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Case Reports

Characteristics of Creutzfeldt-Jakob disease at Siriraj Hospital, Thailand: Case series and literature review

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ABSTRACT

Introduction: Creutzfeldt-Jakob disease (CJD) is a rare, rapidly progressive, fatal, neurodegenerative disease classified as prion diseases. There are many subtypes of this disease, but information about clinical presentation and investigation findings in Thailand is scarce.
Objective: To describe the clinical presentation, radiological and electroencephalographic characteristics of CJD encountered at Siriraj hospital in the past 10 years (between January 1, 2006 and December 31, 2015).
Materials and Methods: This was descriptive epidemiological data (retrospective, observational study). Patients with rapidly progressive dementia who met the diagnostic criteria for sporadic CJD (sCJD) and variant CJD (vCJD) were included. All were investigated in detail to find any other possible treatable cause including brain magnetic resonance imaging (MRI), electroencephalography (EEG), and cerebrospinal fluid (CSF) analysis.
Results: Of the 18 cases, they were classified as sCJD 15 cases and possible vCJD 3 cases. The mean age of the patients was 60.72 years (range: 24-77) and 10 patients were male. The main clinical manifestations were cognitive disturbance (100 %) and myoclonus (14 out of 18 cases, 77 %). Brain imaging abnormalities were observed in 17 patients: Hyperintensities in diffusion weight imaging (DWI) in the cortical regions (temporal, parietal, and occipital) were observed in 94 % of the patients. Classical EEG of periodic epileptiform discharges were observed in 83.33 % of patients.
Conclusions: CJD is a rare but fatal disease that needs to be considered in the patient with cognitive, neuropsychiatric, and movement disorders. Findings of specific abnormalities on brain imaging and/or EEG can support the diagnosis in suspicious cases.

1. Introduction

Creutzfeldt–Jakob disease (CJD) belongs to the group of human prion diseases. These are inevitably fatal disorders that are clinically characterized by progressive neuropsychiatric symptoms and movement disorders. Due to the finding of a spongiform change in the cerebral and cerebellar cortex, furthermore, due to their transmissibility, prion diseases are also called transmissible spongiform encephalopathies (TSEs) [1]. This is associated with the deposition in the brain of an abnormal conformer of the prion protein (PrP^{Sc}, where Sc indicates scrapie).

There are three subtypes of CJD: sporadic, acquired, and genetic form according to pathogenesis of disease [2]. In the sporadic form of CJD, unidentified events lead to the spontaneous production of PrP associated with the disease. In acquired forms (i.e., where the etiology is recognized with high probability) are the following: (1) Kuru: this is related to ritualistic cannibalism and is thought to be extinct; (2) Variant CJD: this is associated with the consumption of tissue infected with bovine spongiformencephalopathy (BSE) or with the receiving transfusion from variant CJD blood donors [3]) (3) Iatrogenic CJD: this is associated with medical procedures, including human growth hormone or gonadotrophin hormone therapy, neurosurgery, dura transplant, corneal transplants and deep electrodes implantation [4]. Finally, genetic forms which are due to mutations in the PrP gene (*PRNP*). This can be further classified as follows [5] (1) Familial CJD; (2) the point

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mutation D178N associated with methionine at codon 129 is associated with selective thalamic neurodegeneration called Fatal Familial Insomnia (FFI); (3) Additional mutations are associated with prominent amyloid deposits, which are called Gerstmann–Sträussler–Scheinker disease (GSS).

Sporadic CJD is the most common form of prion diseases, accounting for 90% of all CJD cases [6]. The clinical presentation is manifested by rapidly progressive dementia and various associated neuropsychiatric symptoms or movement disorders such as myoclonus, cerebellar ataxia, visual symptoms, pyramidal and extrapyramidal signs, and akinetic mutism. The median duration of survival is approximately 4.5 months from the onset of symptoms, with 90% of patients surviving less than 1 year [6]. In the past, we classified variant of sCJD by using clinical presentation into six subtypes: classic CJD variant, Heidenhain variant, Oppenheimer-Brownell variant, cognitive variant, affective variant, and indeterminate variant [7]. Nowadays, subtypes of sCJD are classified according to genotype of PRNP gene at codon 129, heterozygous or homozygous of methionine (M) or valine (V), and the molecular properties of pathological prion protein (PRP^{Sc}), as type 1 or 2 depending on size and electrophoretic mobility of the protease-resistant core fragment [8]. Using this molecular classification, six clinical phenotypes of sCJD have been described as MM1, MV1, VV2, MV2, MM2, and VV1 which each subtype had their own phenotype, MRI findings, EEG findings, and CSF biomarkers which are useful clinically [8].

