Creutzfeldt–Jakob Disease: The Dilemma of Uncertain Diagnosis

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The difficulty in making a definite diagnosis of Creutzfeldt–Jakob disease (CJD) is related to the widely accepted need for neuropathological confirmation, which in some places is difficult or impossible to obtain. This need stems from the presence of atypical cases in which the diagnosis can be made only when such confirmation is available. However, accumulated evidence shows that most cases of CJD eventually turn out to have a typical clinical and EEG picture, where a definite diagnosis can be made without biopsy. This evidence is discussed with reference to the first case of Creutzfeldt–Jakob disease reported from Saudi Arabia. Increased awareness of these features and their significance will hopefully promote case recognition and reporting and facilitate epidemiological studies.

Creutzfeldt–Jakob disease (CJD) is a transmissible degenerative disease of the central nervous system. The incidence ranges between 0.09 and 1.9 per million population, occurring usually in the sixth and seventh decades of life. The causative agent, for which Prusiner coined the term Prion, is thought to be proteinaceous particle which may be devoid of nucleic acids. Prion is considered also to cause Kuru, Gerstmann–Sträussler syndrome, and three other spongiform encephalopathies in animals. Although cases of probable iatrogenic transmission are documented in literature, the route of acquisition in sporadic cases is still a matter of speculation.

The typical clinical picture is that of a subacutely progressive dementia associated with ataxia, dysphasia, visual disturbance, myoclonus, pyramidal and extrapyramidal features. Patients rapidly develop into a decorticate state and 90% of them die within 1 year. This picture is commonly associated with highly characteristic EEG changes, of slow background and periodic sharp wave complexes (PSWC). Histopathological features of CJD are almost pathognomonic. However, this involves obtaining, handling and examining infective materials that are highly resistant to conventional methods of sterilization and need special expertise. Establishing transmissibility, or utilizing immunological tests to detect specific protein in infected tissue, is limited to few centres.
The criteria suggested by Masters et al. for the diagnosis of CJD and used by most workers, consider pathological confirmation as essential for establishing a definite diagnosis. However, other workers recently argue that typical cases fulfilling the triad of subacute dementia, myoclonus and PSWC on EEG can be diagnosed with sufficient certainty on clinical and EEG grounds only. This is extremely important to emphasize especially in areas where pathological evidence is difficult or even impossible to obtain. We will present such a case as basis for the discussion.

Case Report

A 60-year-old Saudi female presented with a 6–8 week history of rapid mental deterioration associated with walking difficulty. She was getting forgetful, confused and neglected herself and her home duties. She was noted to complain of headaches and visual hallucinations. There was a history of herpes zoster 2 years earlier and a lens transplant for cataract 10 months prior to admission. None of her family had a similar condition. On examination, she was non-responsive to verbal commands, spoke incomprehensibly and resisted examination. She had intact cranial nerves, moderate rigidity and grasp reflex as well as symmetrically increased tendon reflexes with upgoing plantars bilaterally. She was unable to stand or walk unaided.

Investigations included a normal full blood count with an ESR of 60 mm/h, normal renal and liver functions, normal brucella and mycoplasma titres and a negative VDRL. Cerebrospinal fluid was examined and showed: protein 0.23 g/l, glucose 2.7 mmol/l and 4 lymphocytes. Immunoglobulins were also normal as were also viral, mycoplasma and brucella titres. Ziehl Nielsen and Indian ink stains, cytology and different cultures were all negative; CT scan of the head showed generalized cortical atrophy. At this stage the diagnosis was far from obvious, as the negative results especially of CSF made an inflammatory aetiology unlikely. The high ESR compelled reassessment before accepting a degenerative aetiology as Alzheimer's disease or rare diseases such as CJD. On the fifth week after admission, the patient became feverish and was found to have tuberculous adenitis on biopsy and was started on antituberculous drugs. This explained the high ESR but not the patient's dementing illness especially with two normal CSF examinations. Soon afterwards, she started to have myoclonic jerks which increased in severity and became rapidly generalized.

EEG findings

Several EEGs and video split-screen EEGs were recorded in the awake and natural sleep states and during intravenous injection of diazepam. The initial EEG showed a diffusely slow background with \( \theta \) and \( \delta \) activity of high amplitude at 3–4 Hz (Fig. 1). After 2 weeks, the EEG showed characteristic PSWC (Fig. 2). These complexes had a duration of 200–300 ms with an interwave period of 0.7–1 s and were not time-locked to the myoclonic jerks. They diminished and became irregular or even disappeared during drowsiness or deep sleep and on alerting the patient or arousing her out of her sleep, the periodic activity returned (Fig. 3). As the
Figure 2. EEG after 2 weeks showing definite periodic sharp wave complexes at 1–1.5/s. They were not time-locked to the myoclonic jerks.

Figure 3. Shows the disappearance of periodic sharp wave complexes during sleep and reappearance on awakening by noise (arrow).
disease progressed, the EEG showed gradual increase in the interburst intervals with diminished amplitude of the background and the PSWC (Fig. 4).

