Creutzfeldt-Jakob Disease: A First Case Series from a Tertiary Hospital in Malaysia and Review of Literature in Southeast Asia

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Abstract
Creutzfeldt-Jakob disease is a rare, human transmissible prion disease which carries a grave prognosis with no specific treatment. Although widely reported in English literature, reports of Creutzfeldt-Jakob disease in Southeast Asia are scarce. The incidence of Creutzfeldt-Jakob disease in this region is unknown. This raises the question of whether Creutzfeldt-Jakob disease is actually rarer in Southeast Asia or under-reported. We retrospectively reviewed the case-mix records of a tertiary hospital in Malaysia from 2009-2013 and found only 4 cases of probable Creutzfeldt-Jakob disease. Here we provide an illustrated report of 2 patients with probable Creutzfeldt-Jakob disease presenting initially with non-specific symptoms of lethargy. Subsequently both patients developed rapidly progressive dementia, myoclonic jerks and various neurological features including visual, extrapyramidal and neuropsychiatric manifestations. Magnetic resonance imaging of brain, electroencephalogram and cerebrospinal fluid 14-3-3 protein provided supportive evidence for the diagnosis. Both patients deteriorated rapidly and succumbed within 3 months of presentation.

ABBREVIATIONS
CJD: Creutzfeldt-Jakob Disease; DWI MRI: Diffusion Weighted Magnetic Resonance Imaging; CSF: Cerebrospinal Fluid; EEG: Electroencephalograph; FLAIR: Fluid Attenuated Inversion Recovery

INTRODUCTION
Creutzfeldt-Jakob Disease (CJD) is a form of transmissible spongiform encephalopathy caused by proteinaceous particle known as prions. It is a progressive and invariably fatal disease with no specific treatment. It is known to have a worldwide distribution with annual incidence of 1 per million population [1]. However there is limited literature on CJD in Southeast Asia with only 5 case series/report published to date. In fact, absence of national surveillance centre in this region made epidemiological study of this rare disease impossible.

To date there is no published report of CJD in Malaysia. Here we describe a case series of CJD in a tertiary centre in Malaysia. We retrospectively reviewed our hospital case-mix records from 2009 to 2013 and found 4 patients with probable sporadic CJD. The patients were between 54 to 68 years old and consist of 3 males and 1 female. Our patients had variable initial presentations. Two patients had initial non-specific symptoms of hypersomnia and lethargy, whereas another had a stroke-like presentation with hemiparesis. All the patients had an initial wrong diagnosis and the diagnosis of CJD was made only after 1 to 2 months. All the patients died within 6 months of diagnosis.

Diffusion Weighted Magnetic Resonance Imaging (DWI MRI) brain showed cortical ribboning in all patients, although 3 patients had a normal MRI initially. Cerebrospinal Fluid (CSF) protein 14-3-3 was positive in all patients and typical Electroencephalograph (EEG) changes of periodic waves were
seen in 2 patients. All 4 patients’ family had refused post-mortem study. Genetic study was not available in our centre. A summary of the patients’ characteristics is showed in Table 1.

In the section below, we describe 2 patients with probable sporadic CJD, diagnosed based on WHO criteria.

**CASE PRESENTATION**

**Patient 1**

A 59-year-old lady presented with 2 months history of lethargy and hypersomnia. She also had nausea and blurred vision of both eyes. One month later, she had vertigo, headache and persistent vomiting. MRI brain showed a pituitary macroadenoma. Serum cortisol, thyroid function and pituitary hormone levels were normal. A diagnosis of non-functioning pituitary macroadenoma was made and she was scheduled for surgery. However, her cognitive function deteriorated rapidly within 2 weeks. She developed behavioural changes, disorientation, incoherence, impaired perception of colours as well as visual and tactile hallucinations. Her conscious level deteriorated rapidly. She became stuporous with mask-like facies, generalised rigidity and spastic tetraparesis. Later, stimulus sensitive myoclonic jerks were also present.

A repeat MRI brain showed asymmetrical hyperintensity of both head of caudate nucleus and cortical ribboning on T2, Fluid Attenuated Inversion Recovery (FLAIR) and Diffusion Weighted Imaging (DWI) (Figure 1). EEG showed diffuse slowing but no periodic waves. CSF analyses including lactate were normal. CSF protein 14-3-3 was positive.