A new variant of Creutzfeldt-Jakob disease was first reported in 1996 [9] and there is now compelling evidence that this novel disease is caused by exposure of humans to the agent that causes bovine spongiform encephalopathy (BSE). A study of the first 14 cases of variant Creutzfeldt- Jakob disease in the United Kingdom, found that all patients had early psychiatric features [10]. Common presentations were depression, anxiety, and behavioral change. At the time of presentation, psychiatric symptoms in variant Creutzfeldt-Jakob disease couldn't differentiate from more common psychiatric disorders, but subsequent neurological and cognitive deterioration led to the eventual clinical suspicion of Creutzfeldt-Jakob disease [10]. Psychiatric features of variant Creutzfeldt-Jakob disease may not different from sporadic from but other clinical features may help to differentiate them such as age of onset, which median age of onset is 27 years old in variant Creutzfeldt-Jakob disease, in contrast to sporadic Creutzfeldt-Jakob disease that median age of onset around 62 years old [11]. Persistent painful sensory symptoms also the clues to differentiate because this condition was found in two-third of variant Creutzfeldt-Jakob disease but never found in sporadic form [12].

Tools for diagnosis of CJD include the demonstration of altered signals in brain Magnetic Resonance Imaging (MRI) [13,14], periodic sharp wave complexes (PSWC) in electroencephalography (EEG) recording [15], presence of the 14-3-3 protein in cerebrospinal fluid (CSF) [14,16] or recently new technique called real-time quaking induced conversion (RT-QuIC) [17]. In Thailand, there are only three previous reports of CJD cases that include Creutzfeldt-Jakob disease: Review of experience at Siriraj Hospital [18], case series from Faculty of Medicine of Thammasat University [19] and report of 13 cases with comprehensive biomarker data from Chulalongkorn hospital [20]. This study aimed to provide more data on the clinical, radiological and electroencephalographic characteristics of CJD cases at Siriraj hospital in the past 10 years (between January 1, 2006 and December 31, 2015).

2. Materials and methods

2.1. Subjects

This study was an IRB-approved retrospective review of the medical records of all patients (18) diagnosed with CJD as found at Siriraj Hospital between the years 2006 and 2015. This record system includes inpatient. Subjects were identified using encoded diagnoses of Creutzfeldt-Jakob disease.

2.2. Inclusion criteria

Criteria used for inclusion of patients as sporadic CJD were according to National Creutzfeldt-Jakob Disease Research & Surveillance Unit criteria [21] and as variant CJD were according to revision of surveillance case definition for variant Creutzfeldt-Jakob Disease of World Health Organization [12]. Definite diagnosis of sCJD and vCJD were need neuropathological confirmation of CJD in the setting of progressive neuropsychiatric symptoms. For diagnostic criteria for probable case are:

- Cases were diagnosed as probable sCJD if there was evidence of (1) rapidly progressive dementia. (2) At least 2 of the following symptoms: myoclonus, visual or cerebellar disturbance, pyramidal or extrapyramidal dysfunction, and akinetic mutism. (3) Typical findings in EEG or brain MRI or positive CSF 14-3-3 protein. Patient who presented with progressive neuropsychiatric symptoms with positive real-time quaking induced conversion (RT-QuIC) can also be diagnosed as probable sCJD. Possible sCJD can be diagnosed if had (1) and (2) with duration of disease less than 2 years.
- Cases were diagnosed with vCJD need combination of history, clinical signs and symptoms, and investigations. Probable vCJD can be diagnosed in the presence of progressive neuropsychiatric symptoms and positive tonsil biopsy. In the absence of tonsil biopsy, diagnosis of probable vCJD requires:
  - o All of the following characteristics: Progressive psychiatric disorder, duration of illness $>$ 6 months, routine investigations do not suggest an alternative diagnosis, no history of potential iatrogenic exposure, no evidence of a familial form of transmissible spongiform encephalopathy
  - o At least 4 of the following 5 clinical characteristics: Early psychiatric features, persistent painful sensory symptoms, ataxia, myoclonus or chorea or dystonia, and dementia
  - o EEG does not show the typical appearance of sCJD in the early stage of disease and MRI brain scan showing bilateral pulvinar high signal
  - o Possible vCJD were diagnosed if had all criteria as probable vCJD with exception that MRI findings are not required.

