Prevalence and Descriptive Analysis of Creutzfeldt-Jakob Disease at Siriraj Hospital

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Abstract

Introduction: Creutzfeldt-Jakob disease (CJD) is rare, rapidly progressive, fatal, neurodegenerative disease classified under transmissible spongiform encephalopathies (TSE) or prion diseases. It is characterized by a long asymptomatic period followed by rapid clinical deterioration leading to the death within months. This disease is still under-reported in Thailand.

Objective: To describe the clinical, radiological and electroencephalographic characteristics of CJD in Siriraj hospital.

Materials and Methods: 18 cases of CJD encountered from 4,435 cases of rapidly progressive dementia (RPD) over the past 10 years in Siriraj hospital (between 2006 and 2015).

Results: Patients with RPD filling the diagnostic criteria for sporadic (sCJD) and variant (vCJD) were included. All were investigated in detail to find out any possible treatable cause including brain MRI, EEG and CSF analysis. There were sCJD 15 cases and vCJD 3 cases. The prevalence of CJD was 0.0094 %, (95% CI: 0.0056% - 0.015%), mean age of patients was 60.72 years, 10 were men. The main clinical manifestations were 18 cognitive disturbance, 14 myoclonus and only 4 ataxia. Time interval (mean) between an onset of disease to death was 8.22 months. Brain MRI abnormalities were noted in 17 patients: FLAIR hyperintensities in the bilateral caudate nucleus, putamen and thalamus. DWI hyperintensities in cortical regions (temporal-parietal-occipital) were seen in 94% of patients. Classical EEG changes of periodic epileptiform discharges were seen in 83.33% of patients. None of the patients underwent brain biopsy.

Conclusion: A strong clinical suspicion aided by characteristic brain MRI and EEG abnormalities is essential for a timely diagnosis of this fatal disease.

Keywords: Clinical manifestation, Creutzfeldt-Jakob disease, diagnosis, prion diseases, Thailand

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Introduction

Creutzfeldt-Jakob disease (CJD) belongs to the group of human prion diseases. These are inevitably fatal disorders that are characterized clinically by progressive neuropsychiatric symptoms.[1,2] Prion diseases also are called transmissible spongiform encephalopathies (TSEs)[1], due to the finding of the spongiform change in the cerebral and cerebellar cortex and being transmissible. This is associated with the deposition in the brain of an abnormal conformer of the cellular prion protein (PrP^C, where C indicates cellular). Prion diseases affect animal. It also includes the natural scrapie in sheep and goats.

PrP^C is synthesised in the endoplasmic reticulum, and after the procession in the Golgi apparatus, it is carried to the cell surface where it is mainly found in lipid rafts.[3] PrP^C has endogenously truncated fragments: a role in neurogenesis, synaptogenesis, neuritogenesis, anti-and pro-apoptotic functions, copper binding, redox homoeostasis, and functions related to hematopoietic cells has been suggested.[4] PrP^C is the major PrP form in the normal non-diseased brain but can still be found in the prion diseased brain as well. The structure of PrP^C is α-helix predominant; indeed, a conformational change is the major difference between PrP^C and the disease-associated form named PrP^{Sc} (where Sc refers to scrapie, a prion disease of sheep).[1] PrP^{Sc} features a predominantly β-pleated structure, it is detergent-insoluble, and resistant to protease treatment (in immunoblotting it is indicated as PrP^{res}).[1] Interestingly, detergent-insoluble and protease-resistant PrP has been reported in non-diseased brains; it was proposed that this may represent dormant infectivity (PrP^*).[5] On the other hand, conformation-dependent immunoassay detected protease-sensitive (PrP^{sen}) but disease-associated transitional forms. In summary, at least four forms of PrP can be defined, which has diagnostic implications: (1) PrP^C, (2) PrP^*, (3) PrP^{Sc} (PrP^{res}), and (4) PrP^{sen}. The first two are detectable in non-diseased brains, the first and the last two in diseased brains.

The most frequent form of CJD is sporadic (idiopathic); in this form yet mysterious events lead to the production of disease-associated PrP.[7] Acquired forms (i.e., where the etiology is recognized with high probability) are the following: (1) Kuru: this is related to ritualistic cannibalism and thought to be extinct; (2) Variant CJD: this is associated with consuming BSE-infected tissue or with receiving transfusion from variant CJD blood donors;[9] (3) Iatrogenic CJD: this is related to medical procedures, including human growth hormone or gonadotrophin hormone therapy, neurosurgery, dura transplant, cornea transplants, and deep electrodes. Finally, genetic (familial) forms are also known, which are associated with mutations in the PrP gene (PRNP). This can be further classified as follows (1) Point mutations associated with spongiform encephalopathy (genetic CJD); (2) The point mutation D178N associated with methionine at codon 129 is associated with selective thalamic neurodegeneration called FFI; (3) Further mutations are related to prominent amyloid deposits, which are called Gerstmann-Sträussler-Scheinker disease (GSS) or PrP amyloidosis. It is characterised by the appearance of multicentric amyloid plaques and biochemically by a low-molecular-weight band in Western blot. Amyloid can appear in the vessels as PrP cerebral amyloid angiopathy. It should be

noted that base pair insertions in the PRNP may associate with atypical disorders but may also show a CJD or GSS phenotype.

The incidence of CJD in the United States is estimated to be 1-1.5 per million per year.[10] In Thailand, there are no official statistics on or national surveillance of CJD. It was estimated that no more than 30 cases had been diagnosed in the previous 20 years.[11] The age of onset is usually between 55-75 years, median 68 years, and both genders are an affected equally. There are four subtypes of CJD: sporadic, familial, iatrogenic, and variant form.[12]

Sporadic CJD is the most common form of prion diseases accounting for 90% of all CJD cases.[13] Clinical presentation is manifested by rapidly progressive dementia and varied associated neuropsychiatric manifestations like myoclonus, cerebellar ataxia, visual symptoms, pyramidal and extrapyramidal signs, and akinetic mutism. The median duration of survival is approximately 4.5 months from onset of symptoms, with 90% of patients surviving less than one year.[13] There is a considerable amount of variability in the presenting symptoms of sCJD, but several studies support the existence of distinct clinical phenotypes that differ from the classic CJD presentation. The sCJD variants include the classic CJD variant, Heidenhain variant, the Oppenheimer-Brownell variant, the cognitive variant, the affective variant and the indeterminate variant.[14] In a prior meta-analytic review,[15] we confirmed an earlier observation made by Wall and colleagues,[16] that neuropsychiatric symptoms are among the most common symptoms of sCJD, particularly in its early stages, which suggests the possible existence of neuropsychiatric sCJD variants.

A new variant of Creutzfeldt-Jakob disease was first reported in 1996,[17] and compelling evidence now exists that this new disease is caused by exposure of humans to the agent that causes bovine spongiform encephalopathy. The initial description of variant Creutzfeldt-Jakob disease—based on the first 10 cases diagnosed—reported a predominantly psychiatric initial presentation, as distinct from the usual clinical course of sporadic Creutzfeldt-Jakob disease. A study of the first 14 cases of variant Creutzfeldt-Jakob disease in the United Kingdom, of which 13 patients had been seen by a psychiatrist early in the clinical course, revealed that all 14 patients had early psychiatric features.[18] Typical presentations were depression, anxiety, and behavioural change. The psychiatric symptoms did not disclose specific features that differentiated variant Creutzfeldt-Jakob disease, at the time of presentation, from more common psychiatric disorders, although subsequent neurological and cognitive deterioration led to the eventual clinical suspicion of Creutzfeldt-Jakob disease.

