Creutzfeldt-Jakob Disease Diagnosable by EEG and Cerebrospinal Fluid Analysis Without Brain Biopsy: A Case Report

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Key Words
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INTRODUCTION

Creutzfeldt-Jacob disease, kuru, and a third progressive familial disease with cerebellar symptoms, Gerstmann-Sträussler-Scheinker disease, are all related in that they are able to be transmitted to humans. Grouped together, they are known as transmissible spongiform encephalopathies (prion disease). Human prion diseases have three differentiated forms, namely, sporadic, inherited, and iatrogenic. However, two additional categories have emerged in recent literature, fatal familial insomnia, and new-variant Creutzfeldt-Jakob disease, that have been isolated in the United Kingdom and thought to be transmitted from cattle to humans by consuming contaminated meat.[1]

Patients affected by prion diseases usually have symptomatology that includes insomnia, dysautonomia, ataxia, EEG disturbances, as well as neuronal loss and astrocytic gliosis within the thalami, and to a somewhat lesser degree the cerebellum. Prion diseases usually have an onset ranging from 25 to 61 years of age with an average age of 48 years. The range for the duration of the disease is 7 to 33 months with an average of 18 months. The prion protein PrP27-30 has been detected at low concentrations at the location of the thalamus and the temporal lobe.[2] Prion diseases are characterized by a specific aberrant isoform and conformation of the normal prion protein PrP^{c}, known as scrapie prion protein PrP^{sc}, which contains a fragment that is thought to be the infectious agent, and a response to protease is absent. Distinguishing features of the different strains of prion disease are the relative molecular mass of the protein resistant segment, which varies and appears to be linked with disease specific phenotypes. One mechanism elucidates the etiology of prion disease as a genetically mutated codon both at position 178 (D178N) and the normal codon for methionine at position 129 of the mutant allele of the prion protein (PNRP). A mutation of the PRNP gene causes fatal familial insomnia that results in the substitution of asparagine for aspartic acid at codon 178, in association with the polymorphic codon 129. As the dominant D178 mutation is coupled with the position 129 substitution of valine, a dementing phenotype, with widely distributed PrP^{sc} and diffuse spongiosis, is seen. It is known as familial Creutzfeldt-Jakob.[2] This case report describes this dementing illness.

An aging population has brought with it an increasing prevalence of dementia. Consequently, the diagnosis of dementia is increasingly made by non-neurologists, and unusual causes of dementing disease may go unrecognized. This case of Creutzfeldt-Jakob Disease (CJD) illustrates the utility of an appropriate work-up, including the use of serial EEG and cerebrospinal fluid (CSF) analysis in rapid onset dementia. More specifically, the diagnosis was made without the need for brain biopsy. The EEG was diagnostic and the CSF 14-3-3 protein was confirmatory.

CASE REPORT

A 64-year-old, right-handed male presented with rapid-onset dementia. During the previous 2 months, the patient's family had noted increasingly confused behavior. On hospital admission, the patient was grossly confused, withdrawn and had difficulty speaking initially, and he became lost in familiar places. Subsequently, he was disoriented to place, time, and familiar people.

The patient was noted to have right hand twitching and myoclonic jerking. A previous outpatient EEG was abnormal, showing periodic and repetitive discharges, at approximately 1/sec (Figure 1). Some activity appeared to be triphasic. There were mixed frequencies with theta activity, and at times delta activity. Prior CT scan and blood work were within normal limits.

The patient was admitted to the hospital with the suspected diagnosis of CJD. He underwent an exhaustive evaluation to rule out other causes of rapid-onset dementia, specifically those that were potentially treatable. Studies included four-vessel angiography which was normal, chest x-ray which showed left apical scarring and overinflation. MRI, with and without contrast, showed minimal age-related atrophy and mild-to-moderate small-vessel ischemic

