Case Report

Case Reports of Two Biopsy-proven Patients with Creutzfeldt-Jakob Disease in Singapore

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Abstract

Introduction: Creutzfeldt-Jakob disease (CJD) is the most common transmissible human subacute spongiform encephalopathy. There is limited literature on CJD in Southeast Asia. We describe the clinical course and diagnostic evaluation of 2 Singapore patients with biopsy-proven CJD. Clinical Picture: Two patients presented with non-specific symptoms such as withdrawal, forgetfulness, asthenia, giddiness and insomnia. Both patients had spontaneous myoclonic jerks and impairment of multiple neurologic systems (visual, pyramidal, cerebellar and neurocognitive systems). Magnetic resonance imaging and electroencephalography provided helpful supportive evidence. Diagnosis of CJD was established on brain biopsy. Histological features included spongioform degeneration, neuronal cell loss and astrocytosis. Treatment/Outcome: Treatment remains palliative. Deterioration in their clinical condition was relentless, progressing to a totally dependent state within 10 to 12 months. Conclusion: The early features of CJD can be varied and non-specific. It is important for physicians from different specialties to be cognisant of the clinical manifestations of CJD and the appearance of supportive and definitive investigations.

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Introduction

Creutzfeldt-Jakob disease (CJD) is the commonest human transmissible subacute spongiform encephalopathy. It has a worldwide distribution with an estimated annual incidence of 0.5 to 1.0 per million population. However, the incidence of CJD in the Singaporean population is not known. With a population of 4 million, an estimated 2 to 4 patients newly diagnosed with CJD per year are expected. A retrospective review identified 5 possible cases of CJD seen in a tertiary hospital in Singapore within a 3-year period.[1] As the initial symptoms experienced by CJD patients are frequently varied and subtle, doctors from diverse disciplines, including family medicine, neurology, geriatrics, psychiatry and ophthalmology may be the physicians first consulted during the early phase of the disease. We report 2 local patients with biopsy-proven CJD, illustrate clinical, neurophysiological, imaging and pathological findings and details of the diagnostic procedures of this important condition.

Case Reports

Patient 1

A 50-year-old Chinese male accountant was admitted for assessment of deteriorating mentation in 1993. Three months before, his family members had noted a change in his personality – he was described to have become quieter, withdrawn, lethargic and forgetful. Prior to his illness, he was recognised to be exceptionally good with numbers, meticulous and organised . His colleagues noted progressive deterioration of these capabilities in the few months prior to his presentation. A month prior to admission, his gait had become unsteady. He became progressively more sedentary and uninterested in his surroundings. His family members noticed jerky movements of his limbs in the weeks leading to his hospitalisation. There was no significant past medical history or family history.

Physical examination revealed a plump, middle-aged man who was disoriented, inattentive, apathetic and with

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impaired memory. He had bladder and bowel incontinence. Spontaneous and startle myoclonic jerks were present and coordination of voluntary movements was poor. Eye movements appeared intact. The patient's condition deteriorated rapidly over the next fortnight to reach a tetraparetic, stuporous and totally dependent state.

Full blood count, serum urea and electrolytes and thyroid function tests were normal. Screenings for human immunodeficiency virus (HIV), hepatitis A, hepatitis B and venereal disease research laboratory test (VDRL) were negative. Chest, abdominal imaging and ophthalmic slit-lamp examination were unremarkable. Brain imaging with computed tomography (CT) scan and magnetic resonance (MR) imaging was normal. Electroencephalography demonstrated generalised slowing with superimposed periodic high-voltage, sharp and slow wave complexes at 1 to 2 Hz over both hemispheres. Brain biopsy (right frontal lobe) showed spongioform degeneration of the cortical grey matter accompanied by astrocytosis.

The clinical history, together with physical signs, electrophysiological features and biopsy results were typical of CJD. The patient was treated with clonazepam to control his myoclonic jerks. He remained in a vegetative state and passed away 12 months later.

Patient 2

A 61-year-old female Chinese former hawker presented in early 2002 with 2 to 3 months of non-specific symptoms including asthenia, poor appetite, "blurring of vision", non-vertiginous giddiness and insomnia. Family members described her to be generally low in mood, with occasional uncharacteristic outbursts of anger and violence. They also noted deterioration of concentration, memory, simple mathematical skills, and that she was developing persecutory paranoid delusions ("family members out to get her"). She also seemed "jittery" to them. The patient was on atenolol and gemfibrozil for hypertension and hyperlipidaemia respectively, and had also been on hormonal replacement therapy for the prior 4 years.

Physical examination revealed a middle-aged lady who was withdrawn and inattentive. Extraocular eye movements demonstrated full range of movements with impaired smooth pursuit. Her voice was spastic with accompanying hyperreflexia of her limbs. Action tremor was seen in the upper extremities. She had truncal ataxia with a broad-based gait. Spontaneous and startle myoclonic jerks were noted predominantly in the upper extremities.

Full blood counts, erythrocyte sedimentation rate, serum urea, electrolytes and liver function tests, vitamin B12, folate, caeruloplasmin, thyroid function tests, VDRL, TPHA, and HIV ELISA were normal. Chest X-ray was unremarkable. Cerebrospinal fluid was bland and polymerase chain reaction based herpes virus DNA tests were negative. MR brain scan, including diffusion-weighted imaging (DWI), showed ribbon-like areas of T2 and diffusion-weighted hyperintense signal, involving the left frontal cortex, head of the left caudate nucleus, thalamus, and part of the head of right caudate nucleus (Fig. 1). Electroencephalography revealed periodic lateralised epileptiform discharges (PLEDs) predominantly over the left frontal and central regions of the brain (Fig. 2). Brain biopsy of the right frontal lobe showed spongioform change, loss of neuronal cells and astrocytosis (Fig. 3). Immunohistochemical staining for PrP^{Sc} was positive with a synaptic pattern of distribution.

The clinical picture, electroencephalogram (EEG) and brain MR imaging findings were consistent with sporadic CJD, with neuropathological confirmation of the diagnosis. The patient is currently bed-bound, mute and totally dependent 10 months after initial clinical presentation.

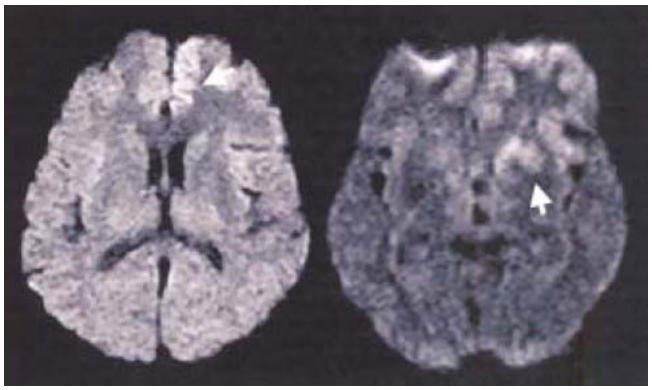
Discussion

CJD is a progressive and invariably fatal neurological condition mediated by a unique transmissible proteineous infectious particle, the prion. The prion protein is an isoform of a naturally-occurring cellular protein, PrP^{C}. Creutzfeldt-Jakob disease is thought to be caused by the conversion of PrP^{C} from its soluble form to a pathogenic form (PrP^{Sc}). The function of PrP^{C} is currently unknown.

CJD exists in a sporadic form, an autosomal dominant familial form (approximately 10% to 15% of cases of CJD), and an iatrogenic form. Several point mutations and insertional mutations have been described in familial CJD. Subtle changes in the PrP protein amino acid sequence encoded by these mutations are thought to alter the susceptibility of cellular PrP to change it to the pathogenic isoform. In sporadic CJD, either spontaneous somatic mutations of PRNP gene or spontaneous conformational change of cellular PrP to PrP^{Sc} occurs. In iatrogenic CJD, PrP^{Sc} is introduced via contaminated substances, including innoculation from contaminated surgical instruments, dural grafts and human pituitary gland extracts from affected donors.

The age of disease onset in the sporadic form ranges from 55 to 75 years with a mean of 61.5 years.[2] Males and females are equally affected. Japan reported an annual incidence rate of 0.49 per million population for males and 0.68 for females.[3] Little epidemiological data from other Asian populations are available.

When confronted by the classical triad of rapidly progressing dementia, myoclonic jerks and characteristic electroencephalographic findings, the diagnosis of CJD is commonly considered. However, the initial presentation



Figs. 1a and b. Diffusion-weighted magnetic resonance images showing increased intensity in the left caudate, putamen and frontal cortex (arrows).

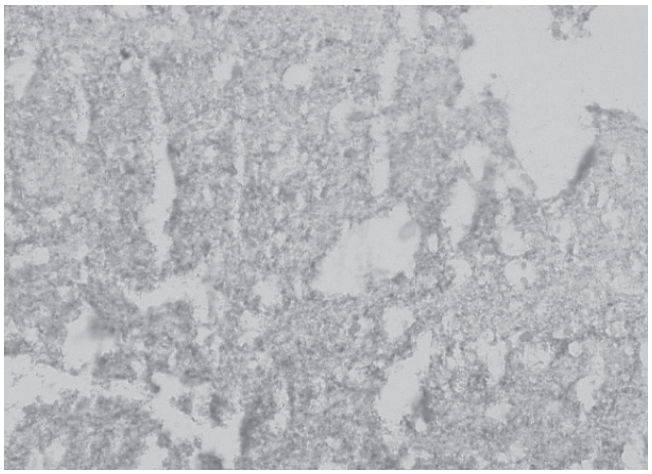


Fig. 3a. Immunostain: PrP immunohistochemistry revealed a diffuse synaptic staining pattern in the cerebral cortex (original magnification x200).

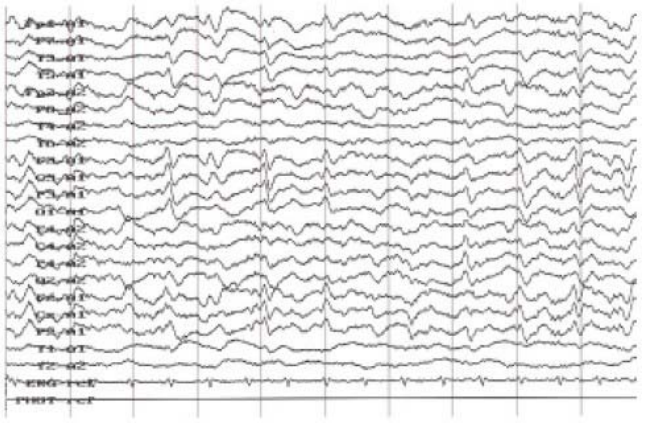


Fig. 2. EEG showing periodic lateralised epileptiform discharges (PLEDs) in the left hemisphere. Semi-rhythmic delta slowing is also demonstrated, giving evidence for an underlying subacute encephalopathy.

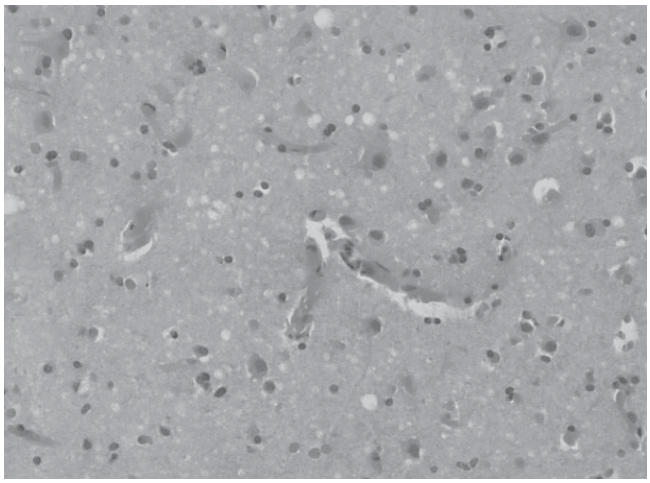


Fig. 3b. HE section: The cerebral cortex of patient 2 showed neuronal loss, reactive astrocytosis and spongiform change (haematoxylin-eosin, original magnification x200).

frequently consists of non-specific symptoms, as illustrated in our 2 patients in this report. Neuropyschiatric manifestations featured prominently in our 2 patients during the course of their illness. Amongst a series of 230 cases of pathologically verified CJD, 36% had non-specific symptoms such as asthenia, and disturbances of sleep and eating patterns. Forty-one per cent presented with features of mental deterioration only, while 36% presented exclusively with neurological symptoms, mostly of cerebellar or visual origin.[2] Visual manifestations included restriction of visual field, homonymous hemianopsia, metamorphopsia, palinopsia, and optic atrophy. Cerebellar gait disturbances were frequently followed by rapidly progressing dementia. Myoclonus (sudden, brief, shock-like involuntary movements) was present in 88% of the patients,[2] usually during the later stages of the disease. Both our patients had myoclonic jerks when they presented to us, a feature which pointed towards the diagnosis. These movements were often precipitated by sudden stimuli or activity. Although characteristic of CJD, myoclonic jerks are seen in varied disease states, such as metabolic or hypoxic encephalopathy, mitochrondrial diseases and post-viral encephalitis. Conditions that can mimic the initial presentation of CJD include chronic meningitis, gliomatosis cerebri, subacute sclerosing panencephalitis, Hashimoto's encephalitis, intracranial vasculitis, paraneoplastic limbic encephalitis, AIDS Dementia Complex, Kufs disease and myoclonic epilepsy with Lafora bodies.

Characteristic EEG findings in CJD consist of periodic lateralised or generalised bursts of spike-wave complexes. Periodic EEG activity was reported in 80% of a series of CJD patients.[2] Other investigators estimated EEG diagnosis of CJD to have sensitivity and specificity of 66% to 67% and 74% to 87% respectively.[4,5] Typical EEG findings may be absent at the initial stages of the disease. However as the clinical syndrome evolves, periodic activity often becomes

apparent. There was no EEG from the early phase of our patients' illnesses. The patients in this report had periodic EEG activity at presentation, which was at several months following onset of their symptoms. The EEG findings, together with clinical features such as the presence of myoclonic jerks, were consistent with later stages of CJD. Periodic EEG activity is not specific to CJD, but can be seen in post-anoxic encephalopathy, Alzheimer's disease, AIDS dementia, multiple cerebral abscesses, MELAS (mitochondrial myopathy, encephalopathy, lactic acidosis and stroke) syndrome and severe metabolic derangement. Co-existence of myoclonic jerks with periodic EEG activity has been reported in Hashimoto's encephalitis.[6]

The presence of 14-3-3 brain proteins in cerebrospinal fluid aids diagnosis.[7] The sensitivity of CSF brain protein 14-3-3 for CJD ranges from 90.6% to 96.0%, with specificity of 84.0% to 96.0%.[5,8,9] False positive results of 14-3-3 protein assay are found in patients with extensive central nervous system (CNS) damage, including recent stroke, subarachnoid haemorrhage, viral encephalitis, Rett's syndrome, paraneoplastic syndromes affecting the CNS (e.g. paraneoplastic limbic encephalitis and cerebellar degeneration), Alzheimer's disease and Dementia with Lewy bodies (DLB).[8-10] The CSF picture in patients with CJD is otherwise bland, aside from occasional elevated total protein.

MR brain imaging in patients with CJD demonstrates increased signals in bilateral caudate nuclei, basal ganglia, thalami and cortical areas on DWI, fluid-attenuated inversion recovery (FLAIR) and T2 weighted sequences. Apparent diffusion coefficient values are low in regions with DW hyperintensities. Abnormalities are more conspicuous on DWI, followed by FLAIR sequences. A retrospective analysis of MR brain imaging found bilateral putamen and caudate nuclei increased T2 signal intensity in 79% of patients who died from CJD.[11] Diffusion-weighted changes may be seen as early as 1 month after symptom onset.[12,13] With disease progression, the abnormal DW hyperintensities become more extensive and conspicuous,[14] following which initial abnormal DW hyperintensities may fade as new areas with abnormal DW signals appear.[15] The appearance of these brain MR imaging abnormalities raise suspicion of CJD, providing impetus to consider invasive investigations such as lumbar puncture or brain biopsy. Serial EEGs may also uncover changes unremarkable in the early phases of the disease. Other conditions that may demonstrate similar basal ganglia abnormalities include Wilson's disease, mitochondrial encephalopathies and cerebral hypoxia.

Proposed criteria for probable sporadic CJD include:

i) progressive dementia;
ii) at least 2 of the following 4 clinical features – myoclonus, visual or cerebellar dysfunction, pyramidal/extra-pyramidal dysfunction or akinetic mutism;
iii) a typical EEG and/or a positive 14-3-3 CSF assay and a clinical duration of less than 2 years before death; and
iv) exclusion of alternative diagnoses with routine investigations.[16]

Definite CJD may only be established by neuropathological examination. Pathological findings include spongiform changes, neuronal loss, reactive astrocytosis in the grey matter and PrP immunoreactivity. It is recommended that neurosurgical instruments used for patients with CJD be destroyed. If re-use of instruments is unavoidable, such instruments must be properly treated.[17] Neurosurgeons, nursing, pathological and other support staff often need a measure of encouragement to undertake the procedure of brain biopsy (as was the case for both our patients), understandably, as the condition is transmissible and invariably fatal with no effective therapy available. Yet, accurate and definitive diagnosis of this condition remains extremely important for the patient, his family and care-givers. Without definitive pathological diagnosis, some treatable conditions (metabolic, inflammatory, tumour, etc.) would potentially remain under-diagnosed and untreated. Familial forms of prion disease (AD-CJD, Gerstmann-Straussler-Scheinker, Familial Fatal Insomnia) and some inherited metabolic diseases with dementia (treatable) also have definite genetic implications for the family. Definitive diagnosis also facilitates and prepares care-givers for the necessary care and placement of the patient. In a larger context, accurate diagnosis also allows for community surveillance of this infective and transmissible condition. Biopsy of the nasal epithelium has recently been reported to be a less invasive and reliable way to obtain tissue for the identification of PrP protein.[18]

Recent forays into treatment regimens for this uniformly fatal disease have seen the use of anti-malarial agents like quinacrine and anti-psychotic agents like chlopromazine though these are still in the investigational stages.[19]

Conclusion

We report 2 Singaporean patients with pathologically proven CJD, illustrating their clinical features and the investigations performed. Creutzfeldt-Jakob disease is a progressive neurological condition with an invariably fatal outcome; definitive and accurate diagnosis is crucial for patients, patients' relatives and healthcare providers. In view of the varied and non-specific presenting features of the disease in its early phase, it is important for physicians from different specialties to be cognisant of the clinical and investigative features of CJD and its differential diagnoses.

REFERENCES

1. Seah AB, Lim SH, Ratnagopal P, Chen CP, Puvanendran K, Wilder-Smith E. Creutzfeld-Jakob disease: the Singapore General Hospital's experience. Neurol J Southeast Asia 1998;3:104.
2. Brown P, Cathala F, Castaigne P, Gajdusek DC. Creutzfeldt-Jakob disease: clinical analysis of a consecutive series of 230 neuropathologically verified cases. Ann Neurol 1986;20:597-602.
3. Nakamura Y, Yanagawa H, Hoshi K, Yoshino H, Urata J, Sato T. Incidence rate of Creutzfeldt-Jakob disease in Japan. Int J Epidemiol 1999;28:130-4.
4. Steinhoff BJ, Racker S, Herrendorf G, Poser S, Grosche S, Zerr I, et al. Accuracy and reliability of periodic sharp wave complexes in Creutzfeldt-Jakob disease. Arch Neurol 1996;53:162-6.
5. Zerr I, Pocchiari M, Collins S, Brandel JP, de Pedro Cuesta J, Knight RS, et al. Analysis of EEG and CSF 14-3-3 proteins as aids to the diagnosis of Creutzfeldt-Jakob disease. Neurology 2000;55:811-5.
6. Seipelt M, Zerr I, Nau R, Mollenhauer B, Kropp S, Steinhoff BJ, et al. Hashimoto's encephalitis as a differential diagnosis of Creutzfeldt-Jakob disease. J Neurol Neurosurg Psychiatry 1999;66:172-6.
7. Saiz A, Nos C, Yague J, Dominguez A, Graus F, Munoz P, Catalan Collaborative Study Group for CJD. The impact of the introduction of the 14-3-3 protein assay in the surveillance of sporadic Creutzfeldt-Jakob disease in Catalonia. J Neurol 2001;248:592-4.
8. Hsich G, Kenney K, Gibbs CJ, Lee KH, Harrington MG. The 14-3-3 brain protein in cerebrospinal fluid as a marker for transmissible spongiform encephalopathies. N Engl J Med 1996;335:924-30.
9. Saiz A, Graus F, Dalmau J, Pifarré A, Marín C, Tolosa E. Detection of 14-3-3 brain protein in the cerebrospinal fluid of patients with paraneoplastic neurological disorders. Ann Neurol 1999;46:774-7.
10. Burkhard PR, Sanchez JC, Landis T, Hochstrasser DF. CSF detection of the 14-3-3 protein in unselected patients with dementia. Neurology 2001;56:1528-33.
11. Finkenstaedt M, Szudra A, Zerr I, Poser S, Hise JH, Stoebner JM, et al. MR imaging of Creutzfeldt-Jakob disease. Radiology 1996;199:793-8.
12. Bahn MM, Parchi P. Abnormal diffusion-weighted magnetic resonance images in Creutzfeldt-Jakob disease. Arch Neurol 1999;56: 577-83.
13. Bahn MM, Kido DK, Lin W, Pearlman AL. Brain magnetic resonance diffusion abnormalities in Creutzfeldt-Jakob disease. Arch Neurol 1997;54:1411-5.
14. Matoba M, Tonami H, Miyaji H, Yokota H, Yamamoto I. Creutzfeldt-Jakob disease: serial changes on diffusion-weighted MRI. J Comput Assist Tomogr 2001;25:274-7.
15. Hirose Y, Mokuno K, Abe Y, Sobue G, Matsukawa N. A case of clinically diagnosed Creutzfeldt-Jakob disease with serial MRI diffusion weighted images. Rinsho Shinkeigaku 1998;38:779-82.
16. Global Surveillance, Diagnosis and Therapy of Human Transmissible Spongiform Encephalopathies: Report of a WHO Consultation. Geneva, Switzerland, 9-11 February 1998.
17. WHO Infection Control Guidelines for Transmissible Spongiform Encephalopathies. Report of a WHO Consultation. Geneva, Switzerland, 23-26 March 1999.
18. Zanusso G, Ferrari S, Cardone F, Zampieri P, Gelati M, Farinazzo A, et al. Detection of pathologic prion protein in the olfactory epithelium in sporadic Creutzfeldt-Jakob Disease. N Engl J Med 2003;348:711-9.
19. Korth C, May BC, Cohen FE, Prusiner SB. Acridine and phenothiazine derivatives as pharmacotherapeutics for prion disease. Proc Natl Acad Sci U S A 2001;98:9836-41.