Case Report

Improving Laboratory Diagnosis of Creutzfeldt-Jakob Disease

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Abstract

Background: Creutzfeldt-Jakob disease (CJD) is a rare human form of prion disease caused by misfolded, transmissible proteinaceous infection particles (prions). As a fatal neurological illness, it mostly presents with rapidly progressive dementia, and most patients die within a year of clinical onset and diagnosis. The lack of an intravital test for CJD limits its timely diagnosis. A brain biopsy/autopsy is considered the gold standard for definitive diagnosis of CJD, however owing to its highly invasive and transmissible nature, it is rarely performed. In this case report, we try to highlight the important role of combining serology, EEG, and CSF investigations, often used for the diagnosis of CJD. Combining these in the laboratory improves the timely diagnosis of this rare and fatal disease.

Case summary: We report a clinical case study of a 65-year-old female, who presented to the Neurology OPD at a tertiary care referral centre, with chief complaints of forgetfulness, behavioural changes, and involuntary movements in the right upper limb for the last 7 months. According to the informant (daughter), the patient was asymptomatic 7 months ago after which she started developing these gradual onset symptoms. Later she was bed-bound and dependent on her family members for her daily chores and had even lost control over her bowel and bladder habits. On physical examination, the patient was found to be disoriented and afebrile with normal vitals, however, CNS examination showed a low Mini Mental Examination Score (MMSE). The patient was admitted to the neurology ward for further evaluation and a definitive diagnosis. Differential diagnosis was ruled out using various lab tests, CSF analysis, and neuroimaging. CSF report tested positive for 14-3-3 protein and CSF protein marker by RT-QuIC was outsourced. The confirmatory diagnosis of sporadic CJD was made based on clinical presentation, CSF analysis, and neuroimaging.

Conclusion: Definitive diagnosis of CJD was possible with the help of various lab tests which helped rule out differential neurodegenerative diseases.

Introduction

Creutzfeldt-Jacob disease (CJD) is a rare, progressive, transmissible, deadly neurodegenerative disease caused by misfolded prion proteins mostly characterized by a long incubation period [1-2]. Most people with clinically diagnosed CJD die within a year of symptom onset [3]. Also, given that CJD can develop asymptomatically in people for decades before showing symptoms, there is a chance that it could spread through iatrogenic means [4]. Due to the lack of specific diagnostic markers and scarcity of genetic testing, only a few cases are reported, with 1-2 cases diagnosed per million people yearly [5]. A prion protein (PrPc) is a normal neuronal protein primarily composed of α-helical structures and random coils usually found on the cellular surface of neurons which maintains neuronal homeostasis and plays a role in cell signalling. Infected prion proteins misfold into β-pleated sheets and are pathological [6]. Abnormally folded PrPsc causes disturbance in neuronal development, homeostasis, circadian rhythm, stress responses, and synaptic plasticity, thereby leading to the presenting features of CJD [7]. There are three major groups of human prion disease: sporadic, genetic, and acquired.

Sporadic CJD is the most common type and accounts for almost 85% of all CJD. It is further subdivided into sporadic fatal insomnia and variably protease-sensitive prionopathy. **Genetic CJD** constitutes about 10-15% of total CJD cases. Genetic forms of CJD are associated with pathogenic mutations in the prion protein gene PRNP and include familial CJD, fatal familial insomnia, and Gerstmann-Schaussler-Scheinker syndrome. **Acquired CJD** constituting less than 1% of total CJD cases, includes kuru, iatrogenic, and variant subtypes [8-9]. Latest data showed few deaths from iCJD and gCJD from 1996 to 2018 but a steady rise in sCJD cases [10-11].

Diagnosis of CJD is often challenging due to its low incidence and its symptoms resembling various other neurodegenerative diseases. These clinical symptoms include a rapid decline in cognitive function, myoclonus, ataxia, extrapyramidal signs, and akinetic mutism [12]. The gold standard test for diagnosing CJD is a highly invasive brain biopsy. However, this is done mostly during an autopsy, which makes it less useful for the patient. Also, prions are highly infectious and clinicians are exposed to this highly transmissible disease during this procedure. Therefore, diagnosis is made based on clinical features, laboratory tests, EEG, MRI findings, and genetic studies. Laboratory findings include CSF studies. CSF 14-3-3 protein is sensitive to CJD. EEG reveals typical periodic short-wave complexes (PSWC). Of late, RT-QuIC assay has been identified as a more sensitive and specific diagnostic tool, that closely resembles brain biopsy findings, and directly detects misfolded prion protein [13-14]. Though CJD is invariably fatal and lacks a definitive treatment, it is highly essential to establish a confirmatory diagnosis to prevent iatrogenic transmission and also to reduce the risk of transmission among healthcare providers. We are reporting a 65-year-old female who presented with neurodegenerative complaints and was diagnosed as a case of sporadic CJD with the help of various laboratory and radiological investigations.

Case Presentation

Chief complaints

A 65-year-old female, presented to the Department of Neurology OPD at a tertiary care referral centre, in Delhi, India, with the chief complaints of forgetfulness, behavioural changesfor 7 months and involuntary movements in the right upper limb for the last 6 months.

History of present illness

The patient was asymptomatic 7 months ago after which she started developing symptoms of forgetfulness and behavioural changes which were insidious in onset and gradually progressive. She started experiencing memory lapses including the inability to recall the route/path to her daughter's house, which she visited frequently. In addition, her relatives noticed repeatability in certain activities like folding and unfolding of clothes eventually leading to incompletion of tasks. This was followed by increased irritability towards her grandchildren, especially when they wanted to play with her. Also, she started misplacing items in her household, often neglecting to position them in their designated positions. They also noticed that she found it hard to speak her usual and started communicating in short sentences which gradually reduced to one/two words, later she answered in yes or no communication, and since last one month she started producing incomprehensive sounds. This was further associated with gradually decreasing oral intake and decreased sleep compared to her pre-illness state. In addition, 6 months back, relatives observed that she developed a new habit of clenching her fist momentarily throughout the day gradually progressing to unusual movements of her right upper limb. This was initially momentarily, but later occurred multiple times a day and persisted even during her sleep. She has been bed-bound and dependent on her family members for her daily activities for the last one month and has even lost control over her bowel and bladder habits.

History of past illness

There was no history of trauma/surgery/similar episodes in the past.

Negative history

There was no history of prolonged fever/rash/joint pain/swelling/visual or auditory hallucinations/ documented weight loss/recurrent focal deficit/seizures.

Past History

The patient did not have any relevant past medical history. There was no history of hypertension/diabetes mellitus/thyroid disorders/TB/drug allergy.

Personal and family history

The patient was a nonvegetarian, non-alcoholic, and non-smoker with 67 Kg weight and 168cm height, Muslim by religion, and a housewife by occupation The patient's medical, dental, and family history was non-contributory.

Physical examination

On physical examination, the patient was found to be disoriented to time, place, and person. She was afebrile with a heart rate of 96 bpm, respiratory rate of 18 bpm, and blood pressure of 118/76 mm Hg. No signs of pallor, icterus, or lymphadenopathy were seen. On palpation, the abdomen was found to be soft with no signs of organomegaly. CNS examination showed spontaneous eye opening, pupil bilateral reactive, not following verbal commands, noncomprehensive speech, withdrawal to pain, and jerky movement of the right upper limb (myoclonus). MMSE scoring revealed a low score.

The patient was admitted to the neurology ward in view of **rapidly progressive dementia** and **persistent myoclonic jerks** and further evaluation was done for a definitive diagnosis.

Diagnosis

A differential diagnosis of Creutzfeldt-Jacob disease, Paraneoplastic Encephalitis, Amyloid angiopathy, Frontal temporal dementia, and Alzheimer's disease, Autoimmune encephalitis, Metabolic encephalopathy were suspected, and following investigations were ordered. The results are shown below.

Laboratory Diagnostics

1. Routine blood investigation

Table 1: Routine blood investigations.

Blood Investigation	Reference range	20/3/2023	14/4/23	25/4/23	2/5/23	9/5/23	20/5/23
Complete blood count							
Hemoglobin	12-15.5gm/dL	12.7	12.5	**8.6**	**8.9**	**5.3**	**7.2**
WBC-TLC	5-10 x10^3/µl	9.4	**19**	**18**	**26**	**15**	**17.9**
Neutrophils	60-75%	65	80	**86**	**86**	80	**96**
Lymphocytes	20-40%	22	**9**	**8**	**7**	**13**	**4**
Platelets	150-400 x 10^3/µL	245	159	319	**415**	293	**22**
Renal function tests							
Urea	18-55mg/dl	28	25	15	17	10	48
Creatinine	0.5-1.2mg/dl	0.8	**1.4**	0.4	0.4	0.2	0.8
Serum electrolytes							
Sodium	135-145 mEq/L	131	**126**	**131**	135	135	**156**
Potassium	3.5-5.3 mEq/L	3.2	**3.4**	3.8	3.8	3.8	**5.6**
Hepatic profile							
Total Bilirubin	0.3-1.2 mg/dL	0.3	0.5	0.2	0.2	0.2	0.3
Total Protein	6-8 gm/dL	5.8	5.9	**5.7**	6.7	**3.7**	**4.9**
Albumin	3.5-5 gm/dL	3.4	3.3	**2.1**	2.2	**1.3**	**1.7**
AST	10-40 U/L	50	**67**	33	43	21	32
ALT	10-40 U/L	60	**113**	15	11	10	08
RBS	<200 mg/dL	100	150	110	110	90	106
Ammonia	9-30umol/L	-	**96**	**80**	**41**	**47**	**57**

2. CSF analysis (23/3/23):

- CSF protein - **23.9** (15- 45 mg/dL)
- CSF sugar - 73 (50-80 mg/dL)
- CSF cytology (TLC/DLC) – Acellular

*CSF analysis for **14-3-3 protein:*** The test was outsourced and resulted **positive.**

CSF for AFB/CBNAAT: No AFB (Acid Fast Bacilli) was present in the sample and resulted **negative.**

3. Special tests

Table 2: Special tests.

Name of test	Reference range	Test result
FT3	2.0-4.4 pg/mL	3.3
FT4	0.93-1.7 ng/dL	1.4
TSH	0.27-4.2 ulU/mL	3.6
Vit B12	211-946 pg/mL	671
CEA	<3.8 ng/mL (non-smoker)	**4.2**
AFP	<5.8 IU/mL	4.88
CA 19.9	<39 IU/mL	29.3
Procalcitonin	<0.05 ng/mL	**0.40**
Anti TPO Ab	<30 IU/mL	9.1

Serum and CSF autoimmune and paraneoplastic panel profile: Negative

ANA profile: The Antinuclear Antibody Test profile was negative by ELISA and Indirect Immunofluorescence.

Viral markers: Negative.

4. Neuroimaging Analysis

EEG: Short interval discharges at the frequency of one per minute were observed.

NCCT Head: No abnormality detected.

MRI Brain (6/4/2023): Revealed FLAIR hyperintense areas showing diffusion restriction involving the cortex of bilateral cerebral hemispheres and left striatum. Findings are consistent with Creutzfeldt-Jacob disease (Figure 1).

Figure 1: MRI brain(T2/FLAIR) showing areas of signal alteration involving the cortex of bilateral hemispheres and left striatum appearing hyperintense on FLAIR images.

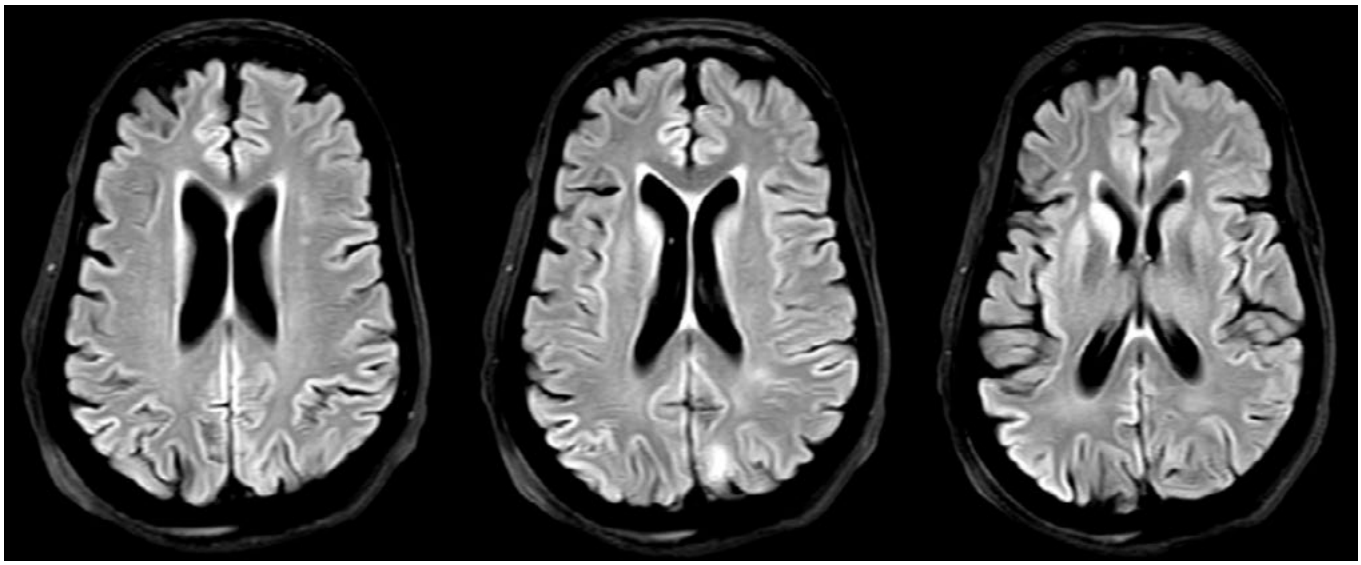
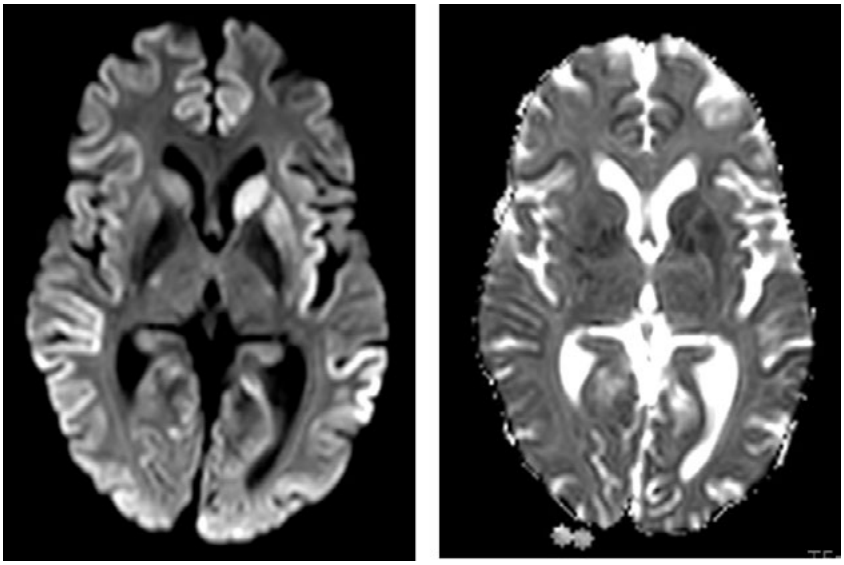


Figure 2: MRI brain (DWI-ADC) showing areas of signal hyperintensity in cortical regions.



Final Diagnosis

Clinical presentation of the patient, lab investigations, EEG, and MRI brain suggested positive findings and confirmed the diagnosis of CJD.

Treatment

During hospital stay, the patient developed high fever and a blood culture was ordered which revealed to be **MRSA positive.** The patient was started on specific antibiotics. However, despite proper management patient landed into respiratory failure for which she was intubated and further tracheostomized 15 days later. Her GCS was found to be profoundly decreasing from **E4V2M5** on the day of admission to **E1VTM1** a month later. Her blood culture and ET tube culture post tracheostomy came positive for Klebsiella pneumonia and Acinobacter. Klebsiella pneumonia is a pan antibiotic-resistant bacteria and patient was started on broad-spectrum antibiotics. Also, her bed sores progressed to grade IV and pus from bed sore was sent for culture; which again was positive for **Klebsiella pneumonia.** The patient gradually went into septic shock and was started on inotropes and extended-spectrum antibiotics. Her inotrope requirement increased gradually; she finally went into cardiac arrest. Despite giving 3 cycles of CPR as per ACLS guidelines she could not be revived and was declared dead.

Discussion

Previous literature and several reports state that sCJD mimics other neurodegenerative conditions including stroke [15-16], acute neuropathy [17], general dementia [18-20], hyperparathyroidism [21], Lewy body dementia [22], Alzheimer's disease [23-24], cerebral amyloid angiopathy [25], aphasia [26], encephalitis [24], psychiatric illness [27], and movement disorder [28]. According to the CDC, a definite diagnosis of CJD can only be determined by a brain biopsy usually performed at the time of autopsy [29]. As such confirming and ruling out CJD diagnosis in a living patient is difficult. The diagnostic criteria for the evaluation of a patient with rapidly progressive dementia is mainly done by a detailed history, CSF analysis and neuroimaging. However, exclusion diagnosis is ruled out with the help of various routine lab investigations.

Our patient presented with the same chief complaint associated with persistent myoclonus and behavioural changes. She was admitted and tests were done for further evaluation and definitive diagnosis. A detailed history revealed that the patient was bedridden and dependent on her family members for her daily routine activities. She was disoriented and afebrile on the day of hospitalization with grade I bed sores. Serial blood investigations showed a trend of decreasing hemoglobin, rising TLC, and increasing serum ammonium value during her hospital stay with normal serum sodium, urea, creatinine, and liver enzyme levels. Levels of total protein and albumin decreased during her stay and albumin significantly lowered to an alarming value of 1.3g/dL. Differential diagnosis of **Creutzfeldt-Jacob disease, Paraneoplastic encephalitis, Amyloid angiopathy, Frontal temporal dementia, Alzheimer's disease, Autoimmune encephalitis and Metabolic encephalopathy** was made and special tests were further ordered for a definitive diagnosis.

CSF analysis revealed high protein and normal sugar levels with no cells suggesting positive results for inflammation. CSF report tested positive for *14-3-3 protein* pointing towards CJD diagnosis [29]. No Acid-Fast Bacilli were seen in the sample, ruling out tubercular meningitis. Another specific test, CSF protein marker by RT- QuIC was outsourced, but the report was unavailable, due to the patient's financial constraints. RT-QuIC assay is a protein aggregation assay in which recPrP aggregation is promoted by shaking and heating it in the presence of an sCJD

seed [30]. The assay has 91% sensitivity and 98% specificity in detecting sCJD [31-32]. Being from a low socioeconomic society, the patient's attendant couldn't get the test done, as RT-QuIC is still a sophisticated and expensive investigation in India. This was a limitation of the study, as if RT-QuIC report were available, we could further match our findings and confirm the diagnosis. However, given the lack of an intravital test, other lab investigations helped us rule out other probable neurodegenerative diseases.

Thyroid function tests revealed no abnormality, ruling out any probable thyroid disorders. Anti TPO antibodies were within normal levels, ruling out evidence for Hashimoto's thyroiditis. Serum vitamin B12 levels were normal excluding deficiency disorder. Tumor markers and paraneoplastic profile also revealed normal levels ruling out any underlying malignancy. The autoimmune and ANA profile was negative, ruling out autoimmune disease. Raised procalcitonin levels depicted the presence of infection. Finally, CSF analysis, EEG, and MRI brain suggested positive findings for CJD and confirmed the diagnosis. However, the patient developed high fever during the hospital stay and was started on specific antibiotics. Despite proper management patient landed into respiratory failure. Her GCS profoundly decreased and her bed sores progressed to grade IV. The patient gradually went into septic shock and was started on inotropes and extended-spectrum antibiotics. Despite proper management provided to our patient, her health kept deteriorating owing to the fatal and highly transmissible nature of CJD. Most patients with CJD die within a year of clinical onset and diagnosis [33]. Eventually our patient went into cardiac shock and succumbed to death.

Conclusion

CJD is a fatal, neurodegenerative disease caused by misfolded, transmissible infectious prions proteins. Having a low incidence worldwide, CJD is a rare condition to be found. However, a definitive diagnosis is important owing to its fatal and highly transmissible nature. The lack of an intravital test for CJD limits its timely diagnosis and is often missed as a diagnosis. It is mostly a diagnosis of exclusion and several tests are required to rule out other neurodegenerative diseases however, RT-QuIC assay is highly sensitive and specific for the detection and definitive diagnosis of CJD. Our case report adds to the knowledge of the clinical presentation and the confirmatory diagnosis of CJD by combining serology, EEG and CSF investigations.

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Author contributions

Masih M contributed to the conception of the idea of the case report and first draft preparation; Chillarige SA, Sehrawat R, contributed to literature review and preparation of reports, Saha PR, contributed to the patient examination, diagnosis, and management, Dabla P K contributed to the interpretation of data and critical revisions. Masih M, Chillarige SA, Sehrawat R, and Saha P Rrevised and finalized the manuscript.

Informed consent statement

Informed written consent was obtained from the patient and the related family.

Conflict-of-interest statement and Author Disclosure

The authors declare no conflict of interest for this article.

Declaration of Helsinki

The given case report details are in compliance with the ethical principles for medical research involving human subjects, in accordance with the Declaration of Helsinki. No further ethical approval is required for the case report.

Ethical approval statement

Not required for case reports.

Abbreviations

- CJD- Creutzfeldt-Jakob disease
- OPD- Out Patient Department
- CNS- Central Nervous System
- MMSE- Mini-Mental State Examination
- RT-QuIC- Real-Time Quaking-Induced Conversion
- PrPc- Cellular Prion Protein
- PrPsc- Scrapie Prion Protein
- PSWC- Periodic Short-Wave Complexes.
- sCJD- Sporadic Creutzfeldt-Jakob disease
- iCJD- Iatrogenic Creutzfeldt-Jakob disease
- gCJD- Genetic Creutzfeldt-Jakob disease
- MRI- Magnetic Resonance Imaging
- DWI- Diffusion-Weighted Imaging
- FLAIR- Fluid-Attenuated Inversion Recovery
- EEG- Electroencephalograph
- MRSA- Methicillin-resistant Staphylococcus aureus
- GCS- Glasgow Coma Scale
- EVM- Eye-opening, Verbal Response, Motor response
- ET- Endotracheal tube
- CPR- Cardiopulmonary Resuscitation
- ACLS- Advanced Cardiovascular Life Support

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