Original Article

Creutzfeldt-Jakob Disease in Sanpasitthiprasong Public Referral Hospital in Ubon Ratchathani Northeast Thailand : A Case Series and Review of the Literature

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Abstract

Creutzfeldt-Jakob Disease (CJD) is a rare human prion-related disease which is incurable and inevitable results in death. Unspecific presentations lead more of misdiagnosis; further with low awareness of disease by non-neurology specialist. Critically importance of accurate diagnosis of CJD brings understanding prognosis and provides best supportive care to the patient, but to differential diagnose other potentially reversible dementias is the true point of critic.

We retrospectively reviewed the case records of Sanpasitthiprasong hospital, public referral hospital in Ubon Ratchathani Thailand from 1997-2018 and found 4 cases of probable sporadic CJD which was tractable.

Here we provide an illustrated report of 4 patients with sporadic CJD. All cases were prior misdiagnosed due to miscellaneous unspecific symptoms, though finally diagnosed by neurologist with the approach of rapidly progressive dementia. Not all of them presented myoclonus hallmark. Interestingly, one case raised us query on the relevance of tuberculous CNS infection with variant CJD. There are no specific, non-invasive tests for definite diagnosis CJD. Likewise none of our 4 cases underwent brain biopsy nor post mortem autopsy. Role of magnetic resonance imaging of brain and electroencephalogram in combi-

nation with clinical features have been main relevant supportive evidences which practically recommended for the diagnosis in Thailand.

Keyword : Creutzfeldt-Jakob Disease; prions; myoclonus; rapidly progressive dementia; Thailand

Introduction

Creutzfeldt-Jakob Disease (CJD) is a rare human prion-related disease which is incurable and inevitable results in death. Unspecific presentations lead more of misdiagnosis especially by non-neurologist. Approximately one case of sporadic CJD occurs per 1,000,000 population per year with a worldwide distribution[1]. However, there is limited official statistics and knowledge on CJD in Thailand, among general practitioner and non-neurology specialist. Very few reports are found published in Thailand to date. These make CJD, a typical characteristic - neurodegenerative disease under-reported and unaware. Here we report 4 tractable case reports of sporadic CJD found in 20 years - record in Sanpasitthiprasong hospital, public referral hospital, Ubon Ratchathani, Thailand; 3 patients with probable sporadic CJD and 1 patient with possible sporadic CJD, by CDC diagnostic criteria. All these scarce CJD cases in Sanpasitthiprasong hospital confirm the epidemiology of CJD in Thailand still is sporadic type same to other reports published prior worldwide. Varieties on initial presentation were found. With or without myoclonus, rapidly progressive dementia is a reliable hallmark to first think of and to start an approach to this fatal incurable disease.

This article aims to raise awareness of approaching rapidly progressive dementia by general practitioner in broad for the sake of ruling out potentially reversible dementias especially one with a rapid progression which has high proportion of reversibility.

A summary of the patients' characteristics were showed in Table 1. In the section below, we describe 4 patients with probable sporadic CJD, diagnosed based on CDC criteria.

Case presentation

Case1

A 46-year-old male with tuberculosis spine presented with 2 months history of confusion, blurred vision and progressive lower limb weakness. Urinary and fecal

incontinence were noted. Off and on headache had also been concerned. He was provisional diagnosed with chronic meningoencephalitis which complied with his risk of extra-pulmonary TB spine infection. CSF analysis showed normal but slightly increased of protein level. No cell was shown. CSF was negative for culture, bacterial CIA, acid-fast bacilli and cytology. None of these was supporting the diagnosis of TB meningoencephalitis. A CT brain with and without contrast were performed to investigate cause of his progressive cognitive declination but the results were unremarkable. One year prior, he developed a progressive lower extremities weakness and low back pain with no constitutional symptom. T-L spine plain film X-ray and MRI thoracic spine was suggestive of T2-4 Tuberculous spondylodiscitis. Anti-TB drug regimen was started with good drug compliance. Unfortunately, the process is ongoing: Eight months later, he developed Thoracic spinal myelopathy from T4 spine compression fracture, becoming bedridden, and coming up with this onset of neurodegenerative symptoms. After one week of hospitalization, he was noted to have rapidly progressive cognitive decline, disorientation and a blank stare. Few days later, He became stuporous, generalized rigidity and spastic tetraparesis, and finally, generalized myoclonic jerks were presented. His DWI and FLAIR MR imaging brain scan showed abnormality of high signal intensity on bilateral precuneus cortices and bilateral medial cortices of parietal lobes. (Figure 1). An EEG revealed pattern of periodic synchronous triphasic sharp wave complexes (PSWC) which is helpful in the differentiation of sCJD from other prion disease. Palliative treatment was proceeded with still now the progression be followed. Together with clinical and investigative findings, patient was diagnosed to have probable sporadic CJD according to CDC Diagnostic Criteria for Creutzfeldt-Jakob Disease 2010[2]

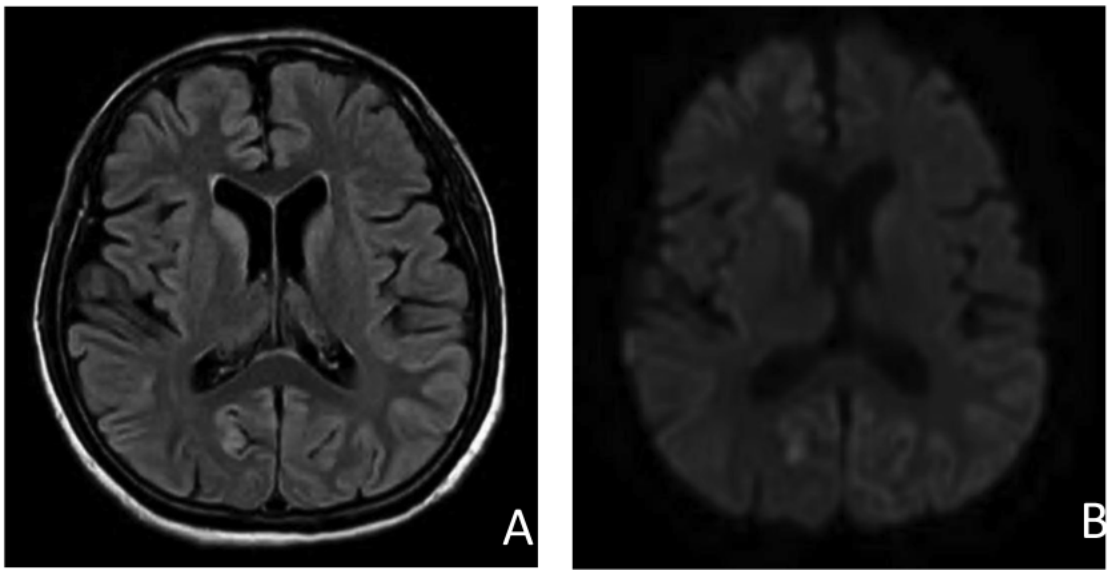

Figure 1. FLAIR (A) and Diffusion-weighted (B) magnetic resonance imaging showing high signal intensity on bilateral precuneus cortices and bilateral medial cortices of parietal lobes. (front-cover page)

Case2

A 69-year-old male with history of 6 months rapidly progressive cognitive impairment presented with 2 months - left sided weakness which was worsening in 1 week. Complaint of his blurred vision; was firstly diagnosed of mild cataract, was noticeable turning into a blank stare. Physical examination did not reveal any myoclonus since first to last, but there was a grade III/V motor weakness on left sided accompanying with left sided spastic tone. He was confused with slurred incomprehensive speech pronounce. Right MCA infarction was provisional diagnosis. Then non-contrast CT brain imaging was proceeded. But the result showed unremarkable. By deteriorating on his progression, a rapidly progressive dementia was approached. Results of laboratory studies were normal. His CSF profile showed no cell and was negative for paraneoplastic screening. CSF Total tau/ Phosphorylated tau protein ratio was sent and a report also showed negative range for both CJD and Alzheimer's disease. MRI brain with and without intravenous gadolinium, including DWI, FLAIR, and ADC sequences, was performed; showing a cortical ribbon sign of bilateral posterior parieto-occipital regions on DWI. His EEG

study showed intermittent right sided 30-50 microvolts rhythmic 3-5 Hz delta wave with polyspike activity over the temporal head regions which was not conclusive for CJD diagnosis. Phenytoin and baclofen was prescribed to treat his spasticity. But no seizure or myoclonic jerking was observed. Every two months follow up was arranged. Each time progressive cognitive and spasticity was impair. Finally, he lost to follow up in eighth month after the first presentation. No further tractable progression was documented.

Together with clinical and investigative findings, patient was diagnosed to have possible sporadic CJD according to CDC Diagnostic Criteria for Creutzfeldt-Jakob Disease 2010[2].

Case3

A 73-year old male presented in outpatient clinic with orobuccal dyskinesia, mutism, and recent memory loss. Apraxia and aphasia were also noted. He was recently diagnosed of epilepsy last six months, after presented with hands spasm and off and on alteration of consciousness. CT brain non contrast was performed with no structural brain lesion otherwise generalized brain atrophy was shown. A rapidly progressive dementia was approached. Anti - NMDA encephalitis was first in his differential diagnosis. Lumbar puncture was proceeded. Serum and CSF paraneoplastic profile, CSF T-Tao: P-Tao ratio, blood PCR prion protein gene mutation was sent with all result to be negative. His DWI MR brain imaging showed faint increase signal within both cortical gyri along anterior inter-hemispheric fissure of both frontal lobe. Early manifestation CJD is considered but artificial demonstration can't be ruled out. Three serial EEG in the drowsy and asleep states showed frequent periodic sharp wave activity (PLEDs - Periodic Lateralized Epileptiform Discharges) at right sided over the parieto-occipital head regions (first two sequential EEG) changing into area of parieto-central head regions in last EEG; all suggestive of a structural lesion with epileptogenic components. Following next seven months till now, no myoclonic jerking has been shown. Immobilization syndrome: pressure ulcer and constipation were complained. Together with clinical and investigative findings, patient was diagnosed to have probable sporadic CJD according to CDC Diagnostic Criteria for Creutzfeldt-Jakob Disease 2010[2].

Case 4

A 70-year old male with known underlying disease of psoriasis presented with sequential worsening neurological illness on time. He was first diagnosed with aseptic meningitis after shows of confused state and fever. CSF profile was atypical. Though, intravenous high intracranial dose antibiotic was prescribed. Treatment took 4 weeks with overall improving in clinical but fever was last to resolve. Drowsiness and lethargy have been observed accompanying with his first onset of focal upper extremity seizure, developing one month after of those. Intracranial lesion was investigated. CT brain with and without contrast show no abnormality, same to CSF profile which was clear. He was treated as a post meningoencephalitis with anti-epileptic drug, sodium valproate; though, a jerking movement was not well-controlled. Following nine months; ataxic gait, sleep disturbance, cognitive and conscious declination were presented. A progressive upper to lower extremities hyperkinetic non rhythmic jerking movement accordingly showed. He turned totally dependent in tenth month. Rapidly progressive dementia was approached. MR brain imaging with GAD was performed. DWI and FLAIR imaging revealed increase signal at bilateral parieto-occipital lobe, predominant on the right cortical region. EEG showed frequent burst of periodic complex sharp wave over bilateral parieto-occipital region. He was diagnosed with sporadic CJD and the symptoms were relieved by anti-spastic and anti-epileptic drug. One month follow up was arranged. No shown and an intractable to prognosis was reported.

Together with clinical and investigative findings, patient was diagnosed to have probable sporadic CJD according to CDC Diagnostic Criteria for Creutzfeldt-Jakob Disease 2010[2].

Age/Sex	Presentation	Provisional / previous diagnosis	DWI MRI brain result	EEG finding	Final diagnosis
46/Male	Early: recently diagnosed TB sine, progressive lower limb weakness, confusion, blurred vision, Later: rapidly progressive cognitive decline, spastic tetraparesis, blank stare, generalized myoclonic jerks	Chronic meningoencephalitis	High signal intensity on bilateral precuneus cortices and bilateral medial cortices of parietal lobes	Periodic synchronous triphasic sharp wave complexes (PSWC)	Probable sporadic CJD
69/Male	Early: confusion, left sided weakness, blurred vision, slurred incomprehensive speech Later: rapidly progressive cognitive decline, blank stare	Right MCA infarction	Cortical ribbon sign of bilateral posterior parieto-occipital regions	Polyspike activity over the temporal head regions	Possible sporadic CJD
73/Male	Early: hands spasm and off and on alteration of consciousness Later: rapidly progressive cognitive decline, orobuccal dyskinesia, mutism, apraxia, aphasia	Epilepsy	Faint increase signal within both cortical gyri along anterior Inter-hemispheric fissure of both frontal lobe	PLEDs (Periodic Lateralized Epileptiform Discharges) at right sided over the parieto-occipital to parieto-central head regions	Probable sporadic CJD

Age/Sex	Presentation	Provisional / previous diagnosis	DWI MRI brain result	EEG finding	Final diagnosis
70/Male	Early: confusion, drowsiness and lethargy, focal upper extremity seizure Later: ataxic gait, sleep disturbance, rapidly progressive cognitive decline, progressive upper to lower extremities hyperkinetic non rhythmic jerking movement	Post meningoencephalitis	Increase signal at bilateral parieto-occipital lobe, predominant on the right cortical region	Periodic complex sharp wave over bilateral parieto-occipital region	Probable sporadic CJD

Discussion

Creutzfeldt-Jakob Disease (CJD) is a rapidly progressive fatal neurodegenerative disorder caused by an abnormal isoform of prion protein, triggers prion protein in the brain to fold into the same abnormal shape, causing brain cell destruction. It is the most common of the human prion diseases, although is still rare. Sporadic (sCJD), familial (fCJD), iatrogenic (iCJD), and variant forms of CJD (vCJD) are all recognized. The vast majority 85 to 95 percent of CJD cases are sporadic, while 5 to 15 percent are familial; iatrogenic CJD generally accounts for less than 1 percent. Approximately one case of sporadic CJD occurs per 1,000,000 population per year with a worldwide distribution[3,4].

In Thailand, there is limited literature of CJD; less than 3 publishes was found since 1917, year of the first announced CJD in Thailand, either as it has been underreported or misdiagnosed. The knowledge of this rare disease still is confined to medical specialists.

CJD may be mistaken for a variety of illness due to unspecific presentation. However, the hallmarks of CJD are rapidly progressive dementia (RPD) especially with myoclonic jerk[5]. We found supportive same

evidence of reaching the final diagnosis of CJD too by RPD approach, but myoclonic jerking was found only in half of our patients.

Various focal neurologic findings reflect predominant involvement of brain regions and that clinical phenotypes, as now known have six, have been associated with molecular subtypes determined by the PRNP gene codon and the pathologic prion protein (PrPSc) type[6]. To correlate to the case; a rapidly progressive dementia with early prominent myoclonus, presented in case no.1 patient, additionally with a cortical blindness, would be counted for MM1, myoclonic - Heidenhain variant of "classic CJD"[6].

Clinician, especially general practitioner, needs high index of suspicion to remind of CJD when rapidly progressive dementia is developed, particularly if accompanied by myoclonus, ataxia, and/or visual disturbances as outlined diagnosis of probable sporadic CJD by The Centers for Disease Control and Prevention (CDC). Variant CJD is not commonly found in Thailand nor Southeast Asia country[5] but the psychiatric symptom and younger age at average should be aware of concern. The differential diagnosis and sufficient investigation for rapidly progressive dementia is critically important, no changing in prognosis of CJD, but potentially reversible causes of rapidly progressive dementia should be definitely excluded. Alzheimer disease/ frontotemporal dementia are examples of which can commonly show a rapidly progressive neurodegenerative dementia with myoclonus; nevertheless, never before earlier progressed than 12 month to death like CJD[7]. Other extensive variety of causes such as infectious, toxic and metabolic encephalopathies, cerebrovascular disease, autoimmune and paraneoplastic encephalopathies should be considered[8,9].

In contrast, the prominent features of cranial nerve abnormalities, sensory abnormalities, and involvement of the peripheral nervous system should raise the suspicion of an alternative diagnosis as it is atypical characteristic of CJD[1].

Appropriate clinical features and investigative findings; including Electroencephalogram, 14-3-3 Cerebrospinal fluid assay (for sCJD), DWI or FLAIR MR brain Imaging; generally are sufficient for a diagnosis of "probable" sporadic CJD or even "suspected" variant CJD by the latest CDC's diagnostic criteria. But a "definite"

diagnosis of all CJD requires features of those with a combination of neuropathology report from brain biopsy or a detection of protease resistant PrPSc from brain material as the gold standard. The procedure is generally discouraged unless is needed to rule out a treatable disorder.

Investigation modalities of each give individually independent yield of sensitivity and specificity for disease diagnosis; moreover; differentiating four types of CJD. Routine laboratory studies are typically normal[10]. CSF contains no cell and usually shows normal glucose level. An elevated CSF protein may occur in about 40 percent of patients[11]. A brain CT scan is generally normal and serves mainly to exclude other diagnoses[12]. 14-3-3 CSF assay is not available in Thailand and also rarely been tested in many countries. Anyhow, it is suggested that the test should be considered as an adjunctive investigation rather than an absolute test for the diagnosis, due to studies have shown mixed results regarding its sensitivity and specificity. Elevated CSF levels of 14-3-3 isoforms are also described in a variety of other conditions including causes that have been differentiated in the diagnosis of CJD; some report suggests that the protein may be a marker of brain cell death rather than CJD[13], indicating none of these is clearly diagnostic of prion disease.

MR brain imaging (The recommended MR imaging protocol for assessment of patients with suspected CJD include T2 and proton density axial images with 3 mm slice thickness, FLAIR axial and sagittal images at 3 mm slice thickness, T1 images, and diffusion-weighted images (DWI)[14].) is an accurate non-invasive diagnostic test for both variant and sporadic Creutzfeldt-Jakob disease according to CDC criteria for diagnosis. With different but high sensitivity and specificity per publication, High signal in caudate/putamen on MRI brain scan or at least two cortical regions (temporal, parietal, occipital), most sensitive on DWI, is fulfilled in a diagnostic criteria of sCJD. A bilateral pulvinar high signal on MRI, most sensitive on FLAIR, is asserted as an investigation for vCJD[15,16]. These findings are not entirely specific for CJD but could reliably distinguish CJD from other causes of rapidly progressive dementia, with a high degree of sensitivity[17].

A characteristic EEG pattern of periodic synchronous bi- or triphasic sharp wave complexes (PSWC) is highly specific for the diagnosis of sporadic CJD. In large series of autopsy confirmed study, objective

EEG criteria for sCJD showed a sensitivity and specificity of 64 and 91 percent, respectively, and positive and negative predictive values were 95 and 49 percent. However, overall specificity is up to 98 percent after combining EEG criteria with a clinical criteria[18].

PSWCs are helpful in the differentiation of sCJD from other prion disease. As PSWCs are not found in patients with vCJD and only occasionally found in patients with fCJD[18,19].

Some studies proposed that the probability of recording PSWCs corresponds to the amount of neuronal loss; false negative was found in initial and later stages of sCJD in a serial EEG during the course of the illness[20,21].

From overall, we recommend practical diagnostic investigations applicable in Thailand are following 1) Cerebrospinal fluid assay 2) DWI and FLAIR MR Brain imaging 3) Electroencephalogram

Plenty of case series review show no report of progressive bilateral lower limbs weakness as first presentation which that might be a supportive evidence of this case no.1 patient's weakness is solely caused by TB spine myelopathy coincidentally, rather than an onset symptom nor the suspicious relationship of his TB spine infection and CJD;

A connection between consumption of meat contaminated with the agent causing bovine spongiform encephalopathy (BSE) and the outbreak of CJD was cited in "Thinking the unthinkable: Alzheimer's, Creutzfeldt-Jakob and Mad Cow disease[22].

In case no.1 patient, a positive pulvinar sign in DWI MRI brain was commented in first radiologist's opinion; raised us an interesting question whether he has variant CJD, which is never before reported in Thailand. Hypothesizing the relationship of his Bovine tuberculosis (TB spine in this case) - BSE (Bovine Spongiform Encephalopathies) - vCJD.

Living in the endemic area of Tuberculosis, Thailand: and a personal history of raw cow meat consumption, also be a supportive evidence to make a connection of Bovine tuberculosis - BSE and finally distracted us to the diagnosis of variant CJD.

To clear cut the diagnosis, a second radiologic opinion was requested and EEG investigation was pursued. The description of triphasic sharp wave in EEG with a cortical ribbon sign at bilateral parietal cortex and precuneus cortices in DWI MRI brain; finally guided us to the diagnosis of

sporadic CJD in case no.1 patient. Anyhow 'did his TB spine caused from Bovine tuberculosis pathogen' still can't definitely be estimated. Since species identification here in Thailand is not carried out routinely.

Together these shows importance of multi-modality investigation and power of radiologic inter-reviewer discrepancy in diagnosing type of CJD and the topic of Bovine tuberculosis - BSE - vCJD relationship.

Creutzfeldt-Jakob Disease is an incurable and inevitably fatal neurodegenerative disorder. Painkillers, muscle relaxants and anti-epileptic drugs are prescribed for symptomatic support. No specific treatment shows benefit so far. Death usually occurs within one year of symptom onset with a median disease duration of six months[23].

In conclusion, diagnosing Creutzfeldt-Jakob Disease in Thailand relies on clinical neurological hallmarks of rapidly progressive dementia presented with various non-specific symptoms. We report 4 cases with probable sCJD hereby, which of all were misdiagnosed prior to meet neurologist special consultation. This represents a narrow range of disease acknowledgement by general practitioner and non-neurology specialist. Most common type of CJD in Thailand is sporadic, same to other epidemiology; and never before variant CJD has been reported in Thailand. MR brain imaging and electroencephalogram are accessible practical diagnostic tools with high sensitivity and specificity filled in CDC diagnostic criteria. Misdiagnosing disease causes no change in prognosis of this uniformly fatal - disease but differentiating other reversible treatable causes which coming in mimicking presentation is definitely vital.

References

1. Brown HG, Lee JM. Creutzfeldt-Jakob disease [internet]. 2017 [cited September 25 2017]. Available from: http://www.uptodate.com/contents/creutzfeldt-jakob-disease.
2. Centers for Disease Control and Prevention. CDC's Diagnostic Criteria for Creutzfeldt-Jakob Disease (CJD), 2010 [internet]. 2015 [cited October 1 2017]. Available from: https://www.cdc.gov/prions/cjd/diagnostic-criteria.html.
3. Masters CL, Harris JO, Gajdusek DC, et al. Creutzfeldt-Jakob disease: patterns of worldwide occurrence and the significance of familial and sporadic clustering. Ann Neurol 1979; 5:177-88.

4. Ladogana A, Puopolo M, Croes EA, et al. Mortality from Creutzfeldt-Jakob disease and related disorders in Europe, Australia, and Canada. Neurology 2005; 64:1586-91.
5. Law ZK, Subramaniam SR, Tan HJ, Azmin S, Osman SS, et al. Creutzfeldt-Jakob Disease: A first case series from a tertiary hospital in Malaysia and review of literature in Southeast Asia. Clin Res Infect Dis 2014; 1 : 1008.
6. Parchi P, Giese A, Capellari S, et al. Classification of sporadic Creutzfeldt-Jakob disease based on molecular and phenotypic analysis of 300 subjects. Ann Neurol 1999; 46:224-33.
7. Josephs KA, Ahlskog JE, Parisi JE, et al. Rapidly progressive neurodegenerative dementias. Arch Neurol 2009; 66:201-7.
8. Roohani P, Saha KM, Rosenbloom M. Creutzfeldt-Jakob Disease in the hospital setting: A case report and review. Minnesota Medicine 2013; 96:46-9.
9. Papageorgiou SG, Koros C. Rapidly progressive dementia - clinical aspects and management. European Neurological Review 2011; 238-45.
10. Tanaka M, Lizuka O, and Yuasa T. Hepatic dysfunction in Creutzfeldt-Jakob disease. Neurology 1992; 42:1249.
11. Zeidler M, Green A. Advances in diagnosing Creutzfeldt-Jakob disease with MRI and CSF 14-3-3 protein analysis. Neurology 2004; 63:410-1.
12. Hayashi R, Hanyu N, Kuwabara T, et al. Serial computed tomographic and electroencephalographic studies in Creutzfeldt-Jakob disease. Acta Neurol Scand 1992; 85:161-5.
13. Satoh J, Kurohara K, Yukitake M, et al. The 14-3-3 protein detectable in the cerebrospinal fluid of patients with prion-unrelated neurological diseases is expressed constitutively in neurons and glial cells in culture. Eur Neurol 1999; 41:216-25.
14. Collie DA, Sellar RJ, Zeidler M, et al. MRI of Creutzfeldt-Jakob disease: imaging features and recommended MRI protocol. Clin Radiol 2001; 56:726-39.
15. Collie DA, Summers DM, Sellar RJ, et al. Diagnosing variant Creutzfeldt-Jakob Disease with the pulvinar sign: MR imaging findings in 86 neuropathologically confirmed cases. American Journal of Neuroradiology 2003; 24 : 1560-9.
16. Macfarlane RG, Wroe SJ, Collinge J, et al. Neuroimaging findings in human

prion disease. Journal of Neurology, Neurosurgery, and Psychiatry 2007; 78:664-70.

17. Vitali P, Maccagnano E, Caverzasi E, et al. Diffusion-weighted MRI hyperintensity patterns differentiate CJD from other rapid dementias. Neurology 2011; 76:1711-9.
18. Steinhoff BJ, Zerr I, Glatting M, et al. Diagnostic value of periodic complexes in Creutzfeldt-Jakob disease. Ann Neurol 2004; 56:702-8.
19. Brown P, Gibbs CJ Jr, Rodgers-Johnson P, et al. Human spongiform encephalopathy: the National Institutes of Health series of 300 cases of experimentally transmitted disease. Ann Neurol 1994; 35:513-29.
20. Bortone E, Bettoni L, Giorgi C, et al. Reliability of EEG in the diagnosis of Creutzfeldt-Jakob disease. Electroencephalogr Clin Neurophysiol 1994; 90:323-30.
21. Lee RG, Blair RD. Evolution of EEG and visual evoked response changes in Jakob-Creutzfeldt disease. Electroencephalogr Clin Neurophysiol 1973; 35:133-42.
22. Broxmeyer L. Thinking the unthinkable: Alzheimer's, Creutzfeldt-Jakob and Mad Cow disease: the age-related reemergence of virulent, foodborne, bovine tuberculosis or losing your mind for the sake of a shake or burger. Medical Hypotheses 2005; 64:699-705.
23. Pocchiari M, Puopolo M, Croes EA, et al. Predictors of survival in sporadic Creutzfeldt-Jakob disease and other human transmissible spongiform encephalopathies. Brain 2004; 127:2348-59.