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CREUTZFELDT-JACOB DISEASE: A ONE IN A MILLION DISEASE

Medicine

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ABSTRACT

Sporadic Creutzfeldt-Jakob disease is a rare neurodegenerative disorder of unknown etiology that causes rapidly progressive dementia. This disease is uniformly fatal and most patients die within 12 months. Clinical findings include myoclonus, visual disturbances, and cerebellar and pyramidal/extrapyramidal signs in addition to rapidly progressive cognitive and functional impairment. These findings are all non-specific and it is often difficult and challenging to diagnose premortem because of low awareness and clinical suspicion. Here, we present the case of a 65 year old female with a 1.5 month history of rapidly progressive dementia. After a series of extensive diagnostic examinations, she was diagnosed with probable sporadic Creutzfeldt-Jacob Disease as per the Centres for Disease Control and Prevention (CDC) criteria, with key findings of rapidly progressive dementia, with visual disturbances along with hallucinations, extrapyramidal signs (cogwheel rigidity), and abnormal hyperintensity signals on diffusion-weighted MRI. Her symptoms progressively worsened and the patient was eventually lost on follow-up. The clinicians should be aware of the existence of such a disease in India and should have an index of suspicion for such disease when a patient presents with above spectrum of symptoms.

KEYWORDS

INTRODUCTION

Creutzfeldt-Jakob disease (CJD) is a progressive neurodegenerative disorder and one of the human prion diseases. It is uniformly fatal and the annual incidence rate is 1–2 per million worldwide. In addition to abnormal prion protein accumulation in the brain, CJD is characterized by spongiform change, neuronal loss, and gliosis.[1] It is often difficult and challenging to diagnose CJD premortem because of a low index of suspicion or a lack of knowledge of this rare disease.

The most common form of CJD is sporadic Creutzfeldt-Jakob disease (s CJD) (85%–90%), while the rest are familial, iatrogenic, and variant forms.[1] The mean onset age of sCJD is 65 years, and most of the cases are distributed within the age group between 60 and 80 years.[2] sCJD in patients aged less than 30 or over 80 years are rare. The etiology is still unknown and both genders are almost equally affected.

Case Vignette

HISTORY

A 65 year old female with no comorbidities presented with complaints of memory loss associated with giddiness in the form of rotatory sensation of self and surroundings causing unable to perform routine activities since 1.5 months, followed by visual hallucinations and altered behaviour since 15 days and seizures of myoclonic type over the past 4-5 days with 4-5 episodes per day associated with altered sensorium in the same period. There were no associated complaints of fever, rash, bowel/bladder incontinence.

Her past medical history was non-contributory. She had not had any past surgeries and her family history was insignificant for dementia or prion disease. She had no known allergies and her medications consisted of naturopathic remedies that she started after the onset of symptoms. She is a resident of Rajasthan, India, and has mixed diet.

EXAMINATION

- She was vitally stable with a blood pressure of 132/78 mmHg and a pulse rate of 86/min.
- **CNS Examination**
- Higher motor Functions: Her physical examination was significant for perseveration, anomic aphasia, alexia, agnosia and apraxia. She was unable to complete Mini-Mental State Examination (MMSE) and perform other complicated tasks.
- Cranial nerves: Her cranial nerves were grossly normal.
- Motor Examination: There was rigidity in all four limbs. Due to her altered sensorium, her power could not be assessed. Her reflexes were brisk in all 4 limbs but the Babinski reflexes were negative.
- Sensory and Cerebellum: Due to her altered sensorium, they could not be assessed.

LABORATORY INVESTIGATIONS

- Blood work was normal.
- CSF studies were performed.
- Cell counts, glucose and proteins were within normal limits.
- CSF viral and autoimmune panel were done which were also negative.

IMAGING AND EEG

- A Magnetic Resonance Imaging (MRI) of her brain showed significant global parenchymal loss, with restricted diffusion in bilateral basal ganglia, right fronto-temporo-parietal cortex, right perisylvian cortex and left frontal cortex. There were no infarcts, masses or extra-axial fluid collection.
- Electroencephalogram (EEG) showed periodic sharp wave complexes.

Treatment included benzodiazepines and anti-epileptics for her myoclonic jerks and rigidity along with prophylactic antibiotics and normal saline. We spent considerable time speaking with her and her family about the course of CJD and regarding the prognosis. She and her family elected to discontinue treatment and leave for home.

DISCUSSION

INTRODUCTION

Prion diseases are otherwise called as protein conformation disorders as it is clear that it is neither a virus nor a viroid which is responsible but transmissible proteinaceous particle labelled by Pruisner as “PRION” in 2004.[1] It can be genetic, sporadic, and spontaneous as well as infective making this disease a very unique one. PRNP is the gene coding PrP protein and located in the short arm of chromosome 20. Creutzfeldt in 1920 and Jakob in 1921 reported dementing illness with spongiform change.[1,2] The first report of transmissibility in human prion disease was reported by Gajdusek and group by transmitting

Kuru to Chimpanzees. The incubation period is very long, but the clinical course is very short. The infectious agent is a protease-resistant 27–30 kDa protein PrPsc, which is a conformer of PrPc. PrPsc has ability to bind to PrPc as a template for its own replication. The normal prion protein takes an infectious form by different folding spontaneously triggering a domino effect which misfolds prion protein throughout the brain based on the genetic variations of the individual. More than 50 prion protein mutations are reported in the inherited forms. This aggregates and cause proteinase resistance, decreased water solubility, and tendency to polymerize causing cell damage.[2] Based on characteristic brain pathology, they are grouped under spongiform encephalopathy affecting both humans and animals. The human forms are Kuru due to endocannibalism, familial fatal insomnia, Gerstmann–Straussler–Scheinker disease, and Creutzfeldt–Jakob disease (CJD). The animal forms are bovine spongiform encephalopathy, or mad cow disease, scrapie affecting sheep and goat, mink and feline encephalopathy, elk, deer forms, etc., Variant CJD is believed to be transmitted from bovine species due to dietary and environmental exposure currently seen only in the UK.[3,4]

EPIDEMIOLOGY

Estimated incidence is 1/million. The sporadic variety is most common. Familial is suspected on family history following a dominant pattern and confirmed by genetic testing. It forms 5–10% in the USA. About 405 cases of infectious CJD are reported. The biggest cluster related to contaminated Dural grafts in Japan, human growth hormone therapy in France, and 189 variant CJD described.[5,6,7] From Bengaluru over 30 years, 69 cases are reported by Shankar *et al*. from 1968 to 1997.[8] Ten cases are reported from Delhi and seven cases from Mumbai.[7]

CLINICAL FEATURES

Sporadic CJD manifests between 55 and 75 years with rapidly progressing dementia and behavioral symptoms in the form of delusions, hallucinations, delirium, depression, apathy, agitation, confusion, disorientation, memory loss, pyramidal, extrapyramidal, and cerebellar features with myoclonus. The myoclonus is typically generalized, nonepileptic and occurs at a frequency of 1 Hz. The myoclonus can be elicited by sound, light, and touch. Patients also have severe asthenia, anxiety, weight loss, altered sleep-wake cycle, and some patients show features of anterior horn cell involvement. Both sexes are equally affected. Ataxia and abnormalities of vision occur in some cases. The visual symptoms may be loss of acuity or distortion of seen objects. Headache, vertigo, and sensory symptoms can be seen in some patients. Patients can develop eye signs in the form of paralysis of convergence and upgaze. The disease progresses very rapidly on a week to week basis resulting in mute state, contractures and death occurs in 1–3 years. Very rarely patients have survived up to 10 years. Familial ones have a variety of phenotypes and given different names. Variant forms affect younger people and have a slightly less catastrophic course.

DIAGNOSIS

It is based on clinical features, course, and electroencephalogram (EEG) changes which are classical in the sporadic ones and not present in variant forms. EEG shows typically 1/s spikes or mid-positive triphasic waves which are symmetrical and synchronous with a normal background in the early stages and background becomes altered as disease advances. Magnetic resonance imaging (MRI) is mandatory criteria for the diagnosis of probable CJD. Diffusion-weighted images have a sensitivity of up to 100%. This is believed to be due the decrease in the isotropic water diffusibility which corresponds to spongiform changes and nerve cell loss as well as accumulation of the pathological form of PrPSc. The typical features are cortical ribboning, signal intensity changes in the thalamus which are bilateral and symmetrical and more often seen in variant CJD but can also be seen in sporadic CJD and called as "Pulvinar sign." Among other basal ganglia structures, caudate is affected in 85–90% of patients and Putamen in 84% of the patients and only about 7% show globus pallidus changes. The combination of caudate and putaminal involvement is seen in 67% and called as "inverted Hockey stick sign."[9] Tonsillar biopsy is helpful in variant form. Detection of 14-3-3 protein in the cerebrospinal fluid (CSF) improves the diagnostic accuracy by 98% in cases of sporadic CJD.

2010 CDC CRITERIA FOR SPORADIC CJD

Definite Detection of protease-resistant Prion Protein or scrapie-associated fibrils by neuro pathology, immunochemical technique, and/or Western blot. Probable No findings indicating alternative diagnoses AND progressive dementia with at least 2 of (i)–(iv) AND at least one of (a)–(c).PossibleNo findings indicating alternative diagnoses AND progressive dementia with duration of less than 2 years AND with at least 2 of (i)–(iv) AND at least one of (a)–©.

(I) Myoclonus
(ii) Visual or cerebellar problems
(iii) Pyramidal or extrapyramidal features
(iv) Akinetic mutism
(a) Periodic sharp wave complexes on electroencephalography
(b) Positive 14-3-3 protein in the cerebrospinal fluid with a disease duration of less than 2 years
(c) High signal abnormalities in caudate nucleus and/or putamen on diffusion-weighted imaging (DWI) or fluid attenuated inversion recovery (FLAIR) MRI

CONCLUSION

Although sCJD is incurable and there is no generally accepted treatment currently available, it is important to make an early and accurate diagnosis because some of the differential diagnoses such as viral or bacterial encephalitis are treatable. Early diagnosis will allow patients and their families to prepare for the expected disease course, consider goals of care, and possibly have palliative care consultation if desired. Treatment is usually symptomatic and extensive research is being done in this area. This patient and her family had the opportunity to discuss this disease thoroughly and had the freedom to choose an alternative, unproven treatment.

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