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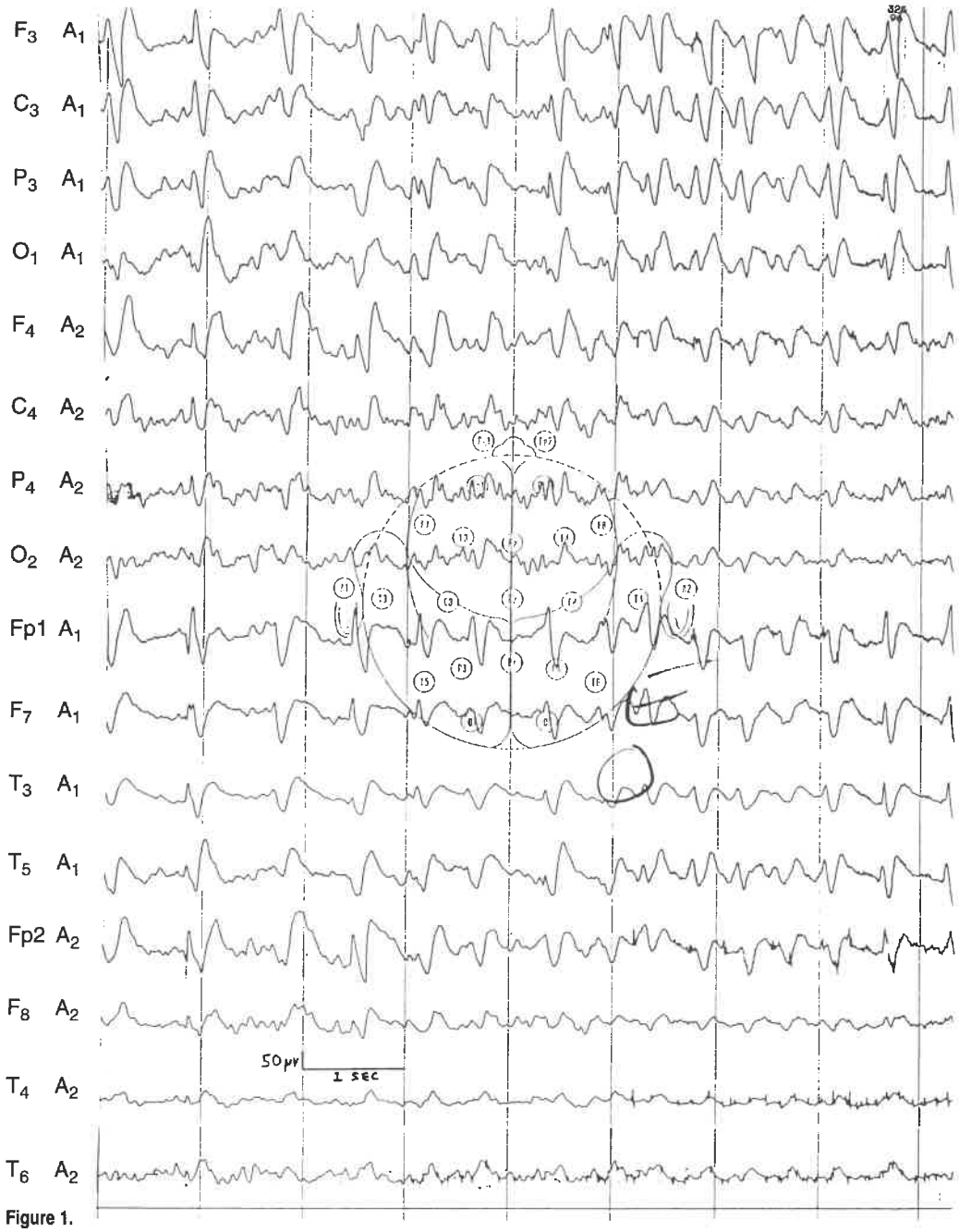

Figure 1.
Adult male: 64-years-old. EEG recording showing triphasic periodic and repetitive discharges.

changes in the enhancement. A cerebral arteriogram showed normal vascular pattern of the basilar, posterior and middle cerebral as well as anterior cerebral branches. No vascular anomalies were seen. EKG showed normal sinus rhythm. Selective injections of the carotids showed the bifurcation to be intact. Complete blood count was normal. Lumbar puncture results were "normal," in that no conventional abnormalities (opening pressure, cells, protein, culture) were found. An EEG was similar to the previous recording showing repetitive 1/sec discharges.

Because the patient was having what appeared to be seizure activity, he was given phenytoin, but the twitching

Table 1
Classification of Creutzfeldt-Jakob Disease

*Sporadic
*Acquired
Iatrogenic (central, peripheral)
*Inherited
Familial
G-S-S syndrome
Fatal familial insomnia

*Associated with human growth hormone, eating meat products.

and myoclonic jerking did not subside. Valproic acid was added, but the seizures continued. The drug combination induced somnolence and lethargy, which diminished when the medications were discontinued.