2.3. Data collection

The medical records were comprehensively reviewed by a neurosurgeon and the data was extracted for demographic characteristics and disease chronology. The results of brain magnetic resonance imaging, EEG, and CSF analysis were also collected. Data were abstracted from medical records using the same abstraction instrument for all cases. Case histories were reviewed and classified into 5 predetermined sCJD variants and indeterminate group [7] as shown in Table 1.

Further clinical information was collected to include the date of onset of CJD symptoms as defined in clinical documentation, the eventual date of CJD diagnosis, the date of death and whether there was a family history positive for CJD. Neurological symptoms (date of onset and type) during the course of the disease 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 recognized as the initial manifestations of the disease course. Demographic information on the date of birth, sex, occupation, and place of residence of each patient was also included. The results of the biological evaluation were also recorded: complete blood count, electrolytes, liver function test, renal function tests (blood urea nitrogen and creatinine), erythrocyte sedimentation rate (ESR), calcium, phosphate, calcium, thyroid function test, vitamin B_{12} level, folate level, human immunodeficiency virus (HIV) screening test, hepatitis B profile, serum Venereal Disease Research Laboratory (VDRL) test, antinuclear antibody (ANA), antithyroid peroxidase antibodies level, antithyroglobulin level, urinalysis, CSF analysis including cell count, cell type, protein, glucose,

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 the onset of the illness, without visual disturbances - Clinical presentation within 1 month of the onset of the illness - Short interval between symptom onset and diagnostic testing (CSF 14–3-3 protein, EEG, and brain MRI) - Survival time ≤ 3 months
Heidenhain	- Onset of diplopia, blurred vision, cortical blindness, and/or visual hallucinations at the onset of the disease - Survival time ≤ 4 months
Oppenheimer-Brownell	- Ataxia in the absence of other presenting symptoms at the onset of the disease - Older age at illness onset (median, 67 years old) - 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 the onset of the disease in the absence of ataxia and visual disturbances - Clinical presentation 2 months after symptom onset - Prolonged interval between the onset of the disease and diagnostic testing - Survival time > 4 months
Affective	- Depression, mood lability, and/or anxiety at the onset of the illness - Age at onset ≤ 65 years old - Prolonged time to clinical presentation - Prolonged time to diagnostic testing - High rate of positive CSF analyses for 14–3-3 protein despite the duration of the illness Survival time > 6 months
Indeterminate	The clinical characteristics that could not be classified into 1 of the aforementioned groups

bacteriological and virological studies, autoimmune and paraneoplastic panel and CSF biomarkers of Alzheimer's disease (total Tau, phosphorylated Tau and beta amyloid protein). All patients underwent 1.5 Tesla brain MRI including diffusion-weighted (DWI) and fluid attenuated inversion recovery (FLAIR) sequences. The EEG was performed using the international 10-20 system.

In that time period, the PRNP genetic testing and RT-QuIC were both unavailable in our country, so none of our patients had results of those test.

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

3. Results

By screening hospital records for Creutzfeldt–Jakob disease diagnosis during the study period, we found 18 cases that met the diagnostic criteria for probable sCJD and possible vCJD. The mean age of the patients at the time of presentation was 60.72 years (sCJD was 66 years and vCJD 34 years). Ten patients were females (female:male = 10:8). In cases of sCJD, the cases were classified into 5 predetermined sCJD variants including Heidenhain variants (7/15), Oppenheimer-Brownell variants (3/15), Cognitive variants (3/15), Classic variants (1/15), and Affective variants (1/15). Demographic and clinical characteristics of the cases are summarized in Tables 2 and 3. The main clinical manifestations were cognitive disturbance (18/18) and myoclonus (14/18), followed by additional pyramidal symptoms/signs (10/18), ataxia (9/18), behavioral change (6/18) and visual disturbance (5/18).

The mean age at the onset of the disease in all sCJD was 66 years. Patients with the Heidenhain variant had a mean age of 66.7 years; the Oppenheimer-Brownell variant (61.67 years); the cognitive variant (71 years); the classic variant (65 years); and affective variant (61 years).

The classic Creutzfeldt–Jakob disease case has the shortest mean survival time from the onset of the symptom (3 months), while the affective variant had the longest median survival times (13 months). The cognitive, Heidenhain, and Oppenheimer-Brownell variants had mean survival times of 6.3 months, 7.2 months, and 7 months, respectively. The symptoms and characteristics of the cases are summarized in Table 4.

The mean age of the three cases of possible vCJD patients at the time of presentation was 34 years (range 24–42). All cases were males (M =

Table 2
Demographic and clinical feature of sCJD.

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

Table 3
Demographic and clinical features of vCJD.

