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Case Series

Creutzfeldt Jakob Disease: An Incurable Malady

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Abstract: Creutzfeldt Jakob Disease is a rare and fatal neurodegenerative disorder characterized by rapidly worsening dementia, myoclonic jerks and akinetic mutism. It accounts for more than 90% of all human prion diseases. Over 90% of patients progress from normal function to death in under a year. There is no definitive treatment and it must be distinguished from other causes of rapidly progressive dementia such as viral encephalitis, autoimmune and paraneoplastic encephalitis which will respond to appropriate therapy. In the following 2 cases, we describe patients with presentation of rapidly progressive dementia which was finally diagnosed as Probable sporadic CJD. It is essential to make early diagnosis as it will allow patient and family to understand the course of disease and prognosis.

Keywords: Creutzfeldt Jakob Disease, Dementia, Myoclonic jerks, Akinetic mutism, Prion disease, Encephalitis.

INTRODUCTION

Creutzfeldt Jakob Disease is a rare and fatal neurodegenerative disorder characterized by rapidly progressive dementia, visual hallucinations, extrapyramidal/pyramidal signs and symptoms. It can manifest as sporadic (85%), familial (5-15%), variant/infectious (2-5%) and iatrogenic (<1%). The incidence of sporadic Creutzfeldt Jacob Disease is 1/million. It involves somatic mutation of PRNP (Prion Protein) gene and disease causing prion protein formation. The disease course follows rapid progression of cognitive and functional impairment with almost 90% of patients progressing to death in under a year. Diagnosis is often delayed in view of low suspicion. There is no definitive treatment and it is essential to evaluate for other causes of rapidly progressive dementia like viral encephalitis, autoimmune and paraneoplastic encephalitis which will respond to appropriate therapy. Therefore, early diagnosis will help patient and family to understand the disease course, prognosis, goals of care and relevant precautions to be undertaken.

Case 1:

A 60 year old female who was a known diabetic and hypertensive, presented to us with history of persistent irrelevant speech, impaired memory and inability to recognize family members. In a peripheral hospital she was found to have urosepsis and septic encephalopathy for which she was managed conservatively but because of worsening symptoms she was referred to us. MRI Brain showed diffusion restriction in right basal ganglia. Metabolic and infectious workup didn't yield any positive result. She was managed as right basal ganglia acute ischemic stroke. Over the next few days her sensorium deteriorated further and she started developing myoclonic jerks and rigidity. EEG showed periodic sharp wave complexes (Figure 1). CSF analysis was within normal limits. CSF autoimmune panel was also negative

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(Table 1). With persisting symptoms, MRI brain was repeated which showed diffusion restriction with corresponding FLAIR hyperintensity in right cerebral cortex and basal ganglia (Figure 2). This raised the suspicion of underlying probable prion disease. CSF analysis was repeated and evaluated for Protein 14-3-3 which was tested positive. She was diagnosed as probable Sporadic CJD according to CDC's diagnostic criteria for CJD. She was managed symptomatically and family counselled regarding the prognosis.

Table 1: CSF analysis of case 1 and case 2

CSF	**CASE 1**	**CASE 2**	
	SAMPLE 1	**SAMPLE 1**	**SAMPLE 2**
Appearance	Clear	Clear	Clear
Colour	Colourless	Colourless	Colourless
Total count	8	1	6
Differential count	lymphocytes	Polymorph-1	Polymorphs-2 Lymphocytes-4
Protein	38 mg/dl	58.9 mg/dl	94 mg/dl
Glucose	144 mg/dl	86 mg/dl	81 mg/dl
Gram stain and Culture	Negative	Negative	Negative
HSV PCR	-	Negative	-
Autoimmune panel	Negative	Negative	-
Protein 14-3-3	>2 ng/ml		>2ng/ml (normal-<1 ng/ml)

Table 2: CDC's Diagnostic Criteria for Creutzfeldt-Jakob Disease (CJD), 2018

1. **Sporadic CJD**

Definite:

- Diagnosed by standard neuropathological techniques; and/or immunocytochemically; and/or Western blot confirmed protease-resistant PrP; and /or presence of scrapie-associated fibrils.

Probable:

- Neuropsychiatric disorder plus positive RT-QuIC in cerebrospinal fluid (CSF) or other tissues

OR

- Rapidly progressive dementia; and at least two out of the following four clinical features:
    1. Myoclonus
    2. Visual or cerebellar signs
    3. Pyramidal/extrapyramidal signs
    4. Akinetic mutism

AND a positive result on at least one of the following laboratory tests

- a typical EEG (periodic sharp wave complexes) during an illness of any duration
- a positive 14-3-3 CSF assay in patients with a disease duration of less than 2 years
- High signal in caudate/putamen on magnetic resonance imaging (MRI) brain scan or at least two cortical regions (temporal, parietal, occipital) either on diffusion-weighted imaging (DWI) or fluid attenuated inversion recovery (FLAIR)

AND without routine investigations indicating an alternative diagnosis.

