A Case Series: Navigating the Clinical Spectrum of Creutzfeldt-Jakob Disease

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Introduction
Creutzfeldt-Jakob Disease (CJD) is a rare, fatal, and rapidly progressive neurodegenerative disorder caused by the misfolding of normal prion proteins (PRPc) into pathological isoforms (PRPsc). This process leads to neuronal loss, spongiform changes, and gliosis, with an annual incidence of 1–2 cases per million. Sporadic CJD (sCJD), the most common form, accounts for 85–90% of cases and typically presents with rapidly progressive dementia, ataxia, and myoclonus. Diagnosis relies on clinical features, cerebrospinal fluid biomarkers, EEG abnormalities, and characteristic neuroimaging findings. This case series presents six patients with CJD encountered between 2022 and 2025, highlighting the diverse clinical presentations, diagnostic challenges, and management considerations.

Case Series
A Case Series of Unusual Presentations of Creutzfeldt-Jakob Disease

Sr. No.	Date	Case Details	Signs and Symptoms	Outcome
1	February 2022	A 66-year-old female with a history of hypothyroidism, type 2 diabetes, and breast cancer presented with progressive right-sided weakness, slurred speech, and difficulty rising from sitting position for 1 month. EEG showed 5–6 Hz posterior dominant activity with bilateral theta waves and occasional sharp waves. CSF 14-3-3 protein was elevated at 76,686 AU/ml. PET-MR revealed hypometabolism with diffusion restriction in bilateral caudate nucleus, anterior putamen, and left temporo-parietal cortex.	Weakness in proximal limbs, mutism, cognitive impairment, rigidity in all limbs, dystonic posturing, slow pursuit movements, and primitive reflexes including positive glabellar and palmomental reflexes.	Treated with IVIG without improvement. Progressed to terminal stage within 3 months of presentation.

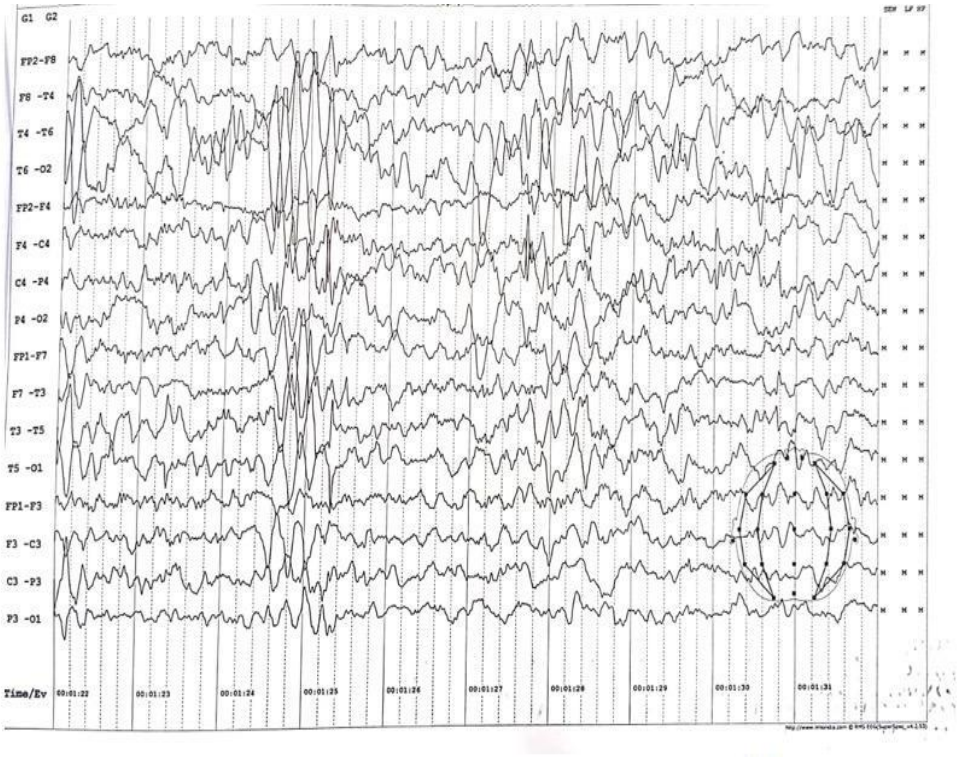
2	15th October 2022	A 58-year-old male professor with an 8-week history of psychiatric symptoms, including paranoia, obsessive behaviors, and insomnia. Initially diagnosed as late-onset psychosis. CSF 14-3-3 protein was positive (78,450 AU/ml). MRI showed cortical ribboning in bilateral parietal and occipital regions. EEG demonstrated periodic sharp wave complexes.	Initial psychiatric manifestations, followed by rapid cognitive decline, myoclonus, visual hallucinations, ataxia, and bilateral extensor plantar reflexes.	Developed akinetic mutism within 3 months and died 4 months after presentation. Autopsy confirmed sporadic CJD with MM1 subtype.
3	7th March 2023	A 42-year-old female pediatrician with a family history of early-onset dementia presented with progressive cerebellar ataxia and dysarthria. Genetic testing revealed E200K mutation in PRNP gene with methionine homozygosity at codon 129. RT-QuIC assay was positive.	Prominent cerebellar ataxia, dysarthria, and nystagmus with minimal initial cognitive impairment. Later developed myoclonus, visual disturbances, dementia, positive startle response and hyperreflexia.	Prolonged course with survival of 14 months after symptom onset. Family members underwent genetic counseling, identifying two asymptomatic carriers.
4	22nd January 2024	A 64-year-old male with hypertension and migraines presented with visual symptoms including cortical blindness and hallucinations. Initially diagnosed as posterior circulation stroke. MRI showed hyperintensity in bilateral occipital cortices. CSF 14-3-3 protein was elevated (82,340 AU/ml) and RT-QuIC was positive.	Initial isolated visual symptoms, including cortical blindness, visual agnosia, and formed visual hallucinations. Cognitive decline began 6 weeks after onset, followed by myoclonus and akinetic mutism.	Rapidly progressive course with death occurring 3 months after symptom onset. Autopsy confirmed Heidenhain variant of CJD with predominant occipital involvement.