**Patient 2**

A 63-year-old male with hypertension and dyslipidemia presented with 2 month history of lethargy and hypersomnia. One month later he was noted to have progressive cognitive decline, abnormal behaviour and jerky limb movements. On examination, he had blank stares with frequent brief myoclonic jerks on both upper and lower limbs. There was generalised rigidity with hypertonia and extensor plantar responses. Glasgow coma scale was 11/15 (E4V2M5). Cranial nerves examination was normal.

Baseline investigations which included full blood count, renal, liver and thyroid function were normal. Lumbar puncture opening pressure was 10cmH2O with CSF protein of 500 mg/dL with normal glucose and cell count (<5 cells/ml). CSF was negative for cryptococcus and acid-fast bacilli with unremarkable cytology. CSF 14-3-3 was positive. MRI brain is shown in figure 2.

Table 1: Clinical features and investigations of patients with sporadic Creutzfeldt-Jakob disease.

<table>
<thead>
<tr>
<th>Age/Sex</th>
<th>Initial Presentation</th>
<th>Initial Diagnosis</th>
<th>Time to Diagnosis</th>
<th>DWI MRI</th>
<th>EEG</th>
<th>CSF 14-3-3 Protein</th>
</tr>
</thead>
<tbody>
<tr>
<td>59/F</td>
<td>hypersomnia, lethargy</td>
<td>pituitary macroadenoma</td>
<td>2 months</td>
<td>1st: Normal. (1 month)</td>
<td>Diffuse slowing</td>
<td>positive</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2nd: Cortical ribboning,</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>caudate nucleus hyperintensity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>63/M</td>
<td>hypersomnia, lethargy</td>
<td>viral encephalitis</td>
<td>2 months</td>
<td>1st: Normal. (1 month)</td>
<td>Periodic sharp waves</td>
<td>positive</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2nd: Cortical ribboning</td>
<td></td>
<td></td>
</tr>
<tr>
<td>54/M</td>
<td>confusion, focal seizure</td>
<td>status epilepticus</td>
<td>1 month</td>
<td>1st: Normal. (2 weeks)</td>
<td>Periodic sharp waves</td>
<td>positive</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2nd: Cortical ribboning</td>
<td></td>
<td></td>
</tr>
<tr>
<td>68/M</td>
<td>Left hemiparesis, left upper limb jerks</td>
<td>stroke with post infarct seizure</td>
<td>1 month</td>
<td>1st: Cortical ribboning, putaminal hyperintensity</td>
<td>Diffuse slowing</td>
<td>positive</td>
</tr>
</tbody>
</table>

Abbreviations: M: Male; F: Female; CSF: Cerebrospinal Fluid; DWI MRI: Diffusion Weighted Imaging Magnetic Resonance Imaging; EEG: Encephalogram

![Figure 1](image_url) MRI brain (T2-weighted sequence) (A) shows hyperintensity in the bilateral lentiform nucleus (black arrows). DWI (B) shows hyperintensity in the lentiform nuclei (black arrows), cortical hyperintensity in both perisylvian regions and right occipital lobe (white arrows).
Electroencephalograph showing generalised slow activity with periodic sharp wave complexes.

Together with clinical and investigative findings, patient was diagnosed to have probable sporadic CJD. He succumbed to his illness 3 month later.

**DISCUSSION**

Creutzfeldt-Jakob disease is a rare, human transmissible prion disease which is inexorably fatal. National surveillance centres in Europe, United States and Australia has consistently quoted an annual incidence of 1 case per million population. However, there is no regional or national surveillance centre for CJD in the Southeast Asia and therefore the actual incidence is not known. In fact, there are only scanty case series of CJD in Southeast Asia. A literature search on epidemiology of CJD in southeast Asia revealed only 4 published case series/reports from Singapore[3-6] and one from Thailand[7] (Table 2). Kandiah et al described the largest case series in Singapore involved 4 definite CJD and 10 probable CJD over a period of 7 years[3]. There are no published reports of CJD in other Southeast Asia countries. This raises the question of whether CJD is under-reported or is actually rarer in Southeast Asia.

