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Case Report

Creutzfeldt-Jakob Disease: A Case Report from a Tertiary Health Care Centre in Bangladesh

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Abstract

Creutzfeldt-Jakob disease (CJD) is an extremely lethal and rapidly progressive spongiform encephalopathy caused by abnormal form of prion protein. It occurs worldwide with an estimated annual incidence about 1−2 cases per million populations. Several forms of the disease have been described−the most common is the sporadic type. Clinical features include briskly progressive dementia, myoclonus, visual or cerebellar signs, and pyramidal/extra-pyramidal signs. Diagnosis of CJD is usually challenging. Combining clinical features with laboratory parameters, electroencephalogram (EEG), and magnetic resonance imaging (MRI) of the brain expedites the diagnosis. It has no definitive treatment; only symptomatic and supportive managements are provided to the patients. Affected patients generally die within 1 year of the onset of illness. We report a 40-year-old lady who presented with 2 months' history of rapidly progressive cognitive decline, vertigo and blurring of vision. Her diagnosis was made by classic findings on EEG, MRI of the brain along with clinical features and laboratory parameters. In spite of continuous supportive treatment, she died after 3 months from the onset of her illness. Early diagnosis, extensive research activities regarding prevention and treatment, raising social awareness and educating health care professionals about the disease might improve the current unsatisfying scenario of CJD.

Key words*: Creutzfeldt-Jakob disease (CJD); Neurodegenerative disease; Human prion disease*

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Introduction

Transmissible spongiform encephalopathies (TSEs) are a group of lethal but infrequent progressive neurodegenerative brain disorders caused by abnormal form of prion protein which affects both humans and animals.[1] Creutzfeldt-Jakob Disease (CJD) also known as sub-acute spongiform encephalopathy is one of the human forms of TSEs characterized by progressive dementia, myoclonus, cerebellar, pyramidal/extrapyramidal, visual symptoms and psychiatric manifestations.[1,2] The name Creutzfeldt-Jakob disease was introduced by Walther Spielmeyer in 1922, after its discoverer German neuro-pathologist Hans Gerhardt Creutzfeldt and Alfons Maria Jakob.[3] The annual incidence rate is approximately 1−2 per million populations worldwide.[4] It occurs most frequently in patients between 40−75 years of age; on

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an average, symptoms manifest between 60–65 years of age.[5]

CJD is classified into four subtypes−sporadic CJD (85%), familial CJD (10−15%), iatrogenic CJD (<1%) and variant CJD (1%).[6,7] Sporadic CJD (sCJD) is caused by the conversion of normal form of prion protein (PrP^{c}*) into an abnormal form of prion protein (PrP^{Sc}**) which accumulates throughout the brain resulting in spongiform neurodegeneration.[2] The clinical features of sCJD include hastily progressive memory loss, behavioral abnormalities such as restlessness, irritability, delirium, hallucination, apathy and confusional spells followed by pyramidal/extrapyramidal, cerebellar symptoms including myoclonus, ocular symptoms such as blurring of vision.[8,9] About 70% of the patients usually die within one year of onset of the disease.[10] Familial CJD (fCJD) is autosomal dominant, secondary to the mutation of the prion protein gene.[7] The symptoms of fCJD are similar to sCJD[7] and usually manifest in people at their early 50s.[5] Variant CJD is caused by consuming meat products contaminated with prion resulting in the formation of cerebral prion plaques in the brain. It manifests relatively in young patients with early psychiatric features, behavioural and or sensory symptoms, followed by jerking movement, cerebellar symptoms, and dementia as the disease progresses.[11] Iatrogenic CJD is an acquired form caused by contamination of tissue from infected person usually as a result of medical procedures, e.g., corneal/meningeal transplant, blood transfusion, use of contaminated neurosurgical instruments etc.[5,7,12]

WHO and MRI-CJD consortium diagnostic criteria for CJD provides an invaluable diagnostic guideline to any physician unacquainted with the disease.[12] Detailed medical histories, clinical features, laboratory parameters, MRI, EEG, blood profile, and cerebrospinal fluid (CSF) analysis are instigated to provide a definitive, probable or possible diagnosis. Brain biopsy is considered the gold standard.[7] There is no cure of CJD, only supportive managements are carried out to alleviate patient's symptoms.[5,13]

*PrPc: Cellular form of prion protein. **PrPSc- Proteinaceous infectious particle, in which Sc stands for scrapie, the prion disease of sheep and goats, which has a primarily beta-pleated sheet structure.

Case report

A 40-year-old lady was admitted into the Intensive Care Unit of Enam Medical College Hospital with the complaints of acute confusional state and inability to speak for 3 days. She was completely well until 2 months ago when she was noticed by family members to be irritable, stressful, always fearful and excessively worried. Initially she was taken to a local hospital and was treated as a case of schizophrenia as no other brain lesions were identified on CT scan. Afterwards, she developed visual blurring and vertigo. She had no history of headache, fever, vomiting or convulsion. She was non-smoker, non-alcoholic with no significant past medical, surgical or psychiatric history. There was no family history of dementia or other neurological disorders. A month later she became mute and disoriented for which she was admitted into a neuroscience tertiary care hospital. On examination, her Glasgow Coma Scale (GCS) was 10 out of 15, vitals were normal and plantar response was flexor on both sides.

On initial laboratory evaluation she had hemoglobin 11 gm/dL, ESR 62 mm in 1st hour, total leukocyte counts 12000 cells/cumm. Liver, renal and lipid profile were normal. Serum electrolytes showed hyponatraemia followed by hypokalaemia. Serum calcium was within normal limit. Microscopic and culture examination of urine showed pus cells 20−22/HPF with growth of Enterococcus faecium. However, blood culture did not show any growth of pathogenic bacteria. Her C-reactive protein was high, blood sugar and HbA1c was normal. Chest radiograph, electrocardiogram and abdomino-pelvic ultrasound were unremarkable.

Thyroid profile was normal including anti-thyroid peroxidase (anti-TPO) antibodies. Serum was negative for human immunodeficiency virus (HIV), veneral disease research laboratory test (VDRL), and hepatitis B surface antigen (HBsAg). Serum was also negative for anti-nuclear antibody (ANA), perinuclear

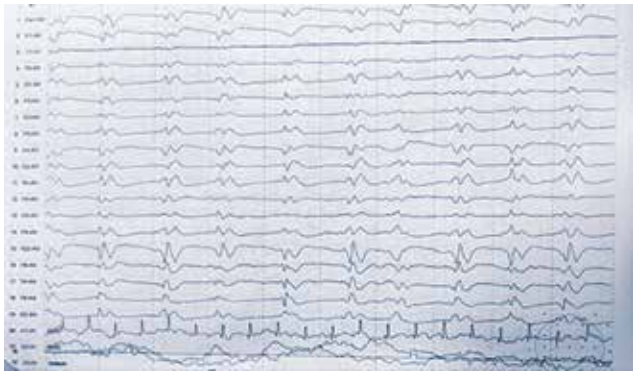

Fig 1. EEG showing generalized periodic sharp wave complexes.

anti-neutrophil cytoplasmic antibodies (pANCA) and cytoplasmic anti-neutrophil cytoplasmic antibodies (cANCA).

Initial MRI of brain findings was unremarkable. However, EEG showed presence of occasional sharp waves with triphasic morphology in both temporal regions at times showing some pseudoperiodic pattern. In appropriate clinical context this pattern is suggestive of slow viral infection (CJD), metabolic and toxic/hypoxic encephalopathies. After 20 days, a second EEG revealed presence of periodic sharp wave complexes with triphasic morphology at an interval of 1−2 sec (Fig 1). The EEG finding along with clinical scenario was highly suggestive of CJD.

The next day after doing EEG patient was admitted into the intensive care unit of our hospital with altered level of consciousness and mute for 3 days. On examination, she was found hypotensive, GCS score was 10 out of 15. SPO2 was 94% with 5L oxygen, plantar reflexes were diminished on both sides. On auscultation both lungs were clear, capillary blood glucose was normal. Naso-gastric feeding and supportive treatment was started with levetracetam, anti-convulsant, intravenous steroids, antiviral, antibiotics, anti-ulcerant, anti-emetics and multivitamins. CSF was sent for analysis which revealed high protein and low glucose level. A second MRI was strongly suggestive of CJD, evidenced by almost symmetrical restricted diffusion on Diffusion-

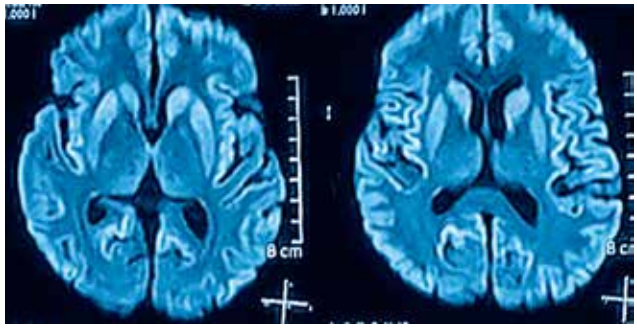

Fig 2. MRI of the brain revealing symmetrical restricted diffusion on DWI at bilateral caudate nuclei, bilateral putamen, frontal, parietal, occipital and temporal cortices.

Weighted Imaging (DWI) at bilateral caudate nuclei, bilateral putamen, bilateral dorso-medial thalami (hockey stick sign), bilateral frontal, parietal, occipital and temporal cortices (cortical ribbon sign) (Fig 2).

Along with other supportive management, all limbs physiotherapy and chest physiotherapy was also going on. As she was recovering, she was shifted to the neuromedicine ward on her family's request. However, 2 days later she was again shifted back to the ICU due to respiratory distress with hypotension. So, she was put on mechanical ventilation on control mode with FiO_2 90% and inotropes were started. However, her condition was further deteriorating and she developed pneumonia which was confirmed by chest radiograph. In spite of providing all supportive management and mechanical ventilation for 9 days, her condition did not improve and finally she expired after 3 months from the onset of illness.

Discussion

CJD is extremely rare and lethal spongiform encephalopathy which imposes diagnostic challenges due to the resemblance of its symptoms with other neurodegenerative disorders. Generally, the diagnosis is made by the combination of clinical, serological data, MRI, EEG, CSF analysis and brain biopsy which is confirmatory.[14] Absence of any significant features in EEG and MRI makes the diagnosis more perplexing. According to the CDC diagnostic

criteria for CJD, our patient fulfills the criteria for the 'probable' sCJD. She presented at the age of 40 years which is closer to the patients presented by Lahiri et al[9] (42 years) and Pasha et al[6] (48 years). Nevertheless, her age was less than the cases presented by Fraga et al[11] (61 years), Kwon et al[14] (76 years), Rahman et al[15] (67 years). Clinically, our patient manifested with restlessness, irritability, fearfulness and anxiety followed by myoclonus, blurring of vision and disorientation which is comparable to the symptoms presented by Ojha et al[16]. However, it is slightly different from the case presented by McWhrter[17] who initially presented with visual disturbance, neck pain, headache, lightheadedness followed by shortness of breath, dizziness and palpitation.

The classic MRI features in sCJD includes "hockey stick sign" which refers to the hyper intense signals in the cortical regions, basal ganglia and thalamus on DWI, T2, and FLAIR sequences and "cortical ribbon sign" which is characterized by persistent restricted diffusion as a ribbon-like signal hyperintensity of cerebral cortical gyri on DWI.[18] Therefore, MRI of the brain with DWI and FLAIR sequences should be performed for all patients with suspected CJD. We found both the signs on MRI of our patient (Fig 2) whereas Raut et al[19] found only 'hockey stick sign' and McWhorter[17] and Esteak et al[20] found 'cortical ribbon signs' for their cases respectively.

In general, EEG demonstrates distinctive changes at different stages of CJD. In early stage, it reveals diffuse slowing and frontal rhythmic delta activity whereas in the middle stage it shows typical periodic sharp-wave complexes (PSWC) with triphasic morphology and active coma traces in late stage.[21] Our patient exhibited the classic EEG features of the middle stage of the disease (Fig 1) similar to the cases presented by Known et al[14], McWhrter[17] and Easteak et al[20] in addition to the MRI and EEG findings, elevated amounts of 14-3-3 proteins in CSF is a marker of CJD.[16] For our patient although we analyzed CSF which showed high protein with low glucose levels, we could not exclude the presence of 14-3-3 protein due to lack of facilities. Duration of survival of CJD varies from patient to patient. Most patients usually die within one year of onset.[10,11] Our patient survived 3 months from the onset of her clinical manifestations which is similar to the case reported by McWhorter[17]. Nonetheless, the cases presented by Kwon et al[14] and Ojha et al[16] survived only for one month whereas Kojima et al[8] reported 7 months survival of their case.

Conclusion

CJD must be considered as a possible diagnosis for patients with rapidly progressive dementia without any evidence of infections or vascular disease. Accurate and timely diagnosis is crucial as some of the differential diagnoses, e.g., viral encephalitis is treatable. Early diagnosis also provides families time to prepare for the anticipated disease outcome. In addition, extensive research activities related to prevention and treatment of CJD is also essential. Further, we need to raise awareness of the disease and educate health care professionals to provide families with social and informational support.

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