In view of the typical clinical picture and results of investigations especially serial EEG, a final diagnosis of CJD was made. Gradually the patient became mute, immobile and non-responsive except to painful stimuli. The myoclonic jerks diminished in severity. Three months after discharge, she died at home. Her illness lasted nearly 11 months. This short duration of the illness strengthened our conclusion. Pathological confirmation was seriously considered earlier but because of reluctant relatives and fear of transmission it was not done and the diagnosis was considered to be secure without the need for biopsy. Autopsy on the other hand is not permitted in this country.

**Discussion**

Epidemiological information is especially important in understanding infectious diseases such as CJD where the natural mode of transmission is still uncertain. Although some epidemiological studies have already been published in some countries, such information is not provided on a worldwide basis. The reason behind this is multifactorial. Growing awareness among neurologists of CJD was suggested by studies from England and Wales, France and Finland to be behind the rise in the figures of incidence of CJD noted in these countries.

However, of more significance worldwide is the generally accepted idea of the inability to diagnose CJD with sufficient certainty if not pathologically confirmed. The criteria of Masters et al. consider such cases diagnosed on clinical and EEG grounds alone as either probable or possible but not definite. In areas where pathological confirmation is unavailable or difficult to obtain, the ensuing uncertainty in the diagnosis, considering also the rarity of the disease, may make neurologists reluctant to endorse the diagnosis let alone try to report it. The main reason behind the strict criteria stems from the noted variability in the clinical and EEG features of the disease. Cases of long duration lasting for 2 years or more constitute up to 15%, and cases with unusual clinical pictures such as ataxic, amyotrophic or CJD's Heidenhain forms are well recognized. The differential diagnosis of such instances includes a long list of diseases and the diagnosis certainly cannot be reached without biopsy. However, the majority of CJD cases turn out to be of short duration and have a typical clinical and EEG picture.

In the study of Will & Mathews, typical cases are most frequently encountered within the subacute form (137 of the 152 instances). The mean duration of illness was 5.5 months. Myoclonus was present in 82% and typical EEG changes in 75% of this group. Brown et al. did not identify particular forms of the disease: 90% of their patients died within 1 year, 88% had myoclonus and a typical EEG was detected in 40% of patients retrospectively, and in 75% prospectively. Few diseases need to be considered for differential diagnosis of such typical cases. These include subacute diencephalic angioencephalopathy of which only two cases so far have been reported in the literature. This entity has a more rapid
course and essentially lacks the EEG abnormalities. Alzheimer's disease can rarely be associated with myoclonus or periodic EEG changes. However, the presence of these two features simultaneously virtually exclude it. Only one such case has been reported in the literature and even then the reported EEG abnormalities were atypical and differ from the PSWC seen in CJD especially regarding their frequency.\textsuperscript{25} Metabolic and post-hypoxic encephalopathies are easily excluded on clinical and laboratory grounds. Few types of viral encephalitis can have a subacute presentation,\textsuperscript{26,27} but the EEG and CSF examinations are sufficient to clarify the diagnosis. Subacute sclerosing panencephalitides are clearly excluded on account of age and typical findings in CSF and the obvious difference in characteristics of periodic EEG discharges.

Brown \textit{et al.} concluded in their study that when the duration of illness is restricted to 1 year, only cases of CJD fit the noted clinical and EEG picture. These cases fulfilled their proposed criteria for a definitive diagnosis.\textsuperscript{10} The role of the EEG in differential diagnosis is paramount. The typical PSWC are bi- or triphasic, of 200–400 ms duration, at a rate of 0.5–2/s. Their characteristics in CJD, as illustrated in our case, distinguish them from many types of periodic activities,\textsuperscript{16,28} making them practically pathognomonic.\textsuperscript{10,16} Detection of PSWC in typical cases of CJD have been increasingly noted in successive studies, mainly due to increased utilization of serial EEGs.\textsuperscript{10,11} Early EEGs may either miss the PSWC or detect atypical periodic activities (Fig. 1). In one study, PSWC were picked up in 94% of cases studied with serial EEGs.\textsuperscript{29} Levy \textit{et al.} consider that almost all typical cases will show PSWC,\textsuperscript{16} while atypical cases are less frequently associated with these changes.\textsuperscript{16,20,21}

In contrast to the diagnostic significance of EEG, other investigations (cerebrospinal fluid, evoked potentials and neuroradiological studies) are either normal or show mild non-specific changes.\textsuperscript{11,30–33}

Pathological confirmation or evidence of transmission is only necessary if clinical or EEG features are atypical or if other investigations show an abnormality that casts doubt on the diagnosis. Otherwise, when the combination of subacute dementia, myoclonus and typical EEG are present, the diagnosis can be considered with sufficient certainty as definite.

References

\textsuperscript{1}Masters CL, Harris JO, Gajdusek DC, Gibbs CJ, Bernoulli C, Asher DM. Creutzfeldt–Jakob disease: patterns of worldwide occurrence and the significance of familial and sporadic clustering. \textit{Ann Neurol} 1979; 5: 177–188.