The tools for the clinical diagnosis of CJD include the demonstration of altered signals on MRI diffusion-weighted imaging,[19] periodic sharp wave complexes (PSWC) on electroencephalography (EEG) recording and presence of the 14-3-3 protein in CSF.[20] In Thailand, there are only two previous reports of CJD cases that include Creutzfeldt-Jakob disease: review of experience at Siriraj Hospital[21] and case series from Faculty of Medicine, Thammasat University.[11] There are under-registration and recognition of the disease due to lack of strong clinical suspicion and paucity of centres or laboratories diagnostic tests. The study was aimed at 1) providing more data on clinical, radiological

and electroencephalographic characteristics of cases of CJD in Siriraj Hospital by reviewing cases encountered in our hospital over the past ten years (between January 1, 2005, and December 31, 2015), and 2) calculating the prevalence of CJD during that period.

Materials and Methods

Subjects

This study was an IRB-approved retrospective medical record review of all patients with encephalitis (ICD code G04, n = 192,095). Eighteen diagnosed with CJD as found in Siriraj Hospital between January 1, 2005, and December 31, 2015. This record system includes inpatient. The subjects were identified using encoded diagnoses of Creutzfeldt-Jakob disease (ICD-10 A81.09).

Inclusion Criteria

The criteria used for inclusion of patients as positive for CJD according to World Health Organization (WHO) criteria.[22] Two criteria were used to determine a clinical diagnosis of sCJD and vCJD in cases that did not have neuropathologic material available for analysis.

- Cases were diagnosed as probable sCJD using the 1998 WHO criteria[22] if there was evidence of progressive dementia and at least 2 of the following symptoms: myoclonus, visual or cerebellar disturbance, pyramidal or extrapyramidal dysfunction, and akinetic mutism. Probable sCJD cases (by WHO criteria) also had either periodic sharp wave complexes on electroencephalography (EEG) or a cerebrospinal fluid (CSF) assay positive for the 14-3-3 protein with a survival time shorter than two years. Cases that met the mentioned symptom criteria for probable sCJD but that did not demonstrate a positive 14-3-3 protein analysis or periodic sharp wave complexes on EEG or did not undergo these studies were classified as probable sCJD according to the University of California-San Francisco criteria[23] if they had subcortical hyperdensity or cortical ribboning on diffusion-weighted imaging.

- Cases were diagnosed as vCJD using the 1998 WHO criteria if patient with a progressive neuropsychiatric disorder with

I. All of the following features: progressive psychiatric disorder, clinical duration >6 months age at onset <50 years, routine investigations do not suggest an alternative diagnosis, no history of potential iatrogenic exposure, no evidence of a familial form of TSE (transmissible spongiform encephalopathies), the EEG does not show the typical periodic appearance, routine investigations that do not suggest an alternative diagnosisand an MRI showing abnormal bilateral high signal from the pulvinar on axial T2- and/or proton-density-weighted images.

II. At least 5 out of the following 6 clinical features: early psychiatric symptoms, early persistent paresthesia/dysesthesia, ataxia, chorea/dystonia or myoclonus, dementia and kinetic mutism.

Variant CJD cannot be diagnosed with certainty on clinical criteria alone; this requires neuropathological confirmation. The following combinations of signs, symptoms and clinical investigations serve to define possible, probable and definite vCJD: The probable vCJD also had

- All of I.
- At least four items under II.
- Bilateral pulvinar high signal on MRI brain

scan

- EEG dose not show the typical appearance of sporadic CJD although generalized periodic complexes may occasionally be seen at the later stages of the disease.

Data Collection

Neurologists(NK,VS) comprehensively reviewed medical records, and data were abstracted for demographic characteristics and illness chronology. Results of brain MRI, EEG and CSF analysis were collected as well. Data were abstracted from medical records using the same abstraction instrument for all cases. Case histories were reviewed and classified into five predetermined sCJD variants and indeterminate group[14]

Further clinical information was gathered to include the date of CJD symptom onset as defined by the clinical documentation, future date of CJD diagnosis, date of death, and whether there was a family history positive for CJD. Patients' clinical charts were also reviewed for evidence of a past psychiatric and neurological history. Neurological symptoms (date of onset and type) during disease course and presenting symptoms (date of onset and type) were recorded in each case. Prodromal or presenting symptoms were defined as the clinical signs and symptoms that led the patient to seek medical attention and were retrospectively recognised as the initial manifestations of the disease course. History of surgical procedure or head trauma, past medical history, medications were recorded in each case. Demographic information regarding each patient's date of birth, sex, occupation, and place of residence was also included. Results of biological workup were also recorded: Complete blood count, electrolytes, liver function test, renal function tests including blood urea nitrogen and creatinine, erythrocyte sedimentation rate (ESR), calcium, phosphorus, thyroid function test, vitamin B12 level, folate level, human immunodeficiency virus (HIV) screening test, hepatitis B profile, serum Venereal Disease Research Laboratory (VDRL) test, anti-nuclear antibody (ANA), anti-thyroid peroxidase antibodies (anti-TPO) level, anti-thyroglobulin level, urinalysis, cerebrospinal fluid (CSF) analysis including cell count, cell type, protein, glucose, bacteriological, virological studies including Total Tau, Phosphorylated Tau and Beta amyloid protein level in CSF. All patients underwent 1.5 Tesla brain magnetic resonance imaging (MRI) including diffusion-weighted (DWI) and fluid attenuated inversion recovery (FLAIR) sequences. EEG was carried out using the International 10-20 system and EEG abnormalities was recorded in detail. The final clinical outcome of each patient was recorded.

SPSS, version 18.0 (SPSS Inc, Chicago, Illinois) was used to perform the statistical analyses. Survival data were calculated using descriptive statistics, mean, minimum, maximum and percentage.

Table 1 Characteristics of 5 sCJD variants

sCJD variant	Characteristics
Classic CJD	Onset of cognitive symptoms (cognitive decline, amnesia, language impairment, executive dysfunction, and/or disorientation) and ataxia at illness onset, without visual disturbances Clinical presentation within 1 mo. of illness onset Short interval between symptom onset and diagnostic testing (CSF 143-3- protein, EEG, and brain MRI) Survival time ≤ 3 mo.
Heidenhain	Onset of diplopia, blurred vision, cortical blindness, and/or visual hallucinations at illness onset Survival time ≤ 4 mo.
Oppenheimer-Brownell	Ataxia in the absence of other presenting symptoms at illness onset Older age at illness onset (median, 67 y) Lack of PSWCs on EEG and basal ganglia hyperintensity on brain MRI
Cognitive	Onset of dementia, memory impairment, language impairment, executive dysfunction, and/or disorientation at illness onset in the absence of ataxia and visual disturbances Clinical presentation 2 mo. after symptom onset Prolonged interval between illness onset and diagnostic testing Survival time > 4 mo.
Affective	Depression, mood lability, and/or anxiety at illness onset Age at onset ≤ 65 y Prolonged time to clinical presentation Prolonged time to diagnostic testing High rate of positive CSF analyses for 143-3- protein despite duration of illness Survival time > 6 mo.
Indeterminate	The clinical characteristics that could not be classified into 1 of the aforementioned groups

Results

This is the first retrospective, observational, the hospital-based study which analyses eighteen cases CJD patients. By screening the hospital records for the diagnosis of CJD during the study period, all eighteen cases satisfying the WHO and the University of California-San Francisco criteria diagnostic criteria for probable sCJD and probable vCJD. In cases of sCJD (15/18) were classified as probable sCJD (12/15) and possible sCJD (3/15) according to World Health Organization (WHO) diagnostic criteria for CJD.[22] Based on the University of California-San Francisco criteria classified as probable sCJD (15/15). In cases of vCJD (3/18) were classified as probable vCJD (3/3) according to World Health Organization (WHO) diagnostic criteria for CJD.[22] During January 2005 to December 2015, 192,095 cases were admitted with suspected encephalitis, with thorough investigation 18 had the diagnosis with CJD. The prevalence of CJD at Siriraj hospital was 0.0000937 (0.0937/1000 population) (95%CI 0.0000555, 0.0001481)

The mean age of patients at presentation was 60.72 years (sCJD was 66 years, and vCJD was 34 years). Ten patients were males (M:F = 10:8). In cases of sCJD were classified into five predetermined sCJD variants including Heidenhain variants (5/15), Oppenheimer-Brownell variants (3/15), Cognitive variants (3/15), Classic variants (1/15), Affective variants (1/15) and Indeterminate group (2/15). Demographic, clinical and paraclinical characteristics of cases are summarised in Table 2 and 3. None of the patients had the head injury in the past.

The main clinical manifestations were cognitive disturbance (18/18) and myoclonus (14/18), followed by extrapyramidal symptoms/signs (10/18), ataxia (9/18), behavioural change (6/18) and visual disturbance (5/18).

Table 2 Demographic and clinical feature of sCJD

Case no	Age/ sex	Classification		Variants	Symptom at onset	Onset to death (months)	Clinical features
		WHO criteria	UCSF criteria				
1	50/M	Probable	Probable	Oppenheimer-Brownell	Ataxia	6	Ataxia, dementia, myoclonus
3	65/M	Probable	Probable	Classic	Language impairment	3	Behavioral change, dementia, sleep disturbance (insomnia), myoclonus, EPS
4	58/M	Probable	Probable	Heidenhain	Visual disturbance	8	Visual hallucination, sleep disturbance (insomnia), behavioral change, myoclonus
5	61/M	Probable	Probable	Affective	Hypomania	13	Sleep disturbance (hypersomnolence), depression, dementia, myoclonus
6	70/F	Probable	Probable	Heidenhain	Dementia	9	Visual disturbance, dementia, EPS, myoclonus
7	66/F	Probable	Probable	Cognitive	Dementia	10	Dementia, memory impairment, sleep disturbance (insomnia), myoclonus, EPS, akinetic mutism
8	77/F	Possible	Probable	Oppenheimer-Brownell	Ataxia	10	Ataxia, dementia, EPS, akinetic mutism
9	58/F	Probable	Probable	Oppenheimer-Brownell	Ataxia	5	Ataxia, dementia, EPS, visual disturbance
10	74/F	Possible	Probable	Cognitive	Language impairment	7	Memory impairment, sleep disturbance (hypersomnolence), akinetic mutism, EPS
11	75/M	Possible	Probable	Indeterminate	Visual disturbance	6	Ataxia, visual disturbance, EPS, myoclonus, akinetic mutism
12	58/F	Probable	Probable	Heidenhain	Visual disturbance	5	Dementia, behavioral change, EPS, myoclonus
13	64/M	Probable	Probable	Indeterminate	Visual hallucination	14	Visual hallucination, ataxia, myoclonus
14	73/F	Probable	Probable	Heidenhain	Visual hallucination	5	Visual hallucination, dementia, EPS, myoclonus
15	69/M	Probable	Probable	Heidenhain	Visual disturbance	4	Visual disturbance, dementia, sleep disturbance (insomnia), ataxia, akinetic mutism
17	73/F	Probable	Probable	Cognitive	Dementia	2	Behavioral change, dementia, akinetic mutism, myoclonus

The phenotype with the largest percentage of cases was the Heidenhain variant (n=5 [33.33%]); 3 cases (20%) were classified as the Oppenheimer-Brownell variant; 3 cases (20%) were classified as the cognitive variant; 1 case (6.67%) was categorized as the classic variant; 1 case (6.67%) was classified as the affective variant; and 2 (13.33%) cases were indeterminate group. The mean age at the onset of illness across the entire sCJD was 66 years. Patients with the Heidenhain variant had a mean age of 65.6 years; the Oppenheimer-Brownell variant (61.67 years); the cognitive variant (71 years); the classic

variant (65 years); the affective variant (61 years) and the indeterminate group (69.5 years). The age at disease of vCJD are demonstrated as Figure 1.

The initial symptoms of each group are presented in Table 2. Four patients (80%) within the Heidenhain variant presented with visual disturbance and visual hallucinations. All patients (100%) within the Oppenheimer-Brownell variant presented with ataxia. Dementia was the primary presenting symptom in those with the cognitive variant of sCJD (n=2 [66.67%]). Patients with indeterminate cases presented with symptoms of visual impairment and ataxia. In cases of sCJD has been characterised by prominent neuropsychiatric symptoms; the affective variant (n=1) present with hypomania; the cognitive variant (n=3) present with behavioural change and nearly one-half of the sCJD patients (7/15) were affected by sleep disturbances, ranging from profound hypersomnolence to insomnia.

The classic CJD cases have the shortest mean survival time from symptom onset (3 months), while the affective variant (13 months) had the longest median survival times. The Heidenhain, Oppenheimer-Brownell, cognitive and indeterminate variant had mean survival times of 6.2 months, 7 months, 6.33 months and 10 months, respectively. The symptoms and characteristics of cases are summarized in Table 4.

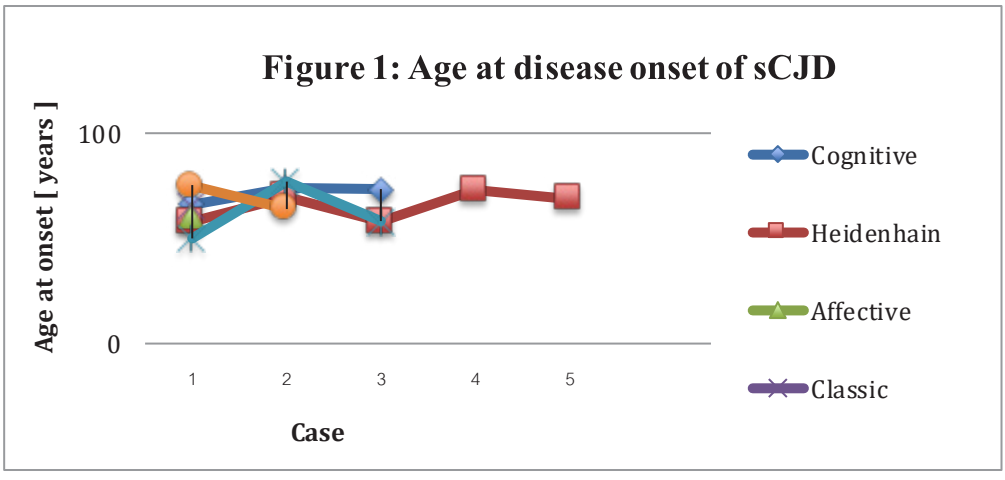


Table 3 Demographic and clinical feature of vCJD

Case no	Age/ sex	Classification (WHO criteria)	Symptom at onsets	Clinical feature	Onset to death (months)
2	42/M	Probable	Paresthesia	Behavioral discontrol (violent), sleep disturbance (insomnia), psychotic symptom (perseveration and confabulation), ataxia, myoclonus, akinetic mutis	14
16	36/M	Probable	Ataxia	Loss of interest, irritability, sleep disturbance (insomnia), myoclonus, EPS	11
18	24/M	Probable	Behavioral change	Behavioral change (aggression), dementia, psychotic symptom (VH), sleep disturbance (insomnia), ataxia, myoclonus, akinetic mutism	16

