

A Case Series of RT-QuIC Positive Sporadic Creutzfeldt-Jakob Disease-First Two Cases from Malaysia

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ABSTRACT

Creutzfeldt-Jakob disease (CJD) is invariably a fatal neurodegenerative disorder that presents rapidly progressive dementia with multifaceted involvement of the nervous system. In this case series, we present case reports of two elderly patients diagnosed with sporadic CJD who presented with rapid progression of cognitive decline and myoclonus. Supportive findings on further investigations included cortical ribboning on diffusion-weighted MRI brain; generalised periodic complexes on electroencephalogram with positive cerebrospinal fluid 14-3-3 and pathogenic prion protein (PrP^{Sc}) detection on RT QuIC confirming the diagnosis of sporadic CJD in both cases to a great extent.

INTRODUCTION

Creutzfeldt-Jakob disease (CJD) is a rare neurological illness that causes dementia, extrapyramidal symptoms, cerebellar symptoms, myoclonus, and abnormal psychiatric aspects. CJD is one of the known clinical classifications of human prion disorders. Sporadic CJD (sCJD) is the most dominant subtype of CJD, accounting for over 90% of cases, with familial, iatrogenic, and variant forms accounting for the rest.^{1,2} The conventional trio of CJD is progressive cognitive deterioration, myoclonic jerks, and ataxia.³ The condition progresses rapidly in terms of functional and cognitive damage, finally leading to akinetic mutism and death within one year of the start of the illness. Furthermore, due to the high index of uncertainty for this rare disorder, diagnosing CJD is typically difficult.⁴ This case series describes two elderly patients with the diagnosis of sporadic CJD made based on clinical presentations, findings on MRI, EEG, and pathogenic prion protein by RT QuIC assay. The misfolded pathogenic prion protein (PrP^{Sc}), a characteristic of transmissible spongiform encephalopathies, is detected using fluorescent dye in this approach.

CASE 1

A 70-year-old woman with a two-week history of progressive cognitive decline, behavioural, and personality

changes, and worsening functional impairment was referred to Hospital Canselor Tuanku Muhriz for a checkup. She was also easily forgetful in the preceding 3 months. On neurological and psychiatric evaluation, she was initially diagnosed with hypoactive delirium and major depressive disorder by a private psychiatrist 3 months earlier but with no significant family history of any neurological disorder. In addition, she had previous hypertension and dyslipidaemia for 5 years. She had memory impairment, was unkempt, and did not respond to commands during admission.

Myoclonus, hypertonia, brisk reflexes, and extensor plantar responses were present. Due to worsening ataxia, she was unable to walk and was subsequently bedridden with episodes of anxiety and agitation. The laboratory analysis for thyroid stimulating hormone, vitamin B₁₂, folate levels, and renal and liver function tests results were all normal. Cerebrospinal fluid (CSF) results were within the normal limits (protein 307mg/dl, sugar 3.73mmol/l, total cell count 0/mm³) and bacterial cultures were negative. Viral and autoimmune encephalitis screening were normal. However, magnetic resonance imaging (MRI) of the brain showed cortical ribboning as in Figure 1A. Simultaneously, the electroencephalogram (EEG) showed generalised periodic discharges and theta activity

as in Figure 2A. The CSF 14-3-3 protein and pathogenic prion protein (PrP^{Sc}) analyses with the RT-QuIC assay were positive. Eventually, there was a rapid functional decline into akinetic mutism that resulted in her demise just two weeks after admission.

CASE 2

A 63-year-old woman, with hypertension and dyslipidaemia presented with 7 months of progressive cognitive decline, and behavioural, and personality changes. Her family members noted she was easily forgetful, and disorderly, and experienced heightened anxiety with worsening functional impairment. Prior to admission, she was diagnosed with schizoaffective disorder after presenting to a psychiatrist and started on an antipsychotic, tablet risperidone 1.5 mg daily. Despite a temporary improvement, she developed upper limb rigidity followed by progressive apathy. Upon admission, she was noted as being quiet, disheveled, and unable to follow any commands with both hands in a flexed position most of the time. Continuous myoclonic jerks were observed in all four limbs, with the right lower extremity being the most affected. She was unable to walk due to worsening ataxia. The preliminary investigations including full blood count, renal, liver, and thyroid function tests, folate, and vitamin B₁₂ levels were all within normal limits.

Screening for syphilis, human immunodeficiency virus, hepatitis B, and autoimmune screening was unremarkable. There were no detectable abnormalities on the chest radiograph, electroencephalogram, and abdominal-pelvic ultrasonography. Routine CSF test results were unremarkable (Table 1), but the 14-3-3 protein level was markedly elevated, more than 4000 pg/uL (N < 200). Pathogenic prion protein was identified in the RT-QuIC assay. MRI of the brain revealed florid cortical ribboning with symmetrical increased signals involving the cerebral cortex of the frontal, parieto-occipital regions, and basal ganglia in Figure 1B. Additionally, EEG demonstrated generalised periodic discharges as in Figure 2B. She was subsequently discharged for home palliative care and succumbed a few months later.