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

3). In this population, they were classified as having at least one psychiatric manifestation during the course of the disease. A psychiatric manifestation was observed in the prodromal or presenting phase of the disease in all cases. The most commonly reported symptoms are sleep disturbance (3/3); insomnia is more common than hypersomnolence. The mean survival time from the onset of the symptoms to the death of vCJD was 13.67 months. The demographic and clinical characteristics of vCJD are summarized in Table 3.

Brain magnetic resonance imaging abnormalities were observed in seventeen of our 18 patients (94%). In twelve patients (66.67%), brain magnetic resonance imaging showed hyperintensities in bilateral caudate and putamen. Three patients (16.67%) had FLAIR hyperintensity in the pulvinar nucleus of bilateral thalami that may consistent with the pulvinar sign. But we could find MRI brain picture only one case from three cases of vCJD and signal in pulvinar is not higher intensity than putamen (Fig. 4), the other two had only document note about their MRI abnormalities, making all of them categorized as possible case of vCJD. Hyperintensities of DWI and hypointensities of the apparent diffusion coefficient (ADC) were observed in the head of the left caudate, left putamen and the bilateral parieto-occipital region in one patient. Hyperintensities of DWI hyperintensities of ADC were observed in the bilateral frontotemporal and parieto-occipital regions (four patients [22.22%]), bilateral parieto-temporal and occipital region (two patients [11.11%]) and the bilateral parieto-occipital and temporal regions (one patient [5.5%]).

In only one patient, brain magnetic resonance imaging showed only diffuse cerebral atrophy predominately in the bilateral parietal lobe. Figs. 1-4 show the characteristic of brain MRI abnormalities in selected cases. Brain MRI characteristics of each patient are summarized in Table 5.

The CSF analysis was carried out in all patients, which showed normal to mildly elevated protein, cell count within normal limits, negative bacteriological/virological studies, and also negative in the autoimmune and paraneoplastic panel. The CSF 14-3-3 protein assay was not carried out in all patients, due to its inaccessibility in our country, but the total tau protein assay was carried out in four patients and shows a very high elevation (> 1000 pg/mL) in all of them.

Classical EEG abnormalities in the form of a periodic sharp wave complex were found in twelve patients (12/18), a generalized diffuse slow wave in five patients (5/18), and a normal awake electroencephalographic finding in only one patient. Fig. 5-6 shows the characteristic EEG abnormalities of selected cases. A patient was given intravenous immunoglobulin with clinical suspicion of immune-mediated encephalopathy, before the results of the CSF study were reported, but without improvement. A postmortem brain examination could not be performed in any of the patients to confirm diagnosis. A comparison of clinical, radiological, and electroencephalographic characteristics of sCJD and vCJD is illustrated in Table 6.

4. Discussion

Creutzfeldt–Jakob disease is a human prion disease with characteristic clinical and diagnostic features. Clinical suspicious of Creutzfeldt–Jakob disease is usually raised when patient presented with rapidly progressive cognitive impairment. Of those three subtypes of Creutzfeldt–Jakob disease [2], sCJD is the most common form. The disease course is usually less than 2 years (generally about 4–7 months). In addition to dementia, cerebellar symptoms (ataxia) or visual complaints (including cortical blindness), pyramidal or extrapyramidal dysfunction, akinetic mutism (in terminal phase), and particularly myoclonus are the most characteristic (Table 7).

Variant CJD presents mostly at an earlier age [12] with distinguishing clinical features, unusual and early sensory (e.g., dysaesthesia, paresthesia) and psychiatric (e.g., depression, paranoid

Table 4
Symptoms and characteristics of sCJD variants.

	sCJD variant (15)				
	Heidenhain (n = 5)	Oppenheimer-Brownell (n = 3)	Cognitive (n = 3)	Classic (n = 1)	Affective (n = 1)
Initial symptom					
Visual disturbance	5 (71.43 %)	–	–	–	–
Dementia	–	–	2 (66.67 %)	–	–
Visual hallucination	2 (28.57 %)	–	–	–	–
Ataxia	–	3 (100 %)	–	–	–
Language impairment	–	–	1 (33.33 %)	1 (100 %)	–
Hypomania	–	–	–	–	1 (100 %)
Onset to death (months)	7.2	7	6.33	3	13

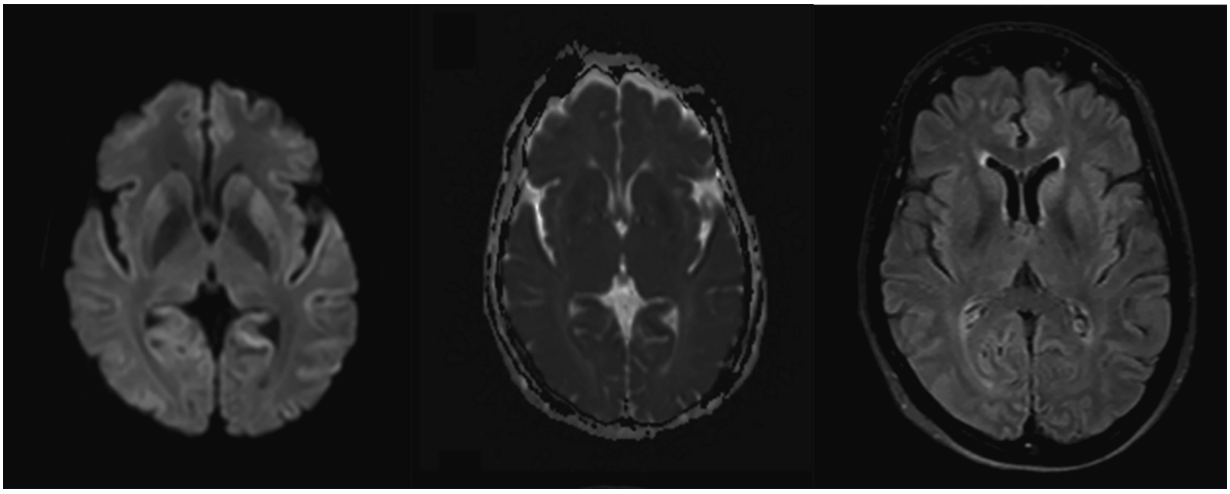

Fig. 1. -2. MRI brain showing hyperintense signal in DWI sequence with hypointense signal in ADC sequence at fronto-parieto-temporo-occipital lobe.

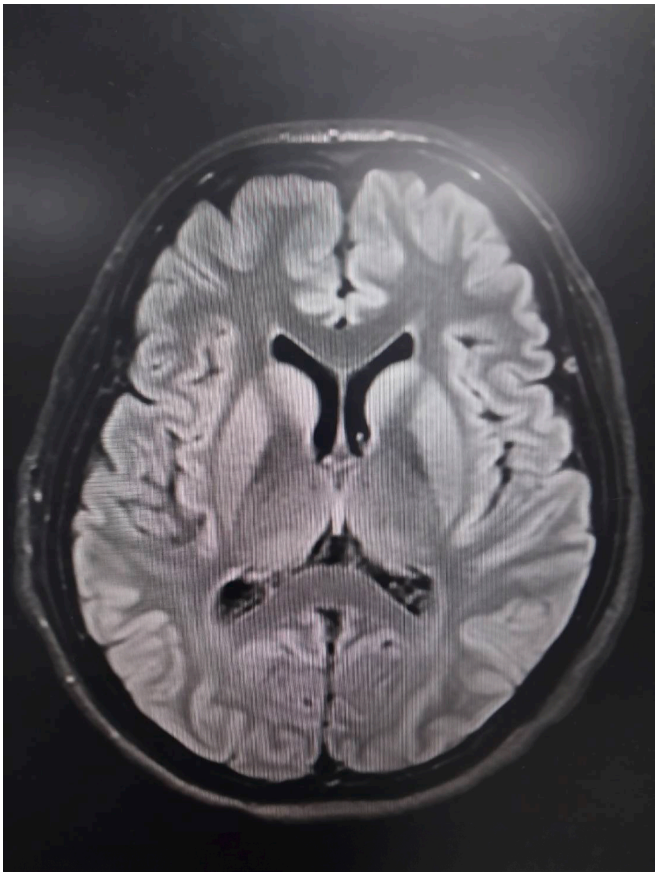

Fig. 3. MRI brain showing hyperintense signal in FLAIR sequence at bilateral caudate and putamen.

components, agitation, aggressivity) symptoms [22,23]. When the disease progresses, dementia and myoclonus often evolve. Other less commonly found signs and symptoms such as chorea, pyramidal signs, cerebellar symptoms and rigidity, and vertical gaze weakness are also described in a later stage of the disease [23] (Table 8).

There are only scanty case series of Creutzfeldt–Jakob disease in Southeast Asia. A literature search on the epidemiology of Creutzfeldt–Jakob disease in southeast Asia revealed only 18 cases from Singapore (1998–2008) [24–27], 18 cases from Thailand (1983–2023) [18–20] and four cases from Malaysia (2014). Kandiah et al. described the largest case series in Singapore involved 4 definite Creutzfeldt–Jakob disease and 10 probable Creutzfeldt–Jakob disease over a period of 7 years [24]. There are no published reports of Creutzfeldt–Jakob disease in other countries in Southeast Asia. This raises the question of whether Creutzfeldt–Jakob disease is underreported or actually rare in Southeast Asia.

In Thailand, Creutzfeldt–Jakob disease has been underreported and misdiagnosed. Published cases of Creutzfeldt–Jakob disease in Thailand include one case from Siriraj hospital (1983), three cases from the Neurology Division, Department of Internal Medicine, Faculty of Medicine, Thammasat University, Pathumthani [19], and 13 cases from Thai Red Cross Emerging Infectious Diseases Health Science Center, King Chulalongkorn Memorial Hospital, Bangkok [20]. Siriraj hospital, our center, is national tertiary referral center which had patients more than three million per year so we expected to had case of Creutzfeldt–Jakob disease around 3–6 cases per year, applying the incidence of 1–2 cases per million individuals across entire worldwide population [28]. For our study, retrospective of ten years, we found Creutzfeldt–Jakob disease cases only 18 cases which far from calculation that should be at least 30 cases. The reason could be that in our country we had multiple tertiary referral center with the same capacity as ours, so case may be distributed to other hospital. In the past, there has been no regional or national surveillance system for Creutzfeldt–Jakob disease in Thailand and, in addition, the knowledge of this disease is limited to medical specialists who raise public awareness, an effective reporting system, advanced medical education, laboratory, neurological, and neuropathological diagnostic capacity are important. Nowadays, we had surveillance system with more awareness of disease, so we can get incidence and information about Creutzfeldt–Jakob disease in our country more accurate in the future.

The mean age of the patients with sCJD was 66 years. In the case series by Lolekha et al [19]., the patients appeared to be younger (57 years) but approximately had same mean age, 68 years, from report by Thanapornsangsuth et al [20]. The comparison of mean age between studies is cautionary because the sample size is small and the apparent differences in the mean age could be due to random fluctuations. We found a female predominance (10/18) in our series. All of our patients had rapidly progressive dementia followed by myoclonus. Other clinical manifestations were behavioral disturbances, ataxia, and extrapyramidal symptoms. Similar observations were noted in the case series by Lolekha et al [19] and Thanapornsangsuth et al [20]. All of our patients were evaluated with other relevant investigations to rule out other causes of encephalopathy such as infectious, metabolic, paraneoplastic, and autoimmune etiologies.

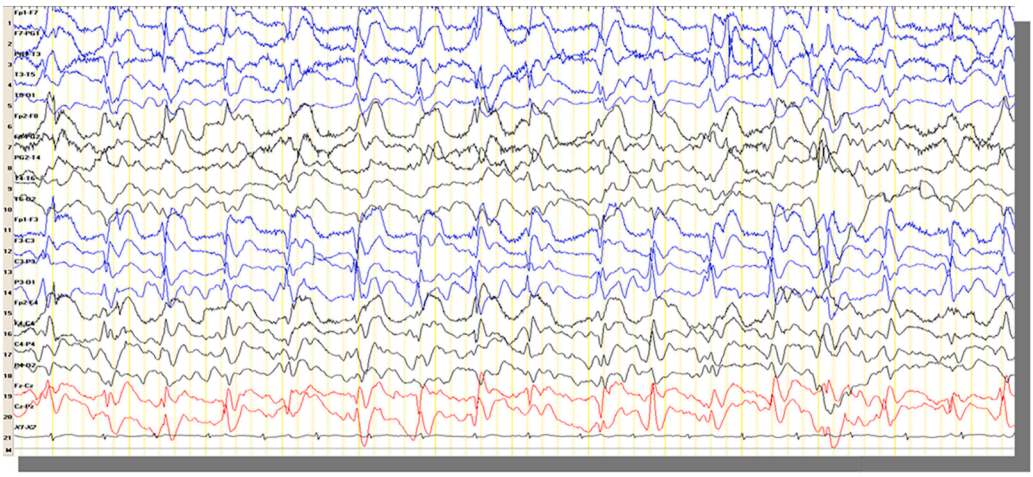

Fig. 4. MRI brain showing hyperintense signal in FLAIR sequence at bilateral caudate, putamen, and pulvina nucleus or bilateral thalami.

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 bilateral 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 bilateral fronto-temporal and parieto-occipital regions.	Generalized periodic sharp wave complex
10	DWI and ADC hyperintensities in bilateral 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 bilateral 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 bilateral 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 at bilateral head of caudate and putamen	Periodic sharp wave complex
18	FLAIR hyperintensities in bilateral caudate, putamen and pulvinar nucleus of bilateral thalami.	Generalized diffuse slow wave

Behavioral changes in Creutzfeldt–Jakob disease as the first symptoms are seen in 20%, with the most common symptoms agitation/irritability (36%) and depression (16%) [29]. In our case series, behavioral change was found in 6 patients (33%) and the most common symptoms is agitation, as in the previous literature. None of the patients had a family history of similar disease. The time interval between the onset of symptoms and diagnosis varied from 2 months to 16 months with a mean of 7.13 months in probable sCJD and 13.66 months in probable vCJD, which was not similar to the findings in the case series of Lolekha et al. (20 months). The difference in this aspect may be due to different presenting symptoms and also number of cases. Although sCJD is known to have a variety of clinical symptoms, our findings indicate that clinical clusters of cases can be delineated by differences in initial symptoms. It is also significant that sCJD variants differ in age at symptom onset and survival time, indicating a difference in disease pathology and/or expression. The heterogeneity of the clinical presentations observed in sCJD and vCJD frequently results in a 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 commonly observed in Creutzfeldt–Jakob disease in addition to the propensity of the disease to be misdiagnosed. Our data may help to provide a basis for developing the clinical identification of sCJD variants and vCJD, which would aid in clinical detection and diagnosis.

Changes in brain magnetic resonance imaging in Creutzfeldt–Jakob disease have been shown to precede EEG or CSF abnormalities. However, it may be without abnormalities early in the disease course. High signals in T2-weighted/FLAIR sequences have been linked to astrogliosis [30]. Combined cortical and deep gray matter hyperintensity (basal ganglia and putamen) hyperintensity and isolated cortical hyperintensity are the two patterns of DWI and/or FLAIR abnormality that have been described [31]. DWI is more sensitive than FLAIR in the detection of cortical abnormalities in the early stages of Creutzfeldt–Jakob disease and from the latest University of California, San Francisco (UCSF) modified Creutzfeldt–Jakob disease MRI criteria 2017, DWI abnormalities is required and need to be more prominent than FLAIR abnormality [32]. DWI hyperintensities are due to restricted diffusion, therefore hypointensities will be observed in the ADC sequence, which is due to PrPSc deposition, vacuolation, or a combination of those two [33]. DWI has a higher sensitivity (92%) and a higher specificity (93%) in the diagnosis of Creutzfeldt–Jakob disease regardless of PSWCs [34]. Involvement of deep gray matter is associated with a shorter disease course with rapidly progressing neurologic deterioration, whereas the absence of basal ganglia involvement correlates with delayed onset of dementia and longer disease course [35]. DWI hyperintensities generally involve both cortical and subcortical gray

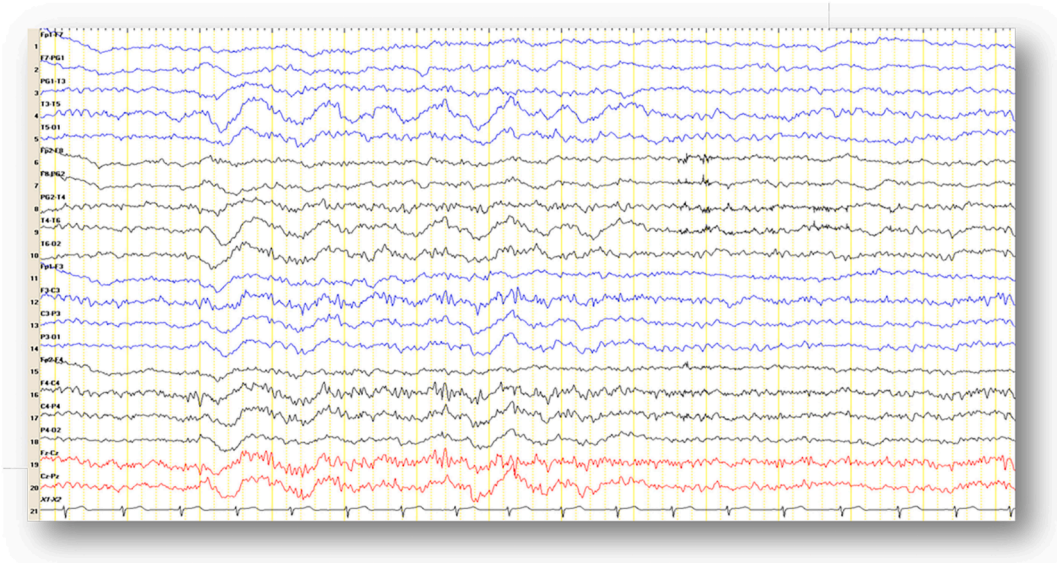

Fig. 5. -6. EEG showing periodic sharp wave complexes at 1–2/seconds with slowing of background rhythm and generalized diffuse slow wave, respectively.

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

Clinical characteristics	Probable sCJD	Possible vCJD
Mean age in years (range)	66 (42–77)	34 (24–42)
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 findings	FLAIR hyperintensities in bilateral caudate and putamen, DWI and ADC hyperintensities in cortex (cortical ribbon sign)	FLAIR hyperintensities in bilateral caudate, putamen and pulvinar nucleus of bilateral thalami (suspected pulvinar sign).
EEG characteristics	Periodic sharp wave complex and generalized periodic sharp wave complex	Generalized diffuse slow wave

Table 7
Diagnostic criteria for sporadic Creutzfeldt-Jakob disease.

I	Rapidly progressive cognitive impairment
II	A. Myoclonus Visual or cerebellar disturbance Pyramidal or extrapyramidal signs Akinetic mutism
Definite: progressive neuropsychiatric symdrome and neuropathological or immunocytochemical, or biomedical confirmation.	
Probable:	
I + two of II + typical EEG findings **OR**	
I + two of II + typical brain MRI **OR**	
I + two of II + positive CSF 14–3-3 **OR**	
Progressive neuropsychiatric syndrome and positive RT-QuIC in CSF or other tissue	
Possible: I + two of II + duration < 2 years	

Adapted from National Creutzfeldt-Jakob Disease Research & Surveillance Unit criteria.

matter (68% of case), with less frequent involvement cortex or basal ganglion alone (24% and 2–5%, respectively) [32]. Autoimmune encephalitis can be presented as a mimic of Creutzfeldt–Jakob disease due

Table 8
Diagnostic criteria for variant Creutzfeldt-Jakob disease.

I	A. Progressive neuropsychiatric disorder B. Duration of illness > 6 months C. Routine investigations do not suggest an alternative diagnosis D. No history of potential iatrogenic exposure E. No evidence of a familial form of transmissible spongiform encephalopathy
II	E. Early psychiatric features F. Persistent painful sensory symptoms G. Ataxia H. Myoclonus or chorea or dystonia I. Dementia
III	A. EEG does not show the typical appearance of sporadic CJD in the early stage of illness B. Bilateral pulvinar high signal on MRI scan
IV	A. Positive tonsil biopsy
Definite: IA and neuropathological confirmation of vCJD	
Probable: I and 4/5 of II and IIIA and IIIB	
OR I and IVA	
Possible: I and 4/5 of II and IIIA	

to its overlap in clinical presentations, but they have different abnormalities in brain magnetic resonance imaging that will be helpful in separating them, especially when waiting for the results of the autoimmune panel in the CSF study, which may take longer duration than brain imaging. The FLAIR sequence in both diseases shows the same abnormalities, hyperintensity, but a true restrictive pattern (high DWI/low ADC) is not commonly found in autoimmune encephalitis and, if presented, highly suggestive of other diagnosis [36,37].

Our twelve patients (66%) had hyperintensities in caudate and putamen on the FLAIR images. DWI hyperintensities were found in eight patients, of which six show increased signal in the bilateral parieto-temporal and occipital region, one of them shows signal in the bilateral parieto-occipital and right temporal region, and the remaining one shows abnormalities in the bilateral caudate and putamen. Nine patients had abnormalities in FLAIR sequence but no information about DWI sequence, it had no record and no picture in our system so we couldn't get that info, making limitation to support the diagnosis of Creutzfeldt–Jakob disease which DWI sequence is more important need than FLAIR sequences [32]. A patient who had a restrictive pattern in the bilateral caudate and putamen had also shown hyperintensities in FLAIR without any abnormalities in the cortical area, these classic abnormalities being present in a very early stage of the disease as shown in the study by GonzálezDuarte et al [38]. Brain MRI of one patient showed

only cortical atrophy without classical changes of Creutzfeldt–Jakob disease. The patient was diagnosed to have extrapyramidal symptoms with dementia with myoclonus and visual disturbance (Case 6). The reason for negativity of the MRI was that it was done during the terminal stage of the illness (9–10 months after onset) when the typical MRI abnormalities could have disappeared [39,40]. Our three cases of vCJD categorized as possible, not probable, because the record noted that MRI brain of patient show hyperintense signal abnormalities in bilateral caudate, putamen, and pulvinar of thalamