

Case Report

Creutzfeldt-Jacob Disease: Cerebrospinal Fluid Protein 14-3-3 in a Saudi Woman

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ABSTRACT

Creutzfeldt-Jacob disease (CJD) is a rare degenerative disease of the brain associated with spongiform changes. It is related to prion infection or mutation in the prion gene. We present a Saudi lady with clinical,

electroneurophysiologic, and CSF findings consistent with sporadic form of CJD. We discuss the importance of CSF protein 14-3-3 in the pre-mortum diagnosis of CJD.

KEYWORDS: Creutzfeldt- Jacob disease, prion, protein 14-3-3

INTRODUCTION

Creutzfeldt-Jacob Disease (CJD) is the most common of a rare group of diseases known as spongiform encephalopathies. The worldwide incidence of the sporadic form of CJD is approximated to be one in a million. It has no special racial or geographic predilection. The new variant CJD has excited the medical and the public media due to its relationship to the consumption of beef products. The iatrogenic form is related to specific risk factors involving direct exposure to nervous tissue during surgical or hormonal therapy. We describe the clinical course of a unique patient who presented with a relatively rapid encephalopathy (rapidly dementing illness, myoclonus and visual disturbance) that led to the death of the patient over a one year period. We also discuss some important new aspects of the current classification and the diagnostic approach.

CASE PRESENTATION

A 55-year-old Saudi diabetic lady was referred for evaluation of an acute confusional state with abnormal behavior and impaired vision of 2 weeks' duration. There was no history of fever, headaches or convulsions. There was no family history of a similar condition, the patient never left her village nor ate any western type of food. She did not receive hormonal therapy or undergo any neurosurgical procedure. Her parents were not related.

Physical examination showed an irritable lady with occasional diffuse myoclonic jerks. The vital signs were normal with no signs of meningeal irritation. She was conscious, responding to verbal stimuli but irritable and disoriented. Her visual acuity could not be assessed. Other cranial nerves

were normal. She moved all limbs, the reflexes were hyperactive, there was no clonus and the plantar reflexes were flexor. She had truncal ataxia.

Routine, serologic and microbiologic laboratory studies were normal. Initial and follow up CSF studies were normal including cultures for TB, fungal and HSV PCR. Brain MRI (Fig. 1a) was normal. An EEG showed diffuse delta slowing with brief bursts of sharp wave discharge, consistent with encephalopathy.

The clinical impression was an infectious or a metabolic encephalopathy. The next day she became febrile. She showed evidence of progressive deterioration with impaired consciousness, myoclonic jerking with startle myoclonus and generalized seizures. There was no response to antibiotics, antiviral, anti-TB or IV pulse steroid therapy. She had profuse sweating, became progressively emaciated, more rigid and less responsive. Repeated EEG showed generalized periodic discharges of 1Hz frequency on a very slow base (Fig. 2), that was clinically associated with myoclonic jerks. Unfortunately no simultaneous surface electromyography was recorded.

The possibility of spongiform encephalopathy i.e. CJD was considered. There was a reluctance to do a brain biopsy. Repeated CSF examination done 2 months after her admission was strongly positive for protein 14-3-3 (Mayo clinic, Rochester, MN, USA). Clinical diagnosis of sporadic CJD was made.

The patient deteriorated and lapsed into a vegetative like state with generalized rigidity, opisthotonus, stimulus induced myoclonus and recurrent profuse sweating. Follow up EEG showed diffuse slowing with disappearance of the periodic discharges. Brain MRI done 1 year from the onset