The hallmarks of CJD are rapid progressive dementia with myoclonic jerks. In a study involving 230 patients, myoclonic jerks are found to be common (88% of patients) but often present as late feature[8]. However, about 30% of patients present with non-specific prodromal symptoms such as lethargy and hypersomnia[8,9], resulting in delay in diagnosis and even misdiagnosis. The patients may also have various presentations including cerebellar, visual, pyramidal, extrapyramidal and neuropsychiatric symptoms. In our patients, the myriad of symptoms leads to suspicion of various differential diagnoses, all which are more common than CJD.

The characteristic MRI brain findings are demonstrated in figure 1 and 2 where there are asymmetrical hyperintensity of putamen, caudate nucleus, medial and posterior thalamus and cortical ribbons. However, it is important to include DWI MRI in the imaging protocol for diagnosis of suspected CJD as it is highly sensitive (96%) and a specificity (93%) [10].

The sensitivity and specificity of cerebrospinal fluid 14-3-3 protein for CJD is 94% and 84%, respectively [11]. However, false positive occurs in Alzheimer’s disease, multiple infarcts, brain neoplasm, Hashimoto’s encephalitis, viral encephalitis and amyotrophic lateral sclerosis. Furthermore, CSF 14-3-3 protein test is not widely available.

Electroencephalograph typically shows periodic biphasic or triphasic sharp waves at 0.5 to 1 Hz while some patients have non-specific diffuse slowing[12]. Periodic sharp waves may not be present at the initial stage but becomes apparent at later stage.

The diagnostic criteria for sporadic CJD include the following:

1. Rapidly progressing dementia (less than 2 years)
2. At least 2 of 4 clinical features:
   a) Visual or cerebellar dysfunction
   b) Myoclonus
   c) Pyramidal or extrapyramidal features

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**Figure 2** Diffusion Weighted Image (DWI) (A) showing hyperintensity indicating fluid restriction within the cortical ribbons in the both frontal and right parietal lobes (arrows). These changes are only vaguely seen on the Fluid Attenuated Inversion Recovery (FLAIR) image (B).

**Table 2:** Creutzfeldt-Jakob disease in Southeast Asia.

<table>
<thead>
<tr>
<th>Authors</th>
<th>Country</th>
<th>Year</th>
<th>Definitive CJD</th>
<th>Probable CJD</th>
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<tbody>
<tr>
<td>Kandiah et al</td>
<td>Singapore</td>
<td>2008</td>
<td>4</td>
<td>10</td>
</tr>
<tr>
<td>See SJ et al</td>
<td>Singapore</td>
<td>2004</td>
<td>2</td>
<td>-</td>
</tr>
<tr>
<td>Lee KE et al</td>
<td>Singapore</td>
<td>1998</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>Lim CC et al</td>
<td>Singapore</td>
<td>2004</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>Poungvarin et al</td>
<td>Thailand</td>
<td>1983</td>
<td>1</td>
<td>-</td>
</tr>
</tbody>
</table>

**Abbreviations:** CJD: Creutzfeldt-Jakob Disease
d) Akinetic mutism

3) Typical EEG changes

While the diagnosis of definitive CJD requires brain biopsy, a probable CJD can be made if all 3 criteria or criteria 1 & 2 plus positive CSF 14-3-3 protein are present [13]. Although brain biopsy was not done in our patients, the diagnosis of sporadic CJD was probable as all patients had diagnostic DWI MRI and positive CSF protein 14-3-3. Both test had high sensitivity and specificity.

In conclusion, CJD often presents with non-specific symptoms leading to wrong diagnosis. High index of suspicion is needed with help of various investigation modalities such as DWI MRI, EEG and CSF 14-3-3 protein. Investigations such as CSF 14-3-3 protein are not readily available in many developing countries in Southeast Asia. Although no specific treatment is available, early diagnosis is important for prognosis and infection control. There has been no study systematically investigating geographical distribution of CJD. Whether CJD is actually rarer in Southeast Asia or under-diagnosed and under-reported remains unanswered. We recommend the establishment of a national or even regional surveillance centre to better understand the epidemiology, to provide diagnostic support and to increase the awareness of health care professional towards CJD.

REFERENCES