5	18th May 2024	A 55-year-old female musician with no significant past medical history presented with progressive fine motor incoordination affecting her ability to play piano, followed by gait instability. Initially diagnosed with possible multiple system atrophy. CSF tau protein was markedly elevated (2,450 pg/ml) and RT-QuIC assay was positive. DWI-MRI revealed asymmetric cortical ribboning in left frontal and parietal lobes with involvement of left putamen.	Progressive apraxia, dysmetria, executive dysfunction, and alien limb phenomenon affecting the right upper extremity. Later developed myoclonus, aphasia, and parkinsonian features with rigidity and bradykinesia.	Diagnosis of probable sporadic CJD with corticobasal syndrome variant. Disease progressed to akinetic mutism within 5 months of symptom onset. Died 7 months after initial presentation.
6	3rd September 2024	A 37-year-old male with history of iatrogenic growth hormone treatment during childhood (1992-1994) for idiopathic short stature presented with rapidly progressive memory impairment and personality changes over 3 months. MRI showed symmetric hyperintensities in bilateral thalami and posterior putamen on FLAIR and DWI sequences. CSF 14-3-3 was positive, and RT-QuIC confirmed prion disease.	Progressive amnesia, apathy, and behavioral disinhibition with early-onset cerebellar ataxia. Later developed myoclonic jerks, pyramidal signs with hyperreflexia, and sleep disturbances.	Diagnosed with iatrogenic CJD. Survived 12 months from symptom onset. Raised concerns about potential historical iatrogenic transmission through contaminated human-derived growth hormone preparations used prior to 1995.

Diagnostic Findings from Case 1

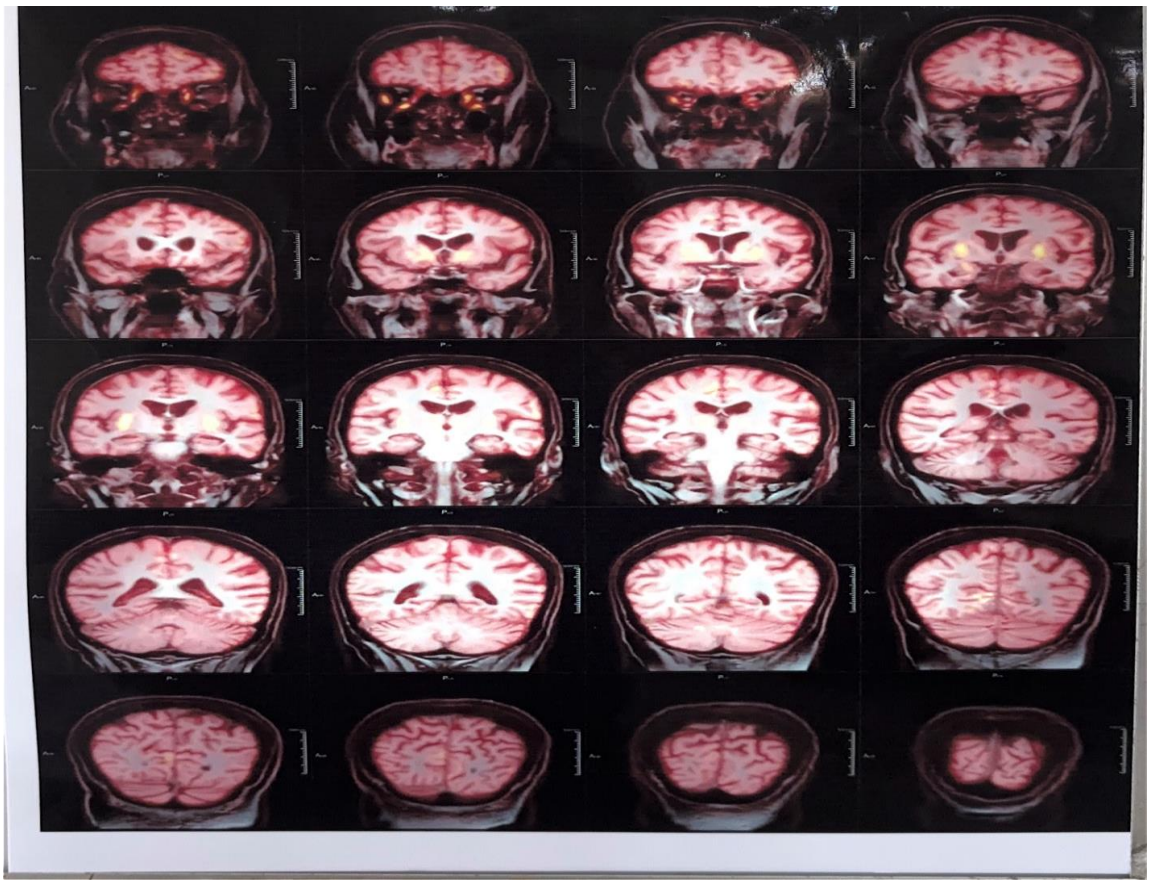
Electrophysiological Findings

The EEG demonstrated a background rhythm of 5–6 Hz posterior dominant activity with bilateral symmetrical theta waves. Intermittent 3–4 Hz generalized theta-delta slowing was noted, more prominent over the right cerebral hemisphere. Occasional generalized sharp and slow waves were also observed, predominantly on the right side.



Neuroimaging Findings

PET-MR brain imaging revealed generalized hypometabolism in the bilateral cerebral hemispheres, cerebellar hemispheres, and brainstem, along with patchy hypometabolism in the bilateral basal ganglia and thalami. Diffusion-weighted imaging showed symmetrical diffusion restriction involving the bilateral caudate nucleus, anterior putamen, and left temporo-parietal cortex—findings characteristic of CJD.



Discussion

Creutzfeldt-Jakob Disease (CJD) is a fatal neurodegenerative disorder caused by the conversion of normal cellular prion proteins (PrPc) into pathological isoforms (PrPsc). This conformational shift leads to the accumulation of PrPsc in the brain, resulting in neuronal loss, spongiform changes, and gliosis.The clinical phenotype of CJD is influenced by codon 129 polymorphism in the PRNP gene, which results in three genotypes: methionine/methionine (MM), methionine/valine (MV), or valine/valine (VV). These genetic variations, along with the type of prion protein (type 1 or type 2), lead to distinct clinicopathological subtypes with various presentations and disease courses.

In this case series, we encountered four patients with CJD who presented with diverse clinical manifestations:

Varied Initial Presentations

1. **Case 1** (66-year-old female) presented with progressive weakness, speech disturbances, and dysphagia, initially suggesting a motor neuron or cerebrovascular disorder. The PET-MR findings of generalized hypometabolism with symmetrical diffusion restriction in basal ganglia and cortical regions were pivotal in diagnosis. This case was particularly notable for the presence of significant imaging findings despite the absence of classic periodic sharp wave complexes on EEG, highlighting the variable electrophysiological manifestations of CJD.
2. **Case 2** (58-year-old male) demonstrated a psychiatric-onset variant, initially misdiagnosed as late-onset psychosis. This presentation is particularly challenging as cognitive changes may be attributed to primary psychiatric disorders, delaying neurological evaluation. The progression from psychiatric symptoms to neurological manifestations occurred rapidly, consistent with the MM1 subtype confirmed at autopsy.
3. **Case 3** (42-year-old female) represented genetic CJD with the E200K mutation, presenting predominantly with cerebellar ataxia and a relatively prolonged disease course. This case emphasizes the importance of genetic testing in patients with family history of early-onset dementia or atypical presentations. The prolonged survival (14 months) compared to sporadic cases illustrates the variable disease progression in genetic forms.
4. **Case 4** (64-year-old male) illustrated the Heidenhain variant of CJD, characterized by predominant visual symptoms at onset. This rare presentation can be mistaken for stroke, posterior cortical atrophy, or other causes of cortical blindness. The preferential involvement of the occipital cortices on neuroimaging correlated with the visual manifestations, demonstrating the clinico-radiological relationship in this variant.
5. **Case 5** (55-year-old female) showcased the corticobasal syndrome variant of CJD with asymmetric motor symptoms, apraxia, and alien limb phenomenon. Initially misdiagnosed as multiple system atrophy, this case highlights how CJD can mimic other neurodegenerative disorders with extrapyramidal features. The asymmetric neuroimaging findings correlated with the lateralized clinical presentation, a characteristic feature of this variant.
6. **Case 6** (37-year-old male) represented iatrogenic CJD, related to historical exposure to contaminated human-derived growth hormone. This case is remarkable for its younger age of onset and relatively longer survival (12 months) compared to typical sporadic cases. It serves as an important reminder of the iatrogenic transmission risk in patients with relevant exposure history, even decades after exposure.

Diagnostic Approach

Across all cases, certain diagnostic principles emerged as crucial for timely recognition:

1. **Neuroimaging**: MRI findings varied from the classic cortical ribboning and basal ganglia hyperintensities (Cases 1 and 2) to more focal signal changes (Case 4). DWI and FLAIR sequences proved most sensitive for detecting the characteristic signal abnormalities. The PET-MR in Case 1 provided valuable information about metabolic changes, showing hypometabolism in regions corresponding to clinical deficits.
2. **CSF Biomarkers**: Elevated 14-3-3 protein was consistently observed across all cases, supporting its value as a diagnostic marker. The significantly elevated level in Case 1 (76,686 AU/ml) strongly supported the diagnosis despite the absence of classic EEG findings. RT-QuIC assay, with its high sensitivity and specificity, provided definitive evidence of pathological prion proteins in Cases 3 and 4.
3. **Electrophysiological Studies**: EEG patterns ranged from classic periodic sharp wave complexes (Case 2) to nonspecific diffuse slowing with sharp waves (Case 1). The evolution of EEG changes correlated with disease progression, though atypical patterns did not exclude the diagnosis when other supportive features were present.
4. **Genetic Testing**: Case 3 highlighted the importance of genetic analysis in patients with atypical presentations or family history of neurodegenerative disorders. The identification of the E200K mutation not only confirmed the diagnosis but also had implications for family members.

Disease Course and Prognosis

Disease duration varied significantly across cases, from 3 months in Cases 1 and 4 to 14 months in Case 3 (genetic CJD) and 12 months in Case 6 (iatrogenic CJD). This heterogeneity in survival time correlates with molecular subtypes, with MM1 typically having shorter courses compared to genetic variants or other subtypes. The first case in our series demonstrated a relatively rapid progression despite treatment attempts with intravenous immunoglobulin, underscoring the poor response to immunomodulatory therapies in confirmed CJD. The presence of early akinetic mutism in this case, along with the significant neuroimaging findings, likely contributed to the rapid decline.

Management Considerations

Management remained supportive across all cases, focusing on symptomatic relief and palliative care. Despite advances in diagnostic techniques, particularly RT-QuIC, effective disease-modifying treatments remain elusive. Therapeutic approaches primarily addressed symptom management, including:

1. Control of myoclonus and seizures
2. Management of behavioral and psychiatric symptoms
3. Prevention of complications from immobility
4. Appropriate nutritional support
5. Genetic counseling for familial cases

Conclusion

This case series illustrates the diverse clinical presentations and diagnostic challenges of Creutzfeldt-Jakob Disease. The varied initial symptoms, ranging from motor weakness to psychiatric manifestations to visual disturbances, highlight the importance of maintaining a high index of suspicion for CJD, particularly in rapidly progressive neurological syndromes.

The integration of clinical features, neuroimaging findings (especially MRI with DWI sequences), CSF biomarkers (14-3-3 protein and RT-QuIC), and electrophysiological studies enables more accurate and timely diagnosis. The characteristic findings in Case 1, including the distinctive EEG pattern and diffusion restriction on MRI, exemplify the importance of comprehensive diagnostic evaluation.

Early recognition is crucial for appropriate management, avoiding unnecessary interventions, and providing timely counseling to patients and families. We look forward to contributing further insights to this article in the future as we encounter additional cases of CJD.

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