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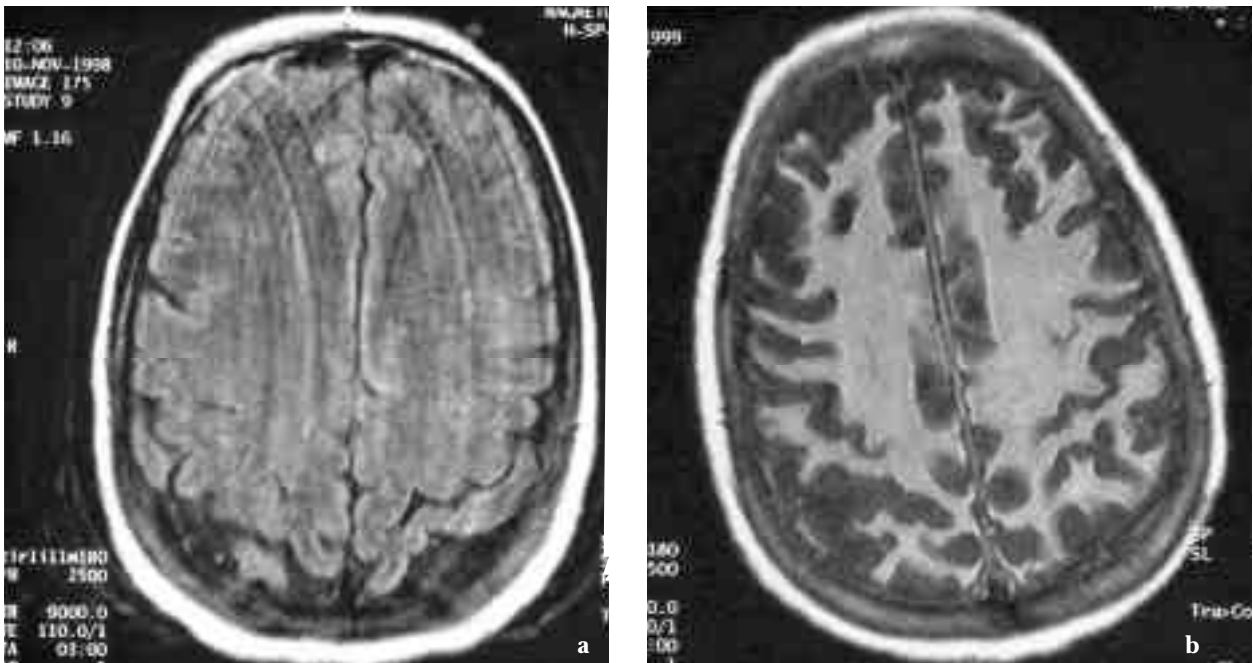


Fig. 1: a, b: Flair sequence brain MRI, TR 9000, TE 110 TA 3 at the same level using GE 1.5 Tesla scanner showing normal brain MRI on admission (1a) and severe cortical atrophy 1 year later (1b)



Fig. 2: EEG showing bilateral periodic sharp waves of 1 Hz with slow background.

(Fig. 1b) showed extensive cortical atrophy and no abnormal signal in the basal ganglia. She died and no autopsy was done.

DISCUSSION

Spongiform encephalopathies (SE) are a group of rare diseases that are usually sporadic but can be familial or iatrogenic. Though rare, they are exciting due to the unique and still poorly understood, way of transmission, pathogenesis and possible relationship to other more common degenerative diseases like Alzheimer's Disease. The recent description of the new variant CJD and its relationship to bovine spongiform encephalopathy (BSE), or mad cow disease made these diseases a major medical, public, economic and political issue. The human SE are Kuru, CDJ (sporadic, iatrogenic,

new variant, familial), Gertsmann-Straussler-Scheinker syndrome (SSG), fatal familial insomnia FFI and fatal sporadic insomnia FSI.

The prion theory is currently the best available explanation for these diseases. Prion is considered to be the infectious or transmissible agent responsible for these diseases. The normal cell membrane contains a normal sialoglycoprotein that is encoded for by short arm of chromosome 20 and is named PrPC (cellular prion). The infected cells contain an isoform of the same protein called PrPSc (scrapie prion). The pathologic isoform differs from the normal one in three important ways: being digested partly by proteinase K yielding PrP 27-30, appearing only during infection and by polymerizing into amyloid rods rather than solubilization. DeArmond et al demonstrated that PrPSc has a major role in prion diseases and is not merely a pathologic product of infection^[1]. The function of the normal isoform is not known. Its presence is a prerequisite for infection to occur as transgenic mice deprived of the gene coding for PrPC were resistant to infection though they looked normal^[2]. The need for another protein, a chaperone, to facilitate transformation of PrPC to PrPSc has been raised^[3]. The different mechanisms of acquiring the disease include: ritualistic cannibalism, prion contaminating human growth hormone, dura and cornea, germline mutations, somatic mutations or spontaneous conversion of PrPC into PrPSc. Different mutations have been described and certain genotypes are more susceptible than others^[4].

CJD is the most common human SE. Its incidence is around 1 in a million population and affects all ethnic groups and geographic areas^[5] perhaps with the exception of Libyan Jews who are at higher risk^[6]. It can be idiopathic (75-80%), inherited mostly autosomal dominant (10%-15%), or iatrogenic (10%). The histopathologic markers of this entity are spongiform degeneration (spongiform change and status spongiosus), neuronal loss and astrocytic gliosis. Only spongiform degeneration has some specificity. Immunohistochemistry with antibodies against prion protein is preferable in all suspected cases of CJD and is mandatory whenever a routine histological workup is inconclusive^[7]. Clinical presentation is a relentless course of rapidly progressive dementia, myoclonus and periodic EEG discharges in middle age-elderly patients (80% between 50-70 years). Pool analysis of the large series reflects the experience of the USA^[8], United Kingdom^[9] and France^[10]. Sporadic CJD showed that later in the course of the disease, memory loss, behavioral change, aphasia and agnosia occurred in 100% of patients. The following signs and symptoms, along with their percentages, were noted: myoclonus in > 80%, cerebellar signs in >50%, pyramidal signs in > 50%, extrapyramidal signs in > 50%, periodic EEG discharges in 60% (USA), visual disturbance in 20%, oculomotor signs each in 20% and headache in 18% (USA), lower motor neuron signs, vestibular dysfunction, seizures, sensory deficit and autonomic abnormalities each occurred in < 20%. Patients usually die in 6-12 months. Until recently the diagnosis was clinical. Only brain biopsy or autopsy was definitive in diagnosis. The use of the EEG for clinical diagnosis was helpful. The periodic sharp wave complexes (PSWCs) on a slow background was neither sensitive nor specific. In a prospective blinded EEG analysis sensitivity and specificity were 67% and 86% respectively, with an excellent interobserver reliability ($\kappa=0.95$)^[11].

The discovery of two 30-kd proteins by two-dimensional electrophoresis, designated protein 130 and 131, correlated well with the diagnosis of CJD. These proteins were found in all 21 CJD patients, but also in 5 of 10 patients with herpetic encephalitis. They were not present in any patient with Alzheimer's Disease, Huntington's Disease, multi-infarct dementia, Parkinsonism dementia of Guam or the specific dementia of the acquired immune deficiency syndrome^[12]. Detection of CSF protein 130 and 131 was not useful for routine testing. Hsich et al^[13] showed the two proteins to be identical to the 14-3-3 protein. This protein 14-3-3 has sensitivity and specificity of 96% and 99%

respectively by immunoassay in biopsy proven cases. In animals the sensitivity and specificity were 87% and 99% respectively. The clinical setting must be appropriate to consider CJD. The test is not recommended for routine evaluation of dementia. It gave a false positive result in patients with recent cerebral infarction and herpetic meningoencephalitis. The test can occasionally be positive in subarachnoid hemorrhage, Rett Syndrome^[14], astrocytoma, delirium, Down's syndrome, tuberous sclerosis, Hashimoto encephalitis, cerebral lymphoma^[15], intracerebral metastasis of a bronchial carcinoma, hypoxic brain injury, metabolic encephalopathy and progressive dementia of unknown type^[16]. Such entities are not considered in the differential diagnosis of CJD or can be appropriately excluded by other diagnostic tests. Protein 14-3-3 is found in the CSF of patients with E200K CJD but not in healthy carriers of the same mutation^[15]. It is a normal component of the nervous tissue and is involved in signal transduction. One recent study showed positive predictive value of 94.7% and negative predictive value of 92.4%, and being positive in 5/10 patients with familial forms of spongiform encephalopathy^[16]. Another study showed sensitivity and specificity of 97% and 87% respectively^[14]. Looking at both PSWCs and protein 14-3-3 in the CSF, Zerr et al showed that PSWCs has a sensitivity and specificity of 66% and 74%, while protein 14-3-3 has 94% and 84% respectively. Combining both would increase the sensitivity but decrease the specificity. They suggested a new classification that will consider protein 14-3-3 in diagnosis of probable CJD^[17].

The new variant CJD differs from the sporadic variant in important ways. Patients are younger (18 to 53 years), have behavioral and psychological changes rather than dementia and myoclonus, and periodic EEG discharges are absent. The CSF protein 14-3-3 is present in 50% and high signal abnormality in the basal ganglia is seen on MRI studies (70%). They have more prolonged course (8 to 38 months) and all patients are homozygous for methionine at codon 129. Diagnostic criteria with high sensitivity and specificity have been formulated^[18]. It was possible to detect the abnormal prion protein in tonsillar tissue from one new variant patient but not in that of sporadic CJD^[19]. The reluctance to do brain biopsy in our patient reflects the general fear perceived in this disease. This fear may not be justified as surgeons, pathologists, butchers, abattoir workers, cooks exposed to blood and uncooked animal products are not at higher risks^[20,21]. Only one unconfirmed case of CJD in a pathologist^[22] and 2 cases^[23,24] in histopathology technicians and one conjugal case^[25] have been reported. Implementing general and

hepatitis\HIV precautions is a must in prevention. We believe that our patient had the sporadic form of CJD because of the following evidence. Firstly, she had a clinical syndrome of rapidly progressive dementia associated with spontaneous myoclonus and later stimulus induced (startle) myoclonus, and autonomic dysfunction (excessive sweating). She then deteriorated to akinetic mutism / vegetative state. Secondly, there was no other possible explanation as she failed to respond to antiviral, antibacterial, anti-tuberculosis and steroid treatment. Thirdly, there was no evidence of an inflammatory process in the CNS as repeated CSF studies were normal and MRI showed progressive atrophy with no radiologic findings consistent with new variant CJD. Fourthly, the EEG showed classic periodic discharges. Finally, the CSF study was positive for the presence of protein 14-3-3, in the absence of any possible etiology leading to false positive results. The patient fits well into the sporadic idiopathic form of CJD rather than to the new variant CDJ because of her age, presentation, course, EEG and MRI findings.

To our knowledge this is the third case of CJD to be reported in Gulf area. The first case was reported in 1991^[26] and the second in 1996^[27]. This is the first case to be diagnosed with positive CSF protein 14-3-3 as it was unavailable before 1998. We would expect 10-20 cases of sporadic CJD annually in Saudi Arabia, the population being 20 million. The current low incidence based on the reported cases may reflect under reporting, misdiagnosis, unawareness, or real low incidence of CJD secondary to environmental and/or genetic factors. National surveillance centers are needed to address this issue. Up to now no cases of infected cattle has been reported in this area. There is no reported cases of new variant CJD in the Gulf area.

We must consider CJD in any patient with rapidly progressive dementing illness and myoclonus. Electroencephalogram and CSF protein 14-3-3 are very important premortum diagnostic tools. It is important to consider this diagnosis in the appropriate clinical setting in the Gulf area.

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