During the hospitalization the family was told that the most likely diagnosis was CJD. Brain biopsy has been a commonly used diagnostic technique for CJD. However, for various technical reasons, a brain biopsy could not be done. Rather, a CSF sample was sent to Dr. Clarence J. Gibbs at the National Institutes of Health for immunoassay for the 14-3-3 protein. The 14-3-3 antibody reacted specifically with CSF proteins 130 and 131 which has been determined to be a positive test for CJD.[3]

DISCUSSION

CJD is a transmissible spongiform encephalopathy first described by Hans-Gerhard Creutzfeldt, a German neuropathologist, who reported a case of a 22-year-old patient with a 6-year history of progressive brain dysfunction.[4,5] It is one of 5 human diseases known to be associated with prions. Prions are generally defined as small proteinaceous infectious particles that resist inactivation by procedures that modify nucleic acid. It is a protein that is bent or folded out of its normal shape. What causes the abnormal folding is not clear, but it is almost certain that genetic factors are involved. A prion is not degraded into proteins in the body. It can turn normal prions into abnormal prions, thus initiating a cascade of prions that can induce disease such as the spongiform encephalopathies.[5,6] In addition to CJD, human diseases associated with prions include kuru, formerly transmitted through ritual cannibalism, Gerstmann-Sträussler-Scheinker syndrome, a hereditary disorder, fatal familial insomnia, and atypical prion disease. Animal prion diseases include scrapie, a disease of sheep, and bovine spongiform encephalopathy (BSE), commonly called "mad cow disease."[3,7]

BSE appeared in Great Britain in the mid 1980s. It was introduced into beef cattle through the practice of feeding them recycled sheep carcasses in the form of meat and bonemeal nutritional supplements.[8] There was great concern that the disease might spread to humans as CJD through the consumption of infected meat. The fear was heightened by the appearance of a "new variant" CJD syndrome (nvCJD) with clinical and pathological features differing from the classic sporadic form of the disease. The first cases were seen about 10 years after BSE was identified. All had been exposed to BSE-contaminated meat products. It is now known there is a 10-to-15 year incubation period between exposure and the onset of symptoms.[7]

New variant CJD appears at a younger age than classic CJD. All cases occurred in patients younger than 50 (mean = 27 years). Onset is characterized by psychiatric and/or sensory symptoms, the absence of characteristic EEG changes, and an unusually long duration (mean = 14 months). However, as is the case with sporadic or classic CJD, progressive dementia, ataxia, and myoclonus are also seen.[6-10] A new outbreak of CJD has been recognized as associated with eating hamburger and other meat products in England. Virtually all affected individuals documented have been from England.

There is considerable controversy over the existence of an association between BSE and nvCJD. The inoculation of BSE-infected brain tissue into monkeys has produced a spongiform neuropathology similar to that seen in human nvCJD cases. On the other hand, scrapie-infected sheep have never been shown to cause CJD in humans, despite the virtual certainty that sheep products contaminated with scrapie have entered the human food chain for centuries. In addition, infectivity has never been detected in muscle or milk, the two most widely consumed livestock products, in animals naturally infected with BSE, scrapie, or any spongiform encephalopathy.[8]

Classic CJD is sub-classified into 3 subtypes: sporadic, acquired, and, inherited (See Table 1). Only sporadic CJD will be discussed further. Sporadic CJD is characterized by: older age (60-65 years), rapidly progressive dementia (total course < 6 months), movement disorders, including myoclonus, cortical blindness, and akinetic mutism. Tracings showing a triphasic abnormality with periodic sharp wave complexes are seen in 60 to 79%.[11]

Diagnosis prior to the present decade was only by brain biopsy. However, because of the transmissible nature of the disease, brain biopsy places patients and health care personnel at risk and invasive probing may miss the site of the disease. Decontaminating the infectious agent is extremely difficult.[3,12,13] The development of the 14-3-3 antibody CSF protein tests at the NIH allows diagnosis of CJD with a specificity of 99% in the correct clinical circumstances, which is the absence of a stroke within the previous month.

EEG is the only routinely done ambulatory test that has recognizable characteristics in CJD. The most characteristic EEG abnormality in sporadic CJD is periodic sharp wave

complexes (PSWC) frequently but not always 1/sec, which are considered to be pathognomonic for CJD.[11,14] PSWC may also be seen in severe encephalopathies and epilepsy. The PSWC may be monophasic, biphasic, triphasic, or multiphasic. Since the sensitivity of PSWCs may be enhanced by a variety of external stimuli, PSWCs may be more common after stimulation.

SUMMARY

This case illustrates a classic example of CJD in its clinical presentation and course and the EEG. It also shows dramatically the utility of a newly developed protein assay in the diagnosis of this disease. This assay has the potential of eliminating the need for brain biopsy in most cases, thus providing a safer diagnostic method for both staff and patients. In addition, the case points out that anatomical structural studies such as CT and MRI do not replace the utility of EEG in the comprehensive evaluation of rapid onset dementia, but rather complement the usefulness of EEG.

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