Table 1: The cerebrospinal fluid parameters in case 1 and case 2

Cerebrospinal fluid (CSF)	Case 1	Case 2
Protein (mg/dL)	307	889
Glucose (mmol/L)	3.73	2.77
Cell count	0	0
Acid-fast bacilli	negative	negative
Culture	negative	negative
Cryptococcal antigen	negative	negative

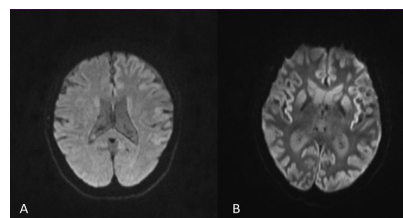


Figure 1A: Magnetic resonance imaging brain diffusion-weighted sequence showed cortical ribboning changes in case 1.

Figure 1B: Magnetic resonance imaging brain diffusion-weighted sequence showed cortical ribboning with bilateral symmetrical increased signal involving the frontal, parieto-occipital cortex, and basal ganglia in case 2.

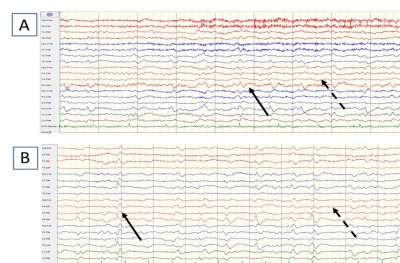


Figure 2: Electroencephalograms for both case 1 (Fig. 2A) and case 2 (Fig. 2B) showing diffuse theta activity (broken arrows) with generalised periodic epileptiform discharges (bold arrows).

DISCUSSION

Creutzfeldt-Jakob disease (CJD) is the most common human prion disease, with sporadic CJD accounting for 85–90% of cases.^{2,3} Theoretically, CJD is categorised as a fatal prion disease caused by the misfolding of the PrP^c protein into PrP^{Sc}. The known peak onset age for CJD is 55 to 75 years old, with a median onset age of 67 years and a mean of 64 years⁵ which corresponds with our patient's age. Moreover, whether familial, sporadic, or iatrogenic, CJD is recognised by a wide range of symptoms with variable clinical characteristics and associated regional distributions of neuropathology.³ There are several subtypes, including cerebellar involvement with cerebellar ataxia; occipital lobe involvement with visual abnormalities; and striatal degeneration with extrapyramidal symptoms.⁶ As a result, CJD disease patients will exhibit a variety of neurobehavioral characteristics that may roughly correspond to the topographical distributions of lesions, which are typically asymmetrical.⁴

The defining clinical picture of sporadic Jakob-Creutzfeldt disease is rapidly progressive dementia accompanied by behavioral issues, gait ataxia, extrapyramidal symptoms, and, eventually, myoclonus.⁵ As a result, these patients meet the "probable" sporadic CJD criteria, which include; rapid cognitive loss, ataxia, myoclonus, and akinetic mutism during hospitalisation. A definitive diagnosis can only be made through direct neuropathological examination and performing various laboratory tests on the brain tissue that is usually obtained at autopsy.³ However, the clinical diagnosis of Jakob-Creutzfeldt disease is typically verified using a combination of symptoms and auxiliary testing, such as; CSF, EEG, and, perhaps most importantly, brain MRI.⁵ Diffusion-weighted imaging (DWI) MRI of the brain has a sensitivity of 92 percent to 96 percent and a specificity of 93 percent to 94 percent in sCJD.⁵

The presence of signal hyperintensity in the basal ganglia (caudate and putamen) or the cortical ribbon is strongly associated with sporadic CJD.⁶ At the time of diagnosis or within a short time after the presentation, MRI may reveal mild to moderate widespread cerebral and cerebellar atrophy. Generally, EEG plays a crucial role in the diagnosis and prognosis of the underlying condition as part of the dementia workup. The EEG abnormalities may evolve throughout the stages of sCJD, from diffuse slowing and frontal rhythmic delta activity (FIRDA) in the early stages to periodic sharp-wave complexes (PSWCs) in the middle stages, and reactive coma traces or alpha coma in the late stages.^{7,9} Other dementias, such as Alzheimer's disease or metabolic encephalopathy, rarely have similar EEG changes to those found in sCJD.⁸ These anomalies, however, frequently do not manifest until the disease is fairly advanced, necessitating serial testing.

These EEG and MRI changes were currently observed in both patients. Surrogate markers of neuronal damage such as CSF 14-3-3 may not be specific for the diagnosis of sCJD as it may be present in viral encephalitis, subarachnoid haemorrhage, and glioblastoma. Thus, a more specific diagnostic method using real-time quaking-induced conversion (RT-QuIC) in sCJD with a sensitivity of 87% and specificity of nearly 100% has been reported.¹⁰ Accordingly, in both our cases the pathogenic prion

protein (PrP^{Sc}) has been detected by the RT-QuIC assay, hence, substantiating their diagnosis as sporadic CJD. The diagnosis of sCJD may be elusive initially and apart from supportive radiological findings and CSF analysis, EEG is of equal importance in achieving the diagnosis. These two cases highlight the need for clinical vigilance and the use of RT QuIC assay as an essential workup in suspected CJD.

CONCLUSION

Sporadic CJD can manifest itself in a variety of ways, thus it is difficult to diagnose early, especially if the symptoms are initially masked by a psychiatric-related illness. Though sCJD is invariably fatal without any treatment option, it is critical to make an early and precise diagnosis to differentiate it from other treatable conditions. Hence, patients and their families will be able to anticipate the prognosis, discuss management goals, and institute early palliative care.

CONSENT

Written informed consent was obtained from the patient and family member for the publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

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