast | Chronic small vessel ischemic changes |
| CT angiogram of the chest abdomen and pelvis | Negative for aortic dissection |
| CT angiogram of the head and neck | No arterial stenosis or venous abnormality. |
| MRI scan of the brain with and without contrast with thin slices of the brainstem | No acute findings |

**TABLE 1: Radiological workup on admission**

During the hospitalization, her left upper extremity weakness progressed with the development of
intermittent rigidity, myoclonic jerk-like movements mimicking hemichorea. The neurologist then recommended lumbar puncture and cerebrospinal fluid (CSF) analysis (Table 2).

| CSF studies on admission |
|--------------------------|
| Glucose                  | 69 mg/dL       |
| Protein                  | 65 mg/dL       |
| Total Nucleated cells    | 0              |
| Multiple sclerosis panel | Negative       |
| Meningitis Panel PCR     | Negative       |
| Paraneoplastic antibody Panel | Negative |
| VDRL                     | Negative       |
| Cryptococcal Antigen, Coccidioides Ab | Negative |
| GAD65 Ab                 | Negative       |
| JC virus PCR             | Negative       |

**TABLE 2: CSF studies on admission**

Venereal Disease Research Laboratory test (VDRL), Glutamic Acid Decarboxylase (GAD), John Cunningham Virus (JC virus), Polymerase Chain Reaction (PCR), cerebrospinal fluid (CSF)

Antinuclear antibody (ANA) was weakly positive (0.8 units) and the autoimmune panel was otherwise negative. Autoimmune etiology remained high on the differentials; therefore, she was given hydrocortisone 1000 mg daily and intravenous immunoglobulin for five days. We noted mild improvement in the left upper extremity weakness and involuntary movements. So, she was discharged home with outpatient neurology follow-up in eight days. At the neurology clinic, she reported word-finding difficulties and poor sleep. Her neurologist noted progressive flexor posturing, movements of the left upper extremity and described the findings as "progressive hemi-dystonia." He started her on clonazepam, baclofen and mirtazapine. He then referred her to a movement disorder clinic at a University Hospital.

Her symptoms rapidly progressed over the next five days; she became increasingly weak, developed difficulty swallowing with abnormal movements in bilateral upper extremities and rhythmic jerking of the left arm. There was some motor agitation in the legs, and she could not ambulate.

She was then readmitted to the hospital; initial vitals and lab studies were unremarkable. Repeat lumbar puncture and additional CSF testing were done (Table 3).

| CSF Biomarker assay on readmission |
|-----------------------------------|
| Neuron Specific Enolase           | 59 ng/mL (H)   |
| RT-QuIC                           | Positive       |
| T-tau protein                     | 3,699 pg/mL (range 0-1,149) |
| 14-3-3 protein                    | Positive       |

**TABLE 3: CSF biomarker assay on readmission**

Real-time quaking-induced conversion (RT-QuIC), cerebrospinal fluid (CSF)

A repeat MRI of the brain with and without contrast showed subtle, patchy bilateral cortical diffusion restriction, significantly progressing from prior MRIs in a pattern suggestive of CJD (Figures 1, 2). A continuous EEG showed periodic sharp wave discharges lateralized to the right hemisphere. In combination with her rapid decline, these findings were highly suggestive of sporadic CJD.
FIGURE 1: MRI brain showing cortical hyperintensity and ribboning
There was rapid worsening in her mentation, dementia, involuntary movements of upper extremities, and difficulty with swallowing. Given her ongoing decline and poor prognosis associated with CJD, her family decided to transition to comfort care measures. The patient passed away in the hospital on hospice, within six weeks of initial symptom onset.

Discussion

CJD is the most common human prion disease, with an incidence of one per 1,000,000 person-years. Most of these cases are sporadic (85%-95%). The mean age of disease onset is 62 years [3-5]. Discovered initially by Creutzfeldt and Jacob in 1920, CJD was considered an atypical form of dementia until 1968 when Gibbs et al. proved experimental transmission to primates by intracerebral inoculation.

