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An unusually protracted case of sporadic Creutzfeldt-Jakob Disease highlighting diagnostic challenges in a low-resource setting: a case report

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Abstract

Creutzfeldt-Jakob Disease (CJD) is a rare, rapidly progressive neurodegenerative disorder characterized by cognitive decline, neuropsychiatric symptoms, and motor dysfunctions. Diagnosis is often challenging due to clinical overlaps with other neurodegenerative or psychiatric diseases. The usual survival period from diagnosis to death ranges from four to eight months. Sporadic CJD is the commonest sub type of CJD.

We report a 51-year-old woman who presented with a gradual decline in cognitive function, behavioural changes and involuntary movements of limbs over a nine-month period. As the disease progressed over two years, she developed a rapid decline of cognitive function, decreased conscious level, intractable myoclonus, and both pyramidal and extrapyramidal signs. The diagnosis of sporadic CJD was made, based on clinical features, electroencephalogram, and magnetic resonance imaging findings. Specific laboratory tests such as cerebrospinal fluid biomarkers were not available, and a delay of eighteen months occurred before the diagnosis was established. She had an unusually protracted course spanning over two years.

This case highlights the diagnostic challenges of CJD in resource-limited settings and the unusually prolonged disease course in this patient compared to the typical rapid progression seen in most cases.

Key words: sporadic Creutzfeldt-Jakob disease, prion diseases, cognitive dysfunction, resource-limited settings

Introduction

Creutzfeldt-Jakob Disease (CJD) is a rare and fatal prion disease, with a global incidence estimated at approximately 1 to 2 cases per million population per year.[1,2] While regional data on epidemiology of CJD is limited, around 20 to 30 cases have been reported in India over the past two decades, while only a few case reports have emerged from Sri Lanka.[3]

CJD is a neurodegenerative disease characterized by a progressive decline in cognitive function. It is invariably fatal and typically progresses through a sequence of clinical stages: the initial stage marked by psychological or behavioural symptoms, second stage involving cognitive decline and final stage showing features of akinetic mutism. The final stage may also involve tetraplegia, abnormal postural rigidity, contractures and myoclonus.[3] CJD is widely considered as the prototypical example of rapidly progressive dementia. The average survival following diagnosis ranges from 6 to 8 months, although rare cases of survival over several years have been reported.[4]

The diagnostic criteria for probable CJD include the presence of rapidly progressive dementia accompanied by at least two additional clinical features such as cerebellar ataxia, pyramidal or extrapyramidal motor signs, myoclonus, akinetic mutism or visual symptoms. In addition at least one supporting investigation must be positive, such as periodic sharp wave complexes on electroencephalogram (EEG), detection of 14-3-3 protein in CSF, detection of scrapie isoform of prion protein (PrP^{Sc}) by Real-Time Quaking-Induced Conversion (RT-QuIC), or characteristic hyperintensities on brain MRI diffusion-weighted-imaging

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regions, flair-attenuation-inversion-recovery (FLAIR) sequences in the caudate and putamen, as well as at least two cortical regions (temporal, parietal, or occipital).[4]

Several sub types of CJD have been identified, including sporadic CJD (sCJD), variant CJD, and iatrogenic CJD. Diagnosing sCJD is particularly challenging, due to limited awareness, low clinical suspicion and inadequate access to advanced diagnostic tools.

Case report

A 51-year-old woman presented with significant behavioural changes, involuntary limb movements and gradual but marked decline in cognitive function over a period of nine months. Initial symptoms included forgetfulness, incoherent speech, aggressive behaviour, and disturbing visual and auditory hallucinations which began just after an acute febrile illness. Her past medical history was unremarkable. She had received childhood immunization including the measles vaccine and had no history of international travel in the past or exposure to exotic animals.

At the initial presentation, her Glasgow Coma Score (GCS) was 12/15. Mini-Mental State Examination (MMSE) score was 10/30, indicating significant impairment in higher cognitive functions. The examination of the cranial nerves, upper and lower limbs was unremarkable. Laboratory investigations revealed a white blood cell count of 8.0×10^9/L, hemoglobin of 12.1 g/dL, and platelet count of 234×10^9/L. CRP was mildly elevated at 8 mg/dL and ESR was 13 mm/hour. Cerebrospinal fluid (CSF) analysis showed elevated protein levels at 50.1 mg/dL (35-45 mg/dL), glucose of 127mg/dL with a corresponding serum glucose of 167 mg/dL, and an absence of white or red blood cells. CSF cultures and polymerase chain reaction (PCR) tests for viral pathogens were negative.

EEG revealed generalized slowing and generalized delta wave activity suggestive of underlying encephalopathy or encephalitis. MRI demonstrated cortical ribboning (cortical diffusion restrictions) most notable in the right occipital and posterior parietal lobes – a pattern which may be seen in a range of conditions such as CJD, encephalitis, metabolic and toxic encephalopathy. Serological screening for autoimmune disorders, including antinuclear antibodies (ANA), thyroid peroxidase (TPO) antibodies, N-methyl-D-aspartate receptor (NMDA-R) antibodies, and onconeural panels, returned negative.

Autoimmune encephalitis, steroid-responsive encephalopathy associated with autoimmune thyroiditis (STREAT) and paraneoplastic encephalitis were considered in the differential diagnosis. However, contrast-enhanced CT (CECT) scan of the thorax, abdomen and pelvis along with a mammogram, showed no evidence of malignancy or ovarian masses. Other possibilities of chronic infections and paraneoplastic syndromes were reasonably excluded.

Although criteria for definite diagnosis of Autoimmune encephalitis were not fully met, a trial of immunotherapy with intravenous methyprednisolone (1 g daily), and intravenous immunoglobulin (20 g daily) was initiated and continued for five days.

As psychotic symptoms persisted two months after treatment with corticosteroids and immunoglobulin, the patient was started on rituximab, given the probable diagnosis of poorly resolving autoimmune encephalitis. Following the initiation of rituximab therapy, a subtle improvement in her behavior was noted. However, five to six months after commencement of rituximab she experienced a progressive deterioration in her functional abilities, with worsening of short-term and long-term memory. She eventually regressed to producing only simple vocalizations, exhibited episodes of emotional lability and myoclonic jerks. Due to worsening clinical status and concern for refractory autoimmune encephalitis, she was started on therapeutic plasma exchange. At this point she discontinued hospital follow up to pursue alternative healing through Ayurvedic medicine.

Approximately 5 months later she returned to the hospital, with a reduced level of consciousness. GCS was 10/15 (E-4, V-4, M-2), with occasional myoclonic jerks, signs of spasticity and cogwheel rigidity suggestive of both pyramidal and extrapyramidal tract involvement.

Due to the persistence and progression of symptoms, the investigations were repeated. CSF showed a marginally elevated protein level of 51.3 mg/dL (35-45 mg/dl) with no cells consistent with cyto-protein dissociation. EEG showed generalized slowing interspersed with periodic sharp wave complexes characteristic of CJD. MRI illustrated progressive cerebral atrophy, marked ventriculomegaly, white matter signal alterations, and 'cortical ribbon sign' along with diffusion restriction in the caudate and lentiform nuclei (Figure 1). A diagnosis of probable sporadic CJD was made based on the Centers for Disease Control and Prevention (CDC) criteria, given the combination of progressive dementia, neurological features, EEG and MRI findings, and the absence of an alternative diagnosis. Immune therapy was discontinued. There was an approximate lag period of one and a half years from the initial onset of symptoms to the establishment of a diagnosis of sporadic CJD.

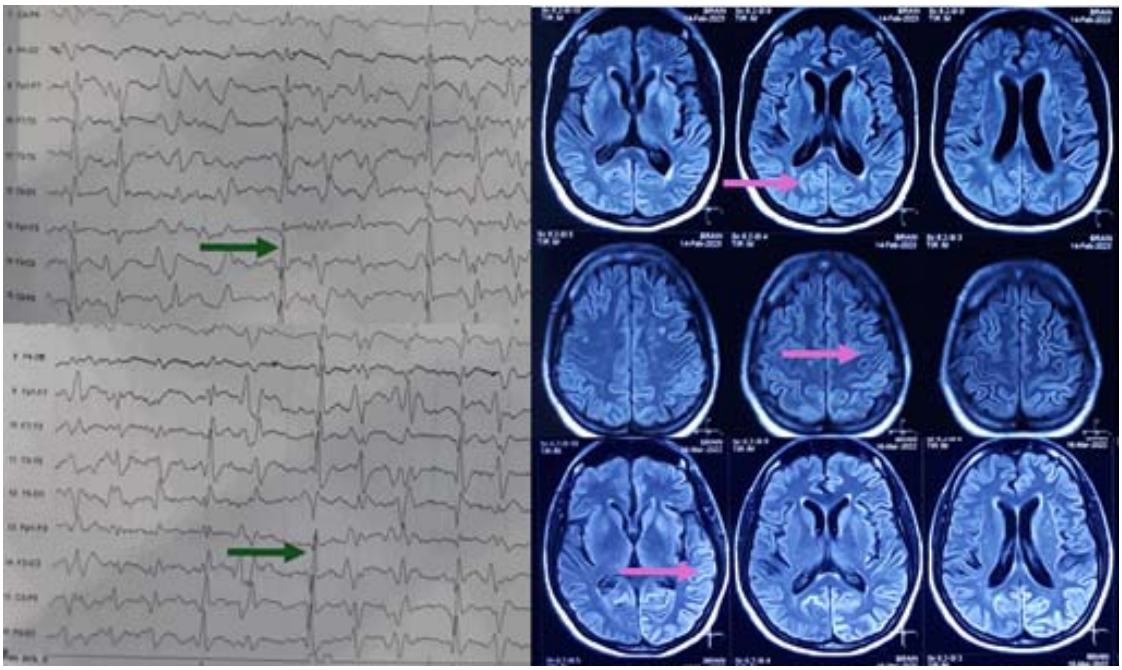

Figure 1. MRI showing evidence of cortical ribboning (Pink arrow) and Periodic sharp waves on the EEG (Green arrow).

Counseling sessions were held with her family, to discuss the challenges associated with the disease condition including limitation in diagnostic facilities, lack of effective treatment options, high morbidity, and poor prognosis and early mortality. Additionally, the family was informed about the unusually protracted course of her illness emphasizing the need for careful planning for long-term care. At the time of discharge, her GCS was 8 (E-4, V-2, M-2), and she was totally dependent on all activities of daily living. Arrangements were made to receive on-going care through long-term home nursing support (Figure 2).

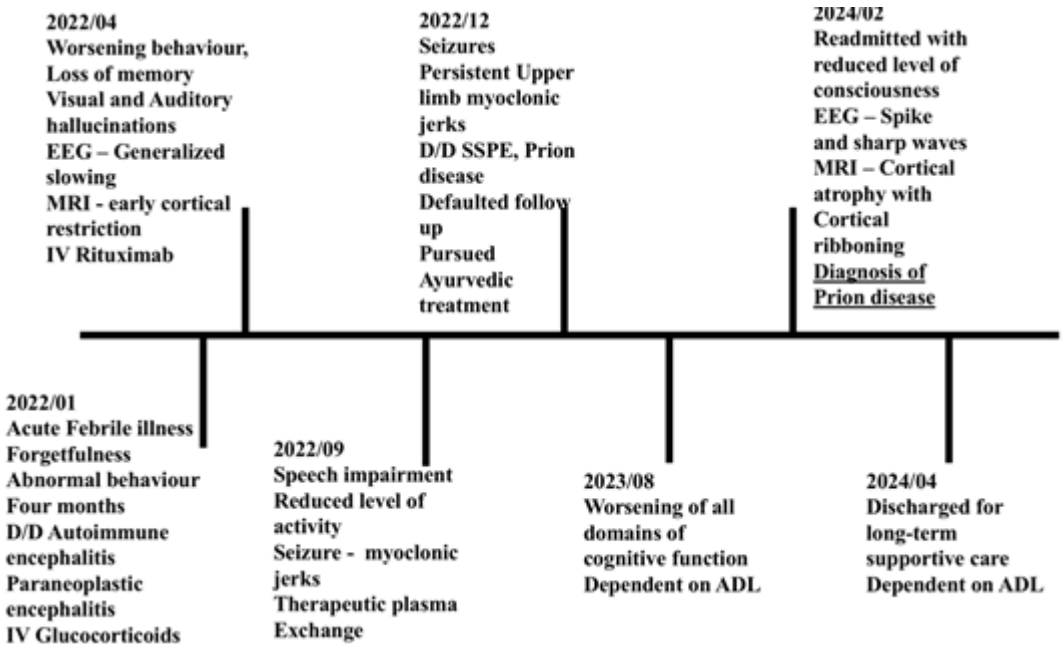

Figure 21. Timeline of the illness.

Discussion

Sporadic CJD is a rare disease that presents significant diagnostic challenges.[1] Most patients are diagnosed clinically with limited investigation support, and to be later confirmed by autopsy. This underscores the importance of maintaining a high index of clinical suspicion to facilitate early diagnosis.[3] Our patient with sCJD highlights the diagnostic challenges, including initial misdiagnoses and the unusually prolonged clinical course, as observed in this case.

Several conditions can invariably mimic CJD. These include autoimmune encephalitis, STREAT, subacute sclerosing panencephalitis (SSP), toxic, metabolic syndromes and paraneoplastic disorders.[2] As prompt intervention is critical in some of these conditions such as autoimmune encephalitis, many clinicians initiate a trial of immune therapy pending a definite diagnosis.[3] With an initial diagnosis of autoimmune encephalitis, and given that early treatment is associated with a favorable prognosis, immunotherapy was commenced in this patient.

Diagnosing prion diseases such as CJD is difficult due limited recognition, lack of advanced diagnostic facilities, and challenges in obtaining a brain biopsy samples for a histological diagnosis.[1] In our patient, the presence of myoclonic jerks with typical EEG and neuroimaging findings favoured a diagnosis of sporadic CJD. Characteristic MRI findings in CJD include high signal abnormalities in the cortical regions and striatum, known as cortical ribboning and EEG findings typically show distinct periodic sharp wave complexes. MRI images are helpful when characteristic findings such as cortical ribboning, pulvinar sign, and inverse hockey stick sign are present. EEG can evolve with progression of disease with initial background slowing and later periodic sharp wave complexes. In contrast, STREAT, the closest differential diagnosis, does not have specific MRI abnormalities.

Key diagnostic markers of CJD include elevated levels of total tau protein, 14-3-3 protein, and the prion protein fragment PrPres, which can be detected in CSF using real-time quaking-induced conversion (RTQuIC).[2] Despite recent advances, a definitive diagnosis of CJD still relies on postmortem pathological examination of the brain tissue, using pathological, immunohistochemical, and biochemical analyses to identify hallmark features of spongiform changes, astrogliosis, or deposits of proteinase-resistant PrP^{Sc}.

However, RT-QuIC assay is increasingly used as a highly sensitive (92%) and specific (100%) biomarker, also potentially replacing the need of brain biopsy.[6] Previously, other CSF markers such as 14-3-3 and tau protein were utilised in the diagnosis. Brain biopsy is rarely performed in living individuals due to ethical concerns, and lack of a specific treatment options despite a confirmed diagnosis.[7]

The diagnosis of CJD in our patient was based on the clinical criteria established by the CDC, which include progressive dementia, myoclonus, other neurological signs, akinetic mutism, and MRI/EEG findings despite the atypical, prolonged course of illness.[8] Sporadic CJD is typically fatal within months to a year after the diagnosis with survival beyond this period being rather unusual. A handful of cases of sCJD with unusually prolonged survival have been reported, with rare patients having survived up to 14 years.[4] Our patient had already survived more than two and a half years from the onset at the time of discharge and continues to live, highlighting the r unusually protracted course of illness in this case.

Currently, there is no definitive treatment for CJD, hence the management is primarily focused on palliative care. However, ongoing clinical trials are actively investigating potential therapies. Several early-stage trials are currently evaluating drugs such as quinacrine and prion protein monoclonal antibody (PRN100) therapy as targeted therapy for CJD.[9,10] Counseling of family members, assessing their understanding of the disease, and supporting them through the disease progression is pivotal in managing the patient. Accurate diagnosis is crucial for patient care and serves as the foundation for effective family counseling, especially in addressing hereditary risks linked to prion diseases and offers emotional closure for family members.[7]

Conclusion

CJD is a fatal neurodegenerative disease. In patients presenting with progressive cognitive decline, it is crucial to investigate potentially treatable causes, particularly when clinical features are atypical, such as an unusually prolonged course of illness. Maintaining a high index of suspicion of sCJD is essential, particularly in low-resource settings where access to advanced diagnostic investigations is limited. The clinical, radiological and EEG correlation supports the diagnosis of sCJD.

Author declaration

Conflict of interests

None.

Criteria for authorship

All the authors contributed to the diagnosis and management of the patient; drafting, critical revision and final approval of the manuscript.

Consent for publication

Informed written consent for publication was obtained from the husband and daughters of the patient.

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