Possible:

- Progressive dementia; and at least two out of the following four clinical features:
    1. Myoclonus
    2. Visual or cerebellar signs
    3. Pyramidal/extrapyramidal signs
    4. Akinetic mutism

AND the absence of a positive result for any of the four tests above that would classify a case as "probable"
AND duration of illness less than two years
AND without routine investigations indicating an alternative diagnosis.

2. **Iatrogenic CJD**

Progressive cerebellar syndrome in a recipient of human cadaveric-derived pituitary hormone; or sporadic CJD with a recognized exposure risk, e.g., antecedent neurosurgery with dura mater implantation.

3. **Familial CJD**

Definite or probable CJD plus definite or probable CJD in a first degree relative; and/or Neuropsychiatric disorder plus disease-specific PrP gene mutation.

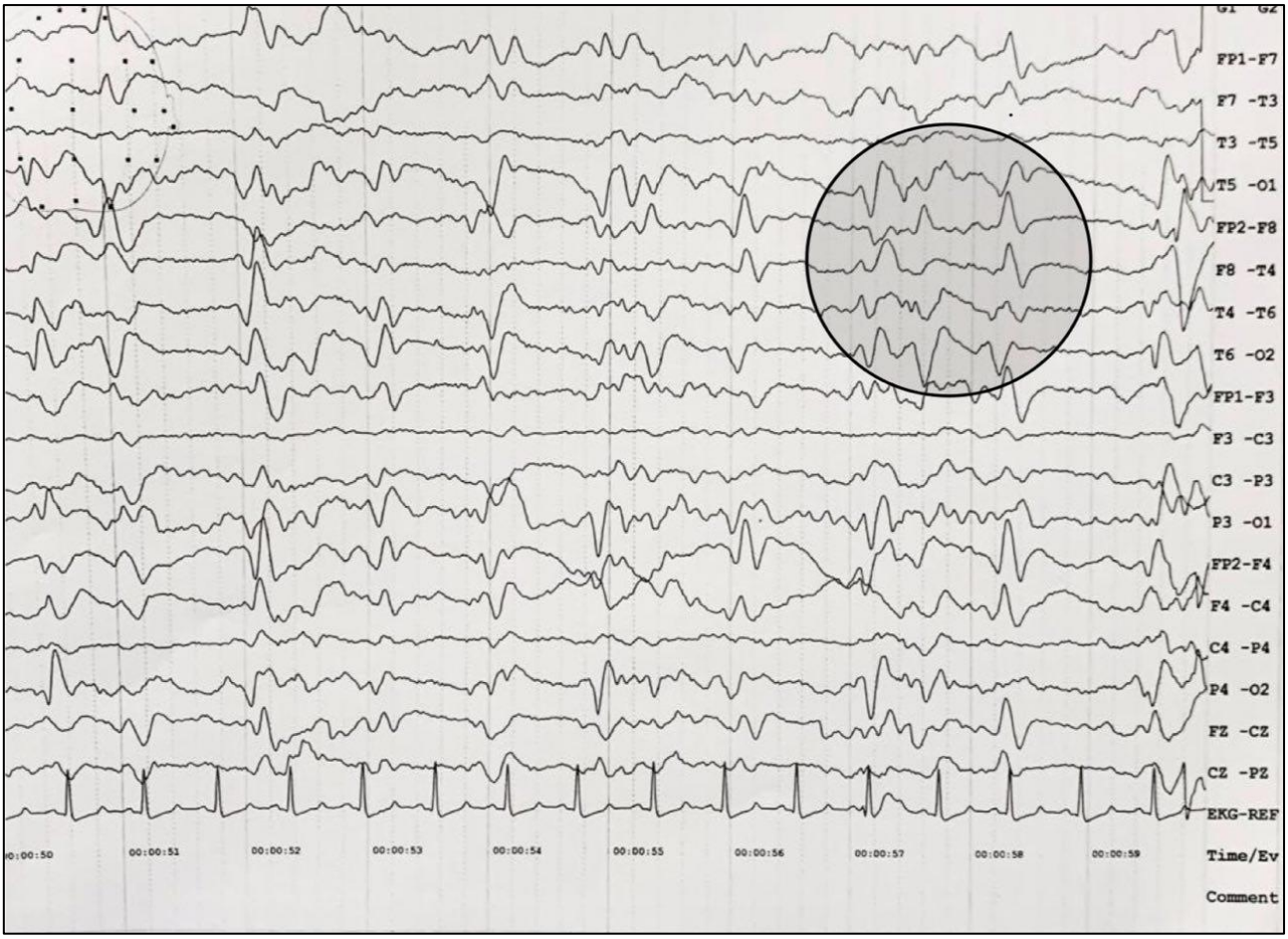

Figure 1: EEG showing Periodic Sharp Wave Complexes

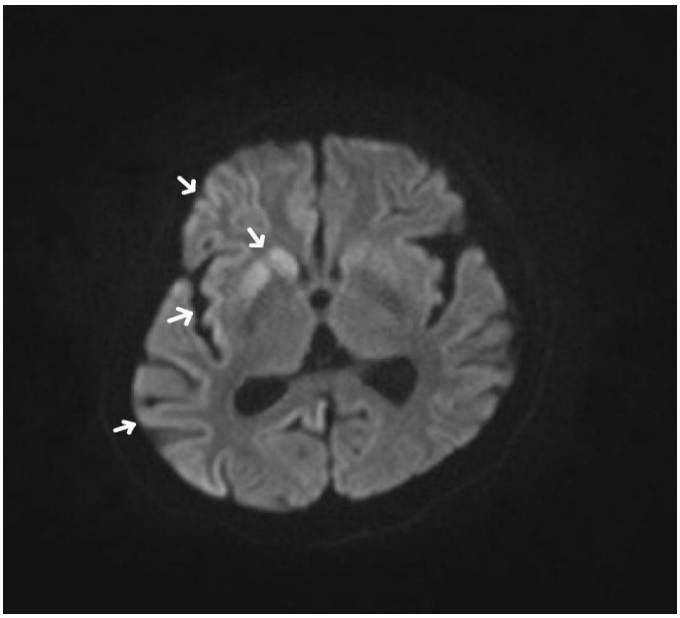

Figure 2: MRI brain showing diffuse areas of restriction on DWI in right cerebral cortex and basal ganglia

Case 2:

A 66 year old female patient was referred to us in view of progressive worsening of sensorium and right focal seizures (refractory status epilepticus). She was intubated and ventilated for airway protection. She was admitted there for progressive dementia and shortness of breath which progressed to Type II respiratory failure for which she was intubated and tracheostomized in view of prolonged weaning. She was a known case of bronchial asthma, rheumatoid arthritis and had a history of herpes zoster 4 months ago for which she was treated with acyclovir. There was also coexisting history of memory

impairment, behavioral abnormality and decrease in food intake for the past few months. On examination, GCS was E1VTM1 with right facial focal myoclonus. MRI brain showed diffuse areas of cortical restriction involving left cerebral hemisphere and basal ganglia (Figure 3). Serial EEG revealed left parieto temporal epileptiform spikes. CSF analysis showed slightly elevated protein. CSF gram stain, culture, HSV PCR, autoimmune and paraneoplastic panel was negative (Table 1). She was managed with antiepileptic drugs, antibiotics and other supportive therapy. Pseudomonas was isolated from lungs and antibiotics were rationalized. With GCS being the same and persisting seizure activity on antiepileptic medications and anaesthetic agents she also received IVIG for 5 days. MRI was repeated which showed similar cortical restriction of left hemisphere. Lumbar puncture was repeated and CSF analysis showed increase in protein when compared to the initial sample. CSF IGLON-5 autoantibodies was negative. With history suggesting rapid cognitive decline, cortical ribboning in DWI of MRI and investigations being negative for infectious, autoimmune and other common neurodegenerative disorders, we suspected CJD and CSF analysis was sent for protein 14-3-3 which was positive. Family was counselled with pertinence to Sporadic CJD and supportive treatment continued.

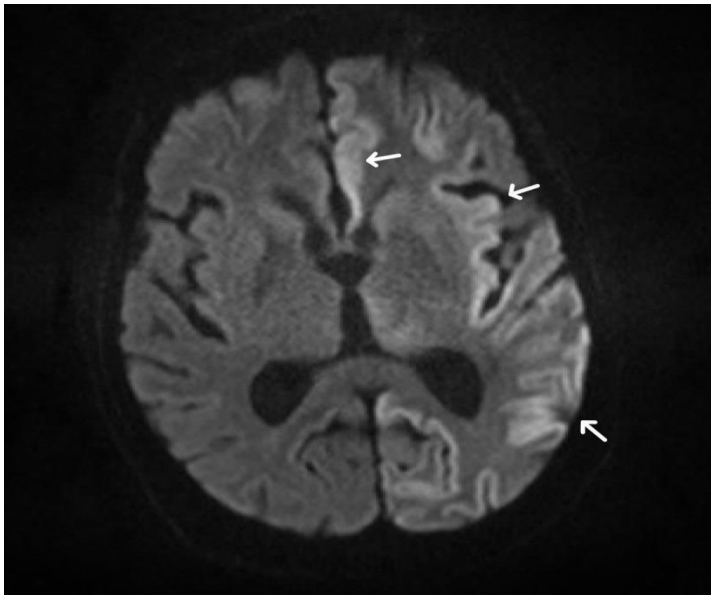

Figure 3: MRI brain showing diffuse areas of cortical restriction on DWI in left cerebral hemisphere and basal ganglia

CLINICAL DISCUSSION

Prion diseases are a group of degenerative disorders that includes CJD. CJD is the most common human spongiform encephalopathy that has a worldwide distribution. It is caused by abnormal misfolded prion protein PrP (Sc). The abnormal form propagates by recruiting the normal form and imposing its conformation [1]. This conversion is the fundamental event underlying all prion diseases. Sporadic CJD accounts for approximately 85% of all cases. Mean age of presentation is 55-75 years. Most patients present with deficits in higher mental function. Behavioral and psychiatric symptoms are very common. These will progress over weeks to a state of profound dementia and akinetic mutism. Extrapyramidal and pyramidal signs can also be present. Some uncommon features like seizures, hypoesthesia, motor neuron disease can also occur. Most of the patients develop myoclonus at various times throughout the illness. In two-third of the patients, EEG shows periodic bi or triphasic complexes [2]. Over 90% of the patients progress to death in under a year. MRI with DWI is the imaging procedure of choice. Diffusion restriction or FLAIR hyperintensity in basal ganglia (caudate or putamen) or in atleast 2 cortical regions (cortical ribboning) are considered highly sensitive and specific. CSF is always near normal but may show protein elevation and rarely mild pleocytosis. Both of our patients had rapidly progressive dementia. There was no significant past history/surgical or travel history/exposure to livestock. Both of our patients were investigated to exclude other treatable causes like metabolic, infective, autoimmune diseases and paraneoplastic. Our first patient was diagnosed initially as acute ischemic stroke of basal ganglia. Later patient developed myoclonus and rigidity during the course of illness. Repeat MRI brain showed diffusion restriction in right cerebral cortex and basal ganglia. EEG showed Periodic Sharp Wave Complexes. This raised the suspicion of probable CJD. CSF was sent for protein 14-3-3 which was positive and she was diagnosed as Probable Sporadic CJD by WHO CDC criteria, 2018 (Table 2).

Our second patient had unusual presentation of progressive dementia, focal seizures (refractory status)

and had a recent history of herpes zoster involving thoracic dermatomes. MRI brain with contrast showed diffuse areas of cortical restriction involving left cerebral hemisphere and basal ganglia. Diffuse cortical involvement of a single hemisphere is rare in viral encephalitis. Also sparing of basal ganglia is a salient feature of herpes encephalitis. Routine CSF analysis was otherwise normal except for slightly elevated protein. HSV PCR was also negative. Therefore, consideration for viral encephalitis was highly implausible in our second patient. Serial EEG revealed left parieto temporal epileptiform spikes. Seizures especially status epilepticus requiring benzodiazepines, is uncommon occurring only in <15% of all Sporadic CJD patients and may mask the utility of EEG in diagnosis [3]. With persistent seizure activity, cortical ribboning on MRI, Sporadic CJD was suspected and CSF was sent for protein 14-3-3 which was positive. Zerr *et al*., in his study concluded that detection of CSF protein 14-3-3 has sensitivity of 94% and specificity of 84% [4]. Y Shiga *et al*., in his study concluded that DWI in MRI can detect characteristic lesions with sensitivity and specificity of 92% and 93% respectively for the diagnosis of Sporadic CJD regardless of the presence of Periodic Sharp Wave Complexes or CSF protein 14-3-3 [5]. The presence of abnormality in DWI of MRI almost always exclude CJD mimics like Alzheimer's disease, Fronto temporal lobar degeneration, progressive supranuclear palsy [6]. Therefore, with history suggesting rapidly progressive dementia, focal myoclonus, characteristic lesions on MRI, presence of 14-3-3 protein and after excluding other differential diagnosis, our second patient was diagnosed with Sporadic CJD. More clinical signs could not be elicited as the patient had a GCS of E1VTM1.

CJD is still underreported throughout the world [7, 8]. This is due to low suspicion, lack of knowledge, variable presentations, presence of many conditions that mimics CJD and nonavailability of investigating modalities [9]. Also, definitive diagnosis can only be made by brain biopsy. There is no known effective therapy for preventing or treating CJD. Most patients progress to death in 6 to12 months. Therefore, it is essential to make early diagnosis that will allow patient and family to understand the course of disease, prognosis and to discuss various goals of care.

CONCLUSION

Eventhough there is no curative therapy for CJD, it is vital to consider it in differential diagnosis in patients presenting with rapidly progressing neuropsychiatric and behavioral symptoms such that timely diagnosis will help in educating patient and family about the disease course and prognosis. Psychological and social support should be ensured. Supportive and symptomatic treatment should be continued.

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