Table 4 Symptom and characteristics of sCJD variants

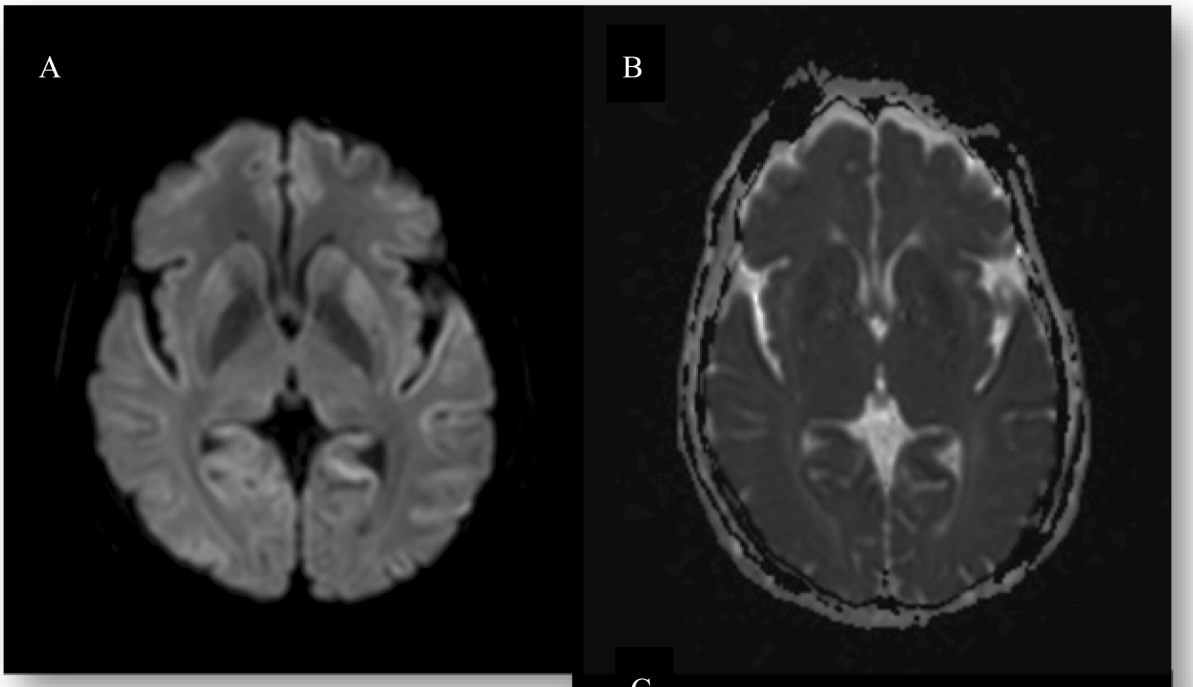
	sCJD variant (n=15)						Total n(%)
	Heidenhain (n=5) (%)	Oppenheimer-Brownell (n=3) (%)	Cognitive (n=3) (%)	Classic (n=1) (%)	Affective (n=1) (%)	Indeterminate (n=2) (%)	
Initial symptom							
Visual disturbance	3 (60)	-	-	-	-	1 (50)	4 (26.67)
Dementia	1 (20)	-	2 (66.67)	-	-	-	3 (20.00)
Visual hallucination	1 (20)	-	-	-	-	1 (50)	2 (13.33)
Ataxia	-	3 (100)	-	-	-	-	3 (20.00)
Language impairment	-	-	1 (33.33)	1 (100)	-	-	2 (13.33)
Hypomania	-	-	-	-	1 (100)	-	1 (6.67)
Onset to death (months)	6.2	7	6.33	3	13	10	

The three patient were classified as the probable vCJD according to World Health Organization (WHO) diagnostic criteria for CJD.[22] The mean age of patients at presentation was 34 years (range 24 - 42). All of the cases were males (M = 3). In this population, 3/3 patients were categorised as having at least one psychiatric manifestation during illness. Symptom onset and timing were determined by noting the documented date of the first symptoms observed as reported by the physician. A neuropsychiatric manifestation in the prodromal or presenting phase of the illness was recorded in 3/3 (100%) of the cases. The most commonly reported symptoms are sleep disturbance (3/3); insomnia more common than hypersomnolence. The mean survival time from symptom onset to death of vCJD was 13.67 months. The demographic and clinical feature of vCJD was summarised in Table 3.

Brain MRI abnormalities were noted in seventeen of our eighteen patients (94%). The brain MRI of twelve patients (66.67%) showed MRI FLAIR with hyperintensities in bilateral caudate and putamen. Three patient (16.67%) had FLAIR hyperintensity in pulvinar nucleus of bilateral thalami being compatible with the pulvinar sign. DWI hyperintensities and apparent diffusion coefficient (ADC) hypointensities were seen in the head of left caudate, left putamen and bilateral parietooccipital region in one patient. DWI hyperintensities and ADC hyperintensities were noted in bilateral frontotemporal and parietooccipital regions (four patients[22.22%]), bilateral parietal-temporal and occipital region (two patients[11.11%]) and bilateral parietooccipital and temporal regions (one patient[5.5%]). Only one patient had brain MRI revealed only diffuse cerebral atrophy predominately at bilateral parietal lobe. Figures 2 and 3 show the characteristic brain MRI abnormalities of selected cases. Brain MRI characteristics of individual patient are summarized in Table 5.

Table 5 Brain MRI findings and EEG characteristics

Case no	Brain MRI findings	EEG characteristics
1	FLAIR hyperintensities in bilateral caudate, lentiform nucleus and thalamus.	Periodic sharp wave complex
2	FLAIR hyperintensities in bilateral caudate, putamen and pulvinar nucleus of bilateral thalami.	Generalized diffuse slow wave
3	DWI and ADC hyperintensities in bilatertal fronto-temporal and parieto-occipital regions.	Periodic sharp wave complex
4	FLAIR hyperintensities in bilateral caudate and putamen.	Periodic sharp wave complex
5	FLAIR hyperintensities in bilateral caudate and putamen.	Periodic sharp wave complex
6	Diffuse cerebral atrophy predominately at bilateral parietal lobe	Periodic sharp wave complex
7	FLAIR hyperintensities in bilateral caudate and putamen.	Periodic sharp wave complex
8	FLAIR hyperintensities in bilateral caudate and putamen.	Normal awake EEG
9	DWI and ADC hyperintensities in bilatertal fronto-temporal and parieto-occipital regions.	Generalized periodic sharp wave complex
10	DWI and ADC hyperintensities in bilatertal fronto-temporal and parieto-occipital regions.	Generalized diffuse slow wave
11	DWI and ADC hyperintensities in bilateral fronto-temporal and parieto-occipital regions.	Generalized diffuse slow wave
12	FLAIR hyperintensities in bilateral caudate and putamen. DWI and ADC hyperintensities in bilatertal parieto-temporal and occipital region.	Generalized periodic sharp wave complex
13	FLAIR hyperintensities in subcortical white matter of bilateral fronto-parieto-temporal region.	Generalized periodic sharp wave complex
14	FLAIR hyperintensities in bilateral caudate and putamen. DWI and ADC hyperintensities in bilatertal parieto-temporal and occipital region.	Periodic sharp wave complex
15	DWI and ADC hyperintensities in bilateral parieto-occipital and right temporal regions.	Generalized periodic sharp wave complex
16	FLAIR hyperintensities in bilateral caudate, putamen and pulvinar nucleus of bilateral thalami.	Generalized diffuse slow wave
17	FLAIR hyperintensities with DWI hyperintensities and ADC hypointensities suggestive of restriction in head of left caudate, left putamen and bilateral parieto-occipital region.	Periodic sharp wave complex
18	FLAIR hyperintensities in bilateral caudate, putamen and pulvinar nucleus of bilateral thalami.	Generalized diffuse slow wave



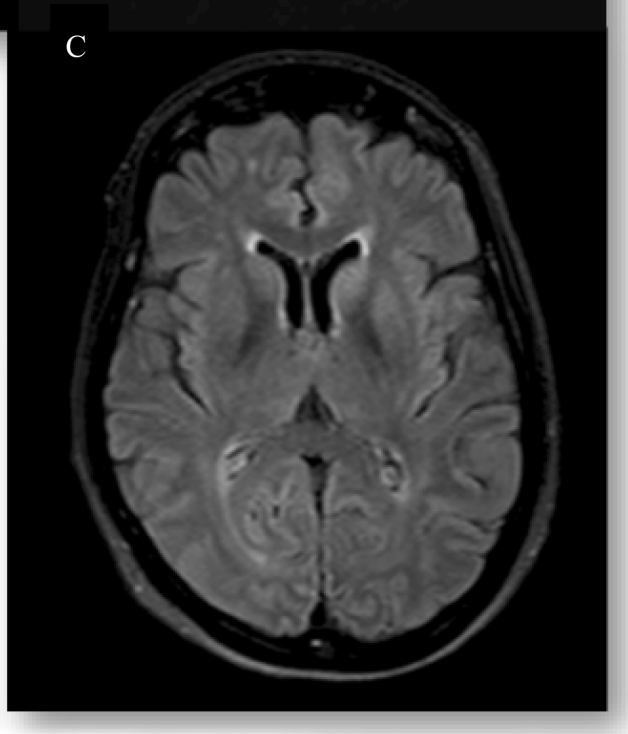


Figure 2 Axial MRI brain (inner back cover)

A) DWI showing hyperintense signal in fronto-parieto-temporo-occipital lobe.

B) ADC showing hypointense signal in fronto-parieto-temporo-occipital lobe.

C) FLAIR showing hyperintense signal in bilateral

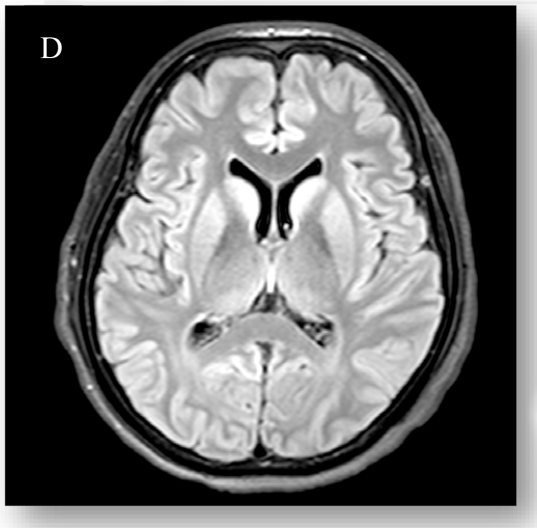


Figure 3: Axial MRI brain (inner back cover)

D) FLAIR showing hyperintense signal in bilateral caudate, putamen and pulvina nucleus of bilateral thalami.

CSF analysis was carried out in all patients, which showed normal to mildly elevated protein, cell count within normal limits and negative bacteriological/virological studies. The CSF 14-3-3 protein assay was not carried out in all patients, but the total tau protein assay was performed in four patients and active in all of them.

Classical EEG abnormalities in the form of periodic sharp wave complex were seen in eight patients (8/18). EEG showed generalized periodic sharp wave complex in four patients, generalised diffuse slow wave in five patient and normal awake electroencephalographic finding in only one patient. Figure 4 shows the characteristic EEG abnormalities of selected cases. One patient was given intravenous immunoglobulin with clinical suspicion of immune-mediated encephalopathy but with no improvement. Postmortem brain examination for confirmation of diagnosis could not be carried out in any of the patients. A comparison of clinical, radiological and electroencephalographic characteristics of sCJD and vCJD is illustrated in Tables 6.

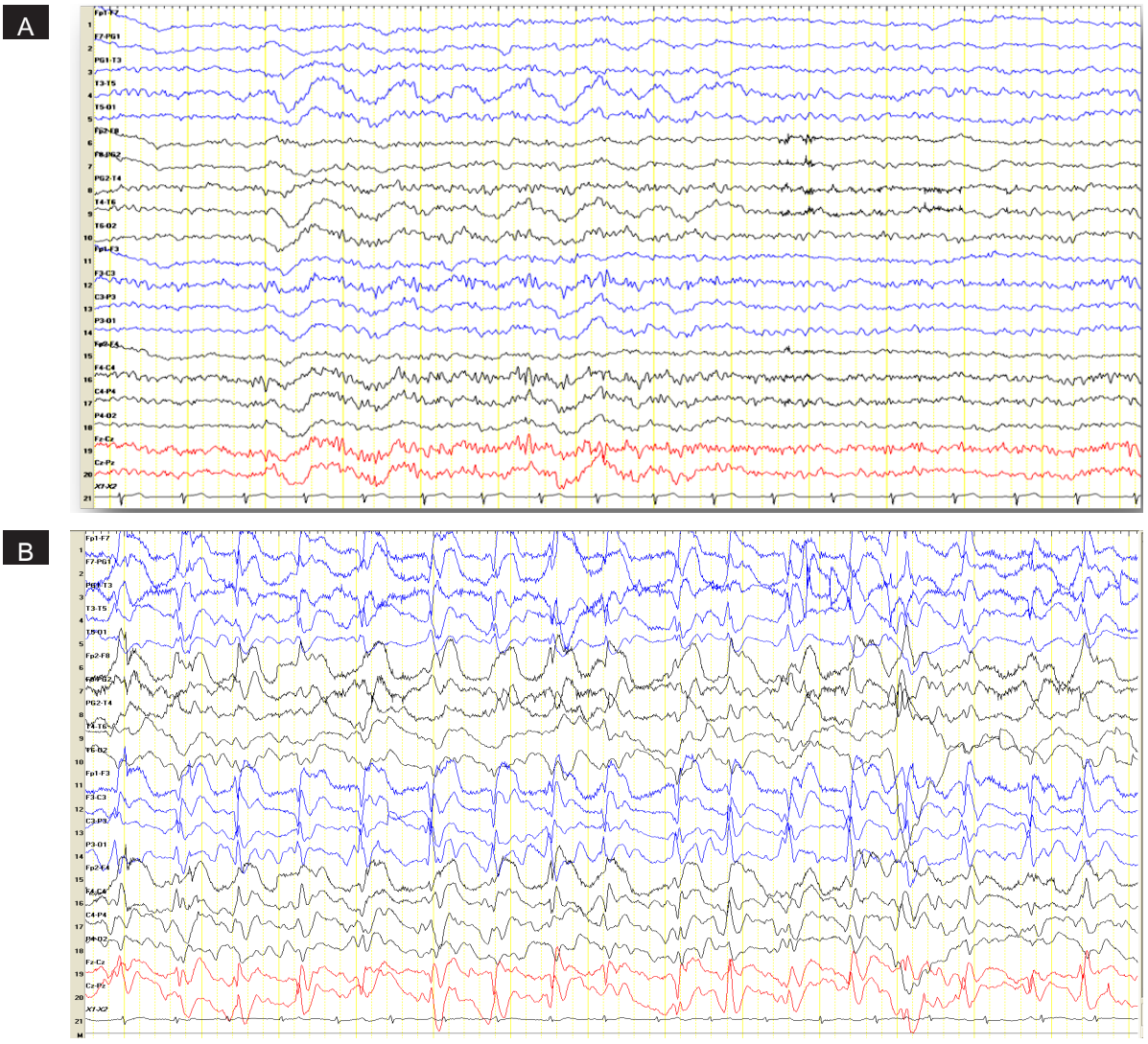


Figure 4 A. EEG showing periodic sharp wave complexes at 1-2/sec with slowing of background rhythm.
B. EEG showing generalized diffuse slow wave.

Table 6 Comparison of clinical, radiological and electroencephalographic characteristics between sCJD and vCJD

Clinical characteristics	Probable sCJD	Probable vCJD
Mean age in years (range)	66 (4277-)	34 (2442-)
Gender (male) (n)	7	3
Typical presentation	Progressive dementia, ataxia, myoclonus	Psychiatric and behavioral symptoms
Interval between onset to death (months) (range)	7.13 (2 - 14)	13.66 (11 - 16)
Family history	Negative	Negative
Brain MRI finding	- FLAIR hyperintensities in bilateral caudate and putamen - DWI hyperintensities in cortex (cortical ribbon sign)	- FLAIR hyperintensities in bilateral caudate, putamen and pulvinar nucleus of bilateral thalami (pulvinar sign).
EEG characterisitc	Periodic sharp wave complex and Generalized periodic sharp wave complex	Generalized diffuse slow wave

Discussion

Clinical suspicion of prion disease is usually raised when rapidly progressive dementia is observed. Although cognitive decline is certainly a major symptom, due to the widespread involvement of different anatomical structures, prion diseases show various combinations of clinical signs.

CJD is a human prion disease with characteristic clinical and diagnostic features. That has a long asymptomatic period and a fatal outcome. There are four subtypes of CJD: sporadic, familial, iatrogenic, and variant form.[12]

sCJD is the most common type of CJD, accounting for 90% of all CJD cases.[13] The disease course is usually less than two years (generally about 4-7 months). In addition to dementia, cerebellar symptoms (ataxia), visual complaints (including cortical blindness), movement disorders (parkinsonism, dystonia, as well as chorea), pyramidal signs, and particularly myoclonus are the most characteristic, however, in various combinations. Indeed, diagnostic criteria require the detection of rapidly progressive dementia (<2 years) and at least two further symptoms mentioned above.[22] In the terminal phase, akinetic mutism is observed.

Variant CJD presents at an earlier age;[24] distinguishing clinical features are the unusual and early sensory (e.g., dysaesthesia, paraesthesia) and psychiatric (e.g., depression, paranoid components, agitation, aggressivity) symptoms[25,26] Later dementia and myoclonus evolves, but chorea, pyramidal signs, cerebellar symptoms and rigidity, and vertical gaze weakness are also described.[26]

In fact, there are only small case series of CJD in Southeast Asia. A literature search on the epidemiology of CJD in south-east Asia revealed only 18 cases from Singapore (1998-2008)[27-30] Four cases from Thailand (1983-2015)[11,21] and 4 cases from Malaysia (2014). Kandiah et al. described the largest case series in Singapore involved four definite CJD and ten probable CJD over a period of 7 years.[27] There are no published reports of CJD in other Southeast Asia countries. This raises the question of whether CJD is under-reported or rare in Southeast Asia.

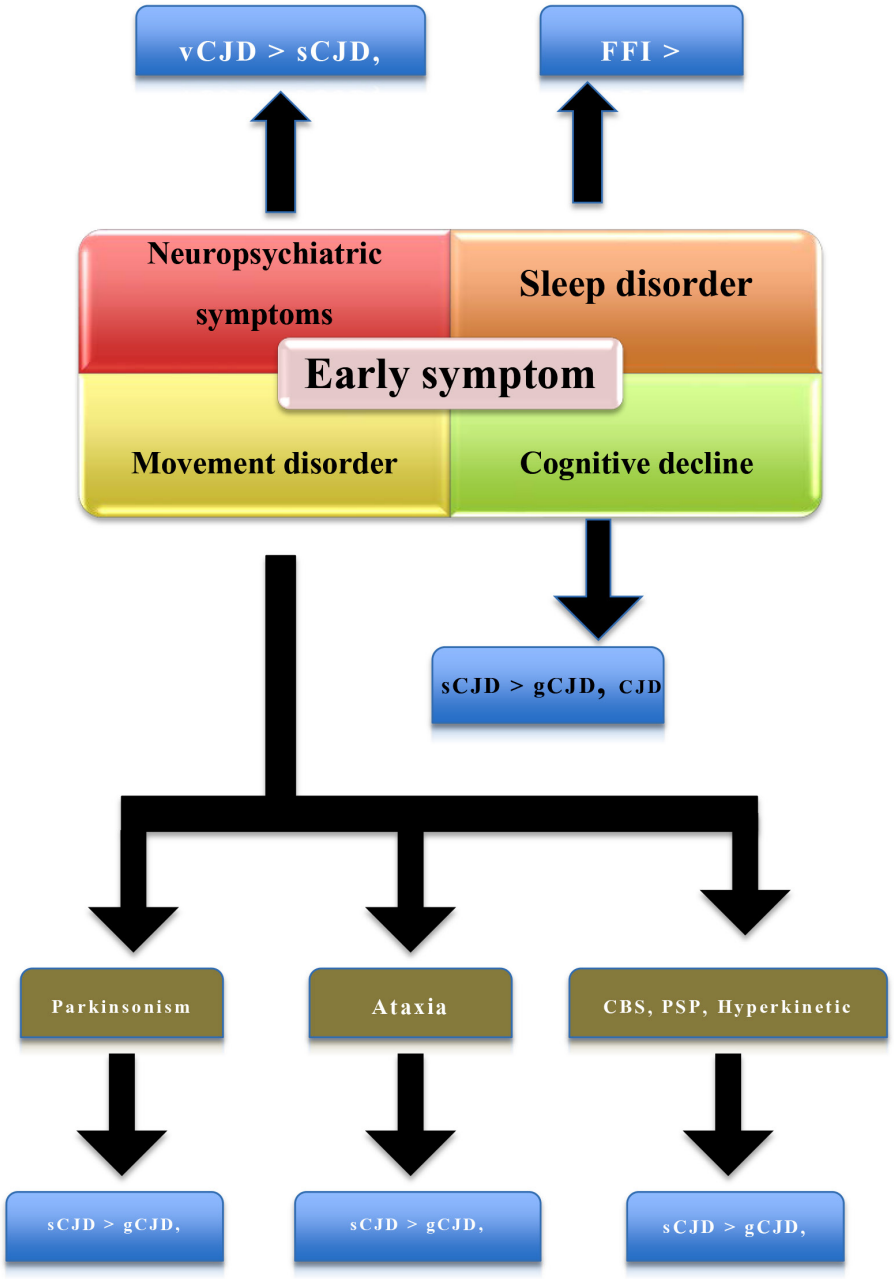
In Thailand, CJD has been underreported and misdiagnosed. Published cases of CJD in Thailand include one case from Siriraj Hospital[21] (1983) and three cases from The Neurology Division, Department of Internal Medicine, Faculty of Medicine, Thammasat University, Pathumthani.[11] There is no regional or national surveillance system for CJD in Thailand. Also, the knowledge of this disease is limited to medical specialists. The public awareness, an efficient reporting system, advanced medical education, laboratory, neurological and neuropathological diagnostic capacity are critical.

The mean age of sCJD patients was 66 years. In the case series by Lolekha, et al.[11], the patient seemed to be younger (57 years). The comparing mean age between studies to be cautions because the sample size is small and the apparent differences in the average age are due to random fluctuations. We found male predominance (10/18) in our series. All of our patients had rapidly progressive dementia and followed by myoclonus. Other clinical manifestations were behavioural disturbances, ataxia, and extrapyramidal symptoms. Similar observations were noted in the case series by Lolekha, et al.[11] All of our patients were evaluated with other relevant investigations to rule out other causes for encephalopathy like infective, metabolic, paraneoplastic and autoimmune etiologies.

Behavioural change in CJD occurs in 30% of patients at the onset of disease and in 57% at later stages.[10] But it was seen in 50% of patients in our series. None of the patients had a family history of similar disease. The time interval between the onset of symptoms and diagnosis varied from 2 month to 16 months with the mean of 7.13 months in probable sCJD and 13.66 months in probable vCJD which was not similar to findings in case series by Lolekha, et al.[11] (20 months). Although sCJD is known to have a range of clinical symptoms, our results indicate that differences in initial symptoms may delineate clinical clusters of cases. It is also significant that the sCJD variants differ on age at symptom onset and survival time, indicating a difference in disease pathology and expression. Differences in survival time not only imply differences in the natural history of the illness but also suggest the possibility of differences in the underlying pathologic process of the disease. Clinical sCJD variants may be a reflection of PrP^{Sc} type and PRNP codon 129 genotypes as previously reported.[31-33] The formalisation of sCJD phenotypes is valuable for some reasons. The heterogeneity of clinical presentations observed in sCJD and vCJD frequently results in the delayed diagnosis or misdiagnosis of prion diseases. Thus, it is reasonable to conclude that the delineation of various sCJD subtypes and vCJD can be used to educate clinicians about the variability of clinical symptoms that are commonly observed in CJD in addition to the disease's propensity to be misdiagnosed. Our data may help to provide a basis for developing clinical identification of sCJD variants and vCJD, which would aid in clinical detection and diagnosis.

Due to the unspecific initial complaints, the suspicion of prion disease is usually raised later when already dramatic clinical symptoms are seen. Clinicians desperately search for reversible or curable disorders, but the inevitably following course strengthens the suspicion of CJD. From previous clinical feature of prion disease has been reported. Depending on the early clinical features, like rapidly progressive cognitive decline, neuropsychiatric symptoms (behavioural dyscontrol,

depressive symptoms and psychotic symptoms),[25] sleep disorder, or movement disorder (parkinsonism, ataxia, or other),[14] the likelihood of the type of prion disease can be already predicted. We propose flow chart of the prediction of human prion disease types based on the early symptoms is illustrated in figure 5



s: sporadic; v; variant, i: iatrogenic; g: genetic CJD (Creutzfeldt- Jakob disease), CBS: corticobasal syndrome, PSP: progressive supranuclear palsy, GSS: Gertsmann-Sträussler-Scheinker disease; FFI: fatal familial insomnia.

Figure 5 Prediction of human prion disease types based on the early symptoms

The brain MRI changes in CJD has been demonstrated to precede EEG or CSF abnormalities. However, it may be without abnormality early in the disease course. High signals in T2-weighted/FLAIR sequences have been linked to astrogliosis.[34] Combined cortical and deep gray matter (basal ganglia and putamen) hyperintensity and isolated cortical hyperintensity are the two patterns of DWI and/or FLAIR abnormality that have been described.[35] DWI is more sensitive than FLAIR in the detection of cortical abnormalities in early stages of CJD. The DWI hyperintensities are due to restricted diffusion and thus are often hypointense (dark) on the ADC map. This restricted diffusion is due to PrP^{Sc} deposition, vacuolation, or a combination of the two.[36] DWI has higher sensitivity (92%) and specificity (93%) in the diagnosis of CJD regardless of PSWCs.[37] Involvement of deep gray matter is associated with shorter disease course with rapidly progressing neurologic deterioration whereas absence of basal ganglia involvement correlates with delayed onset of dementia and longer disease course.[38] The caution is FLAIR MRIs had findings that overlap with those seen in CJD, but whose DWI/ADC sequences did not show these results. These patients usually had non-prion disorders, often treatable autoimmune encephalopathies.[39,40]

Our twelve patients had hyperintensities in caudate and putamen on FLAIR images. DWI hyperintensities were noted in parietooccipital in all six DWI hyperintensities were observed in bilateral frontotemporal and parietooccipital regions in four, bilateral parietal-temporal and occipital region in two and bilateral parietooccipital and temporal regions in one patients. But the corresponding ADC maps in these cortical areas were hyperintense suggesting no diffusion restriction. Two our patient had bilateral basal ganglia and putamen hyperintensities on FLAIR with diffusion restriction with no cortical hyperintensities or restriction on DWI/ADC. Similarly, brain MRI of seven patients with CJD studied by González-Duarte et al.[41] One our patient had FLAIR hyperintensities with DWI hyperintensities and ADC hypointensities suggestive of restriction in head of left caudate, left putamen and bilateral parietooccipital region. Similarly, brain MRI of ten patients with CJD studied by Biswas et al.[42] Brain MRI of one patients showed only cortical atrophy without classical changes of CJD. The patient diagnosed to have extrapyramidal symptom with dementia with myoclonus and visual disturbance (Case 6). The reason for MRI negativity was the brain MRI was done during the terminal stage of illness (9-10 months after onset) wherein the typical MRI abnormalities might have disappeared.[43,44]

The classical EEG changes (PSWC and triphasic waves) were observed in twelve the patients except in six, whose EEG showed the diffuse slowing of background activity and normal awake EEG. EEG has a sensitivity of 67% and specificity of 74-86% in the diagnosis of CJD.[41,43] Repeated EEG during disease increases the probability of demonstrating characteristic EEG abnormality.[45] EEG abnormalities are rarely seen in patients with other cause of dementia like Alzheimer's or vascular dementia.

CSF examination was carried out in all patients except one patient (case 3) because patient's family was denied to perform the lumbar puncture. All of seventeen cases, the CSF did not reveal pleocytosis. The detection of the 14-3-3 protein in CSF has been one of the markers for

diagnosis of CJD.[46] In our series, the assay was not carried out in all eighteen patients. In our series used brain MRI typical finding to additional diagnosed CJD, according to Zerr et, al.[47] reported that MRI results are equivalent to elevated levels of the 14-3-3 protein in the diagnosis of probable sporadic CJD.

This study represents a single-center experience from Thailand. All our eighteen patients were the resident of Thailand. This geographical clustering assumes significance. This study demonstrates the fact that CJD is prevalent in Thailand. There is a need for spreading awareness about early suspicion and recognition of this fatal disease among the treating general medical practitioner, physicians and psychiatrist. The prompt referral to the tertiary centre with neuroscience expertise is also warranted. However, we need further research and national surveillance in Thailand. The CJD surveillance in Thailand has to be improved utilising availability of advanced tests like CSF biomarkers, facilities for antemortem diagnosis of CJD and prion protein genotyping which is lacking.

The limitation of our study. Firstly, postmortem brain examination for confirmation of diagnosis could not be carried out in any of the patients. Histological examination and immunostaining for protease-resistant protein (PrPSc) are the gold standard for the diagnosis. As a result, all our cases were suggestive of prion pathy due to lack of histological confirmation. We suggest multicenter study with postmortem evaluation in the future study. Secondly, the 14-3-3 protein assay could not be carried out in all patients due to financial constraints and logistic problems for transferring to a foreign laboratory. Recently, Total tau has been the purpose of their good relationship with CJD. Five cases of this study had high elevated of total tau in CSF level.

Conclusion

CJD is the fatal neurodegenerative disease. It has a broad range of clinical manifestations including cognitive decline, myoclonus, ataxia, pyramidal and extrapyramidal signs/symptoms, behavioural abnormalities and psychosis. The diagnosis is based on the constellation of clinical symptoms, CSF biomarkers like 14-3-3 protein, CSF-tau and neuron-specific enolase level, periodic sharp waves in EEG, and signal alterations in brain MRI. A high clinical suspicion together with characteristic MRI and EEG abnormalities despite low availability of the CSF 14-3-3 protein assay are essential in the timely diagnosis of this fatal disease.

Finally, although there is no currently known treatment for CJD, the quality of life for the patient and caregivers may be improved with symptomatic treatment of neuropsychiatric manifestations. Consequently, close observation and early intervention may improve the quality of care for those with this lethal and terrifying disease.

References

1. Kovacs GG, Budka H. Molecular pathology of human prion diseases. Int J Mol Sci 2009;10:976-99.
2. Liberski PP. Historical overview of prion diseases: a view from afar. Folia Neuropathol 2012;50:1-12.
3. WestergardL, Christensen HM, Harris DA. The cellular prion protein (PrP(C)): its physiological function and role in disease. Biochim Biophys Acta 2007;1772:629-44.
4. Caughey B, Baron GS. Prions and their partners in crime. Nature 2006;443:803-10.
5. Zou WQ, Gambetti P. Prion: the chameleon protein. Cell Mol Life Sci 2007;64:3266-70.

6. Safar J, Wille H, Itri V, Groth D, Serban H, Torchia M, et al. Eight prion strains have PrP(Sc) molecules with different conformations. Nat Med 1998;4:1157-65.
7. Quadrio I, Perret-Liaudet A, Kovacs GG. Molecular diagnosis of human prion disease. Expert Opin Med Diagn 2011;5:291-306.
8. Brown P. Environmentally acquired transmissible spongiform encephalopathy. In: Zou WQ, Gambetti P, editors. Prions and diseases, New York, Heidelberg Dordrecht, London: Springer; 2013:73-88.
9. Ironside JW. Variant Creutzfeldt-Jakob disease: an update. Folia Neuropathol 2012;50:50-6.
10. Brown P, Gibbs CJ Jr, Rodgers-Johnson P, Asher DM, Sulima MP, Bacote A, et al. Human spongiform encephalopathy: the National Institutes of Health series of 300 cases of experimentally transmitted disease. Ann Neurol 1994;35:513-29.
11. Praween Lolekha, Ahmed Rasheed, Chutanat Yotsarawat. Creutzfeldt-Jakob disease in a tertiary care hospital in Thailand: A case series and review of the literature. J Mov Disord 2015;8:136-40
12. Ladogana A, Puopolo M, Croes EA, Budka H, Jarius C, Collins S, et al. Mortality from Creutzfeldt-Jakob disease and related disorders in Europe, Australia, and Canada. Neurology 2005;64:1586-91.
13. Bucelli RC, Ances BM. Diagnosis and evaluation of a patient with rapidly progressive dementia. Mo Med 2013;110:422-8.
14. Appleby BS, Appleby KK, Crain BJ, et al. Characteristics of established and proposed sporadic Creutzfeldt-Jakob disease variants. Arch Neuro 2009;66:208-15.
15. Appleby BS, Appleby KK, Rabins PV. Does the presentation of Creutzfeldt-Jakob disease vary by age or presumed etiology a meta-analysis of the past 10 years. J Neuropsychiatry Clin Neurosci 2007;19:428-35.
16. Wall CA, Rummans TA, Aksamit AJ, Krahn LE, Pankratz VS. Psychiatric manifestations of Creutzfeldt-Jakob disease: a 25-year analysis. J Neuropsychiatry Clin Neurosci 2005;17:489-95.
17. RG, Ironside JW, Zeidler M, Cousens SN, Estibeiro K, Alperovitch A, et al. A new variant of Creutzfeldt-Jakob disease in the UK. Lancet 1996;347:921-5.
18. Zeidler M, Johnstone EC, Bamber RW, Dickens CM, Fisher CJ, Francis AF, et al. New variant Creutzfeldt-Jakob disease: psychiatric features. Lancet 1997;350:908-10.
19. Demaerel P, Sciot R, Robberecht W, Dom R, Vandermeulen D, Maes F, et al. Accuracy of diffusion-weighted MR imaging in the diagnosis of sporadic Creutzfeldt-Jakob disease. J Neurol 2003;250:222-5.
20. Geschwind MD, Martindale J, Miller D, DeArmond SJ, Uyehara-Lock J, Gaskin D, et al. Challenging the clinical utility of the 14-3-3 protein for the diagnosis of sporadic Creutzfeldt-Jakob disease. Arch Neurol 2003;60:813-6.
21. Poungvarin N, Panyathanya R, Viriyavejakul A, et all. Creutzfeldt-Jakob disease in Thailand: a case report with ultrastructural findings and review of the literature. J Med Assoc Thai 1983;66:475-81.
22. World Health Organization. Global surveillance, diagnosis and therapy of human transmissible spongiform encephalopathies: report of a WHO consultation. Geneva, Switzerland: World Health Organization; February 9-11,1998.
23. Geschwind MD, Josephs KA,Parisi JE, Keegan BM. A 54-year-old man with slowness of movement and confusion. Neurology 2007;69:1881-7.
24. Ironside JW. Variant Creutzfeldt-Jakob disease: an update. Folia Neuropathol 2012;50:50-6.
25. Zeidler M, Johnstone EC, Bamber RW, Dickens CM, Fisher CJ, Francis AF, et al. New variant Creutzfeldt-Jakob disease: psychiatric features. Lancet 1997;350: 908-10.
26. Zeidler M, Stewart GE, Barraclough CR, Bateman DE, Bates D, Burn DJ, et al. New variant Creutzfeldt-Jakob disease: neurological features and diagnostic tests. Lancet 1997;350:903-7.
27. Kandiah N, Tan K, Pan AB, Au WL, Venketasubramanian N, Tchoyoson Lim CC, et al. Creutzfeldt-Jakob disease: Which diffusion-weighted imaging abnormality is associated with periodic EEG complexes. Journal of Neurology 2008;255:1411-4.
28. See SJ, Pan A, Seah A, et all. Case reports of two biopsy-proven patients with Creutzfeldt-Jakob disease in Singapore. Ann Acad Med Singapore 2004;33:651-5.
29. Lee KE, Loh NK, Tan AK, Lee WL, Tjia HT. Creutzfeldt-Jakob disease presenting with visual blurring, diplopia and visual loss: Heidenhain's variant. Ann Acad Med Singapore 1998;27:854-6.
30. Lim CC, Tan K, Verma KK, Yin H, Venketasubramanian N. Combined diffusion-weighted and spectroscopic MR imaging in Creutzfeldt-Jakob disease. Megn Reson Imaging 2004;22:625-9.

31. 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.
32. Monari L, Chen SG, Brown P, et al. Fatal familial insomnia and familial Creutzfeldt-Jakob disease: different prion proteins determined by a DNA polymorphism. Proc Natl Acad Sci U S A 1994;91:2839-42.
33. Kong Q. Inherited prion diseases. In: Prusiner SB, ed. Prion Biology and Dis- eases. Cold Spring Harbor, NY: CSHL Press 2004:673-5.
34. Urbach H, Klisch J, Wolf HK, Brechtelsbauer D, Gass S, Solymosi L. MRI in sporadic Creutzfeldt-Jakob disease: Correlation with clinical and neuropathological data. Neuroradiology 1998;40:65-70.
35. Meissner B, Kallenberg K, Sanchez-Juan P, Krasnianski A, Heinemann U, Varges D, et al. Isolated cortical signal increase on MR imaging as a frequent lesion pattern in sporadic Creutzfeldt-Jakob disease. AJNR Am J Neuroradiol 2008;29:1519-24.
36. Geschwind MD, Potter CA, Sattavat M, et al. Correlating DWI MRI with pathologic and other features of Jakob-Creutzfeldt disease. Alzheimer Dis Assoc Disord 2009; 23:82-7.
37. Shiga Y, Miyazawa K, Sato S, Fukushima R, Shibuya S, Sato Y, et al. Diffusion-weighted MRI abnormalities as an early diagnostic marker for Creutzfeldt-Jakob disease. Neurology 2004;10:443-9.
38. Meissner B, Körtner K, Bartl M, Jastrow U, Mollenhauer B, Schröter A, et al. Sporadic Creutzfeldt-Jakob disease: Magnetic resonance imaging and clinical findings. Neurology 2004;63:450-6.
39. Geschwind MD, Haman A, Miller BL. Rapidly progressive dementia. Neurol Clin 2007;25:783-807.
40. Geschwind MD, Tan KM, Lennon VA, et al. Voltage-gated potassium channel autoimmunity mimicking Creutzfeldt-Jakob disease. Arch Neurol 2008;65:1341-6.
41. González-Duarte A, Medina Z, Balaguer RR, Calleja JH. Can prion disease suspicion be supported earlier. Clinical, radiological and laboratory findings in a series of cases. Prion 2011;5:201-7.
42. Biswas A, Khandelwal N, Pandit A, Roy A, Guin DS, Gangopadhyay G, et al. Case series of probable sporadic Creutzfeldt-Jakob disease from Eastern India. Ann Indian Acad Neurol 2013;16:659-63.
43. Kim JH, Choi BS, Jung C, Chang Y, Kim S. Diffusion-weighted imaging and magnetic resonance spectroscopy of sporadic Creutzfeldt-Jakob disease: Correlation with clinical course. Neuroradiology 2011;53:939-45.
44. Matoba M, Tonami H, Miyagi H, Yokota H, Yamamoto I. Creutzfeldt-Jakob disease: Serial changes on diffusion-weighted MRI. J Comput Assist Tomogr 2001;25:274-7.
45. Chiofalo N, Fuentes A, Gálvez S. Serial EEG findings in 27 cases of Creutzfeldt-Jakob disease. Arch Neurol 1980;37:143-5.
46. Geschwind MD, Martindale J, Miller D, et al. Challenging the clinical utility of the 14-3-3 protein for the diagnosis of sporadic Creutzfeldt-Jakob disease. Arch Neurol 2003;60:813-6.
47. Zerr I, Kallenberg K, Summers DM, Romero C, Taratuto A, Heinemann U, et al. Updated clinical diagnostic criteria for sporadic Creutzfeldt-Jakob disease. Brain 2009;132:2659-68.