Classic clinical features of CJD are rapidly progressive dementia, ataxia, myoclonic jerks/involuntary movements [6]. The mean duration of illness is six months [7]. This rapid progression of symptoms distinguishes CJD from other common forms of dementia. Evaluation should include detailed clinical history, neuroimaging, lab studies to rule out infectious and autoimmune differential diagnoses (Table 4), electroencephalogram, and CSF analysis.
Differential diagnoses to consider when working up CJD

- Alzheimer's dementia
- Dementia with Lewy bodies
- Atypical meningitis/encephalitis
- Autoimmune encephalitis
- Paraneoplastic syndromes
- Huntington’s chorea
- Korsakoff Psychosis
- Conversion disorder

### TABLE 4: Differential diagnoses

MRI is superior to a CT scan of the brain to identify changes in CJD. A hyper-intense signal on diffusion-weighted imaging (DWI), fluid-attenuated inversion recovery (FLAIR), and T2-weighted images involving the cerebral cortex and corpus striatum, caudate head, and putamen are the most common patterns on MRI in patients with sporadic CJD [8-10]. Although a gray matter disease, CJD can affect white matter in early-intermediate stages [11].

Synchronous bi- or triphasic periodic sharp wave complexes (PSWC) on EEG can support the diagnosis in 67% to 95% of patients with CJD [12].

CSF analysis for specific markers is vital in the diagnosis of CJD (Table 5) [13-15]. The Centers for Disease Control (CDC) and Prevention have proposed diagnostic criteria for probable CJD (Table 6) and no longer recommend brain biopsy for the definitive diagnosis [16].

| Cerebrospinal Fluid markers | Sensitivity % | Specificity % | To remember |
|-----------------------------|---------------|---------------|-------------|
| RT-QuIC                     | 95            | 100           | Assay monitoring disease associated PrPsc transforming recombinant Prion protein (recPrP) resulting in formation of amyloid, that can be monitored in real time. The National Prion Disease Pathology Surveillance Center based at Case Western Reserve University is the only clinical laboratory in the United States that performs RT-QuIC |
| 14-3-3 Protein              | 92            | 80            | Adjunctive test; higher chance for false positives considering low prevalence of disease |
| Tau Protein (>1300pg/mL)    | 94            | 90            | Tau-protein ELISA is easy to use in routine laboratories |

### TABLE 5: Cerebrospinal fluid markers

Enzyme-linked immunosorbent assay (ELISA), real-time quaking-induced conversion (RT-QuIC), scrapie isoform of the prion protein (PrPsc)
Neuropsychiatric disorder with a positive RT-QuIC test or progressive dementia, and at least 2/4 clinical features

Myoclonus
Visual or cerebellar disturbance
Pyramidal or extrapyramidal dysfunction
Akinetic mutism

Supportive findings on one or more of the following tests
A typical EEG, e.g., PSWC during an illness of any duration
Positive 14-3-3 CSF assay with a clinical duration to death less than two years
MRI of the brain showing hyperintensity in caudate nucleus/putamen and/or in at least two cortical regions (temporal, parietal, and occipital) on DWI or FLAIR
Routine investigations should not suggest an alternative diagnosis

| TABLE 6: CDC criteria for the diagnosis of CJD |
|-----------------------------------------------|
| Periodic sharp-wave complexes (PSWC), Centers for Disease Control (CDC), Creutzfeldt-Jakob disease (CJD) |

Conclusions

CJD is an extremely rare disease that may manifest with a wide range of neurological symptoms as in this case. CJD is to be suspected in any case of rapidly progressive dementia or presentation with unexplained movement disorder of the limbs. A high index of suspicion, awareness of specific biomarkers, and radiologic signs are crucial in the diagnosis of this condition. Unfortunately, there are no effective treatment options for prion diseases and they are universally fatal, with a median disease duration of six months. Once a diagnosis is confirmed, physicians should provide symptomatic treatment for neuropsychiatric symptoms, communicate effectively with family regarding the biology of the disease and the expected poor outcome, and have end-of-life conversations.

Additional Information

Disclosures

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References

1. Otto M, Wiltfang J, Cepek L, et al.: Tau protein and 14-3-3 protein in the differential diagnosis of Creutzfeldt-Jakob disease. Neurology. 2002, 58:192-7. 10.1212/wnl.58.2.192
2. Masters CL, Harris JO, Gajdusek DC, Gibbs CJ Jr, Bernoulli C, Asher DM.: Creutzfeldt-Jakob disease: patterns of worldwide occurrence and the significance of familial and sporadic clustering. Ann Neurol. 1979, 5:177-88. 10.1002/ana.410050212
3. Ladogana A, Puopolo M, Crous EA, Budka H: Mortality from Creutzfeldt-Jakob disease and related disorders in Europe, Australia, and Canada. Neurology. 2005, 10:1586-91.
4. Bürler H, Aguzzi A, Sailer A, et al.: Mice devoid of PrP are resistant to scrapie. Cell. 1995, 2:1539-47. 10.1016/0092-8674(95)00060-3
5. Monreal J, Collins GH, Masters CL, Fisher CM, Kim RC, Gibbs CJ Jr, Gajdusek DC: Creutzfeldt-Jakob disease in an adolescent. J Neurol Sci. 1981, 52:541-50. 10.1016/0022-510x(81)90015-0
6. de Silva R, Findlay C, Awad I, Harries-Jones R, Knight R, Will R: Creutzfeldt-Jakob disease in the elderly. Postgrad Med J. 1997, 73:557-9. 10.1136/pgmj.73.863.557
7. Will RG: Clinical features of human prion diseases. Diseases of the Nervous System. Ashbury AK, McKhann MG, McDonald WI, Goadsby PJ, McArthur JC (ed): Cambridge University Press, Cambridge; 2002. 1716-27.
8. Brown P, Rodgers-Johnson P, Cathala F, Gibbs CJ Jr, Gajdusek DC: Creutzfeldt-Jakob disease of long duration: clinicopathological characteristics, transmissibility, and differential diagnosis. Ann Neurol. 1984, 16:295-304. 10.1002/ana.410160505
9. Appleby BS, Yobs DR: Symptomatic treatment, care, and support of CJD patients. Handb Clin Neurol. 2018, 153:399-408. 10.1016/B978-0-444-63945-5.00021-0
10. Collie DA, Sellar RJ, Zeidler M, Colchester AC, Knight R, Will RG: MRI of Creutzfeldt-Jakob disease: imaging features and recommended MRI protocol. Clin Radiol. 2001, 56:726-39. 10.1053/crad.2001.0771
11. Schröter A, Zerr I, Henkel K, Tschampa HJ, Finkenstaedt M, Poser S: Magnetic resonance imaging in the clinical diagnosis of Creutzfeldt-Jakob disease. Arch Neurol. 2000, 57:1751-7. 10.1001/archneur.57.12.1751
12. de Priester JA, Jansen GH, de Kruijk JR, Wilmink JF: New MRI findings in Creutzfeldt-Jakob disease: high signal in the globus pallidus on T1-weighted images. Neuroradiology. 1999, 41:265-8. 10.1007/s002340050744
13. Caverzasi E, Mandelli ML, DeArmond SJ, et al.: White matter involvement in sporadic Creutzfeldt-Jakob disease. Brain. 2014, 137:3339-54. 10.1093/brain/awu299
14. Steinhoff BJ, Rickel S, Herrendorf G, et al.: Accuracy and reliability of periodic sharp wave complexes in Creutzfeldt-Jakob disease. Arch Neurol. 1996, 53:162-6. 10.1001/archneur.1996.00550020074017
15. Green AJ, Zanusso G: Prion protein amplification techniques. Handb Clin Neurol. 2018, 153:357-70. 10.1016/B978-0-444-63945-5.00019-2
16. Muayqil T, Gronseth G, Camicioni R: Evidence-based guideline: diagnostic accuracy of CSF 14-3-3 protein in sporadic Creutzfeldt-Jakob disease: report of the guideline development subcommittee of the American Academy of Neurology. Neurology. 2012, 79:1499-506. 10.1212/WNL.0b013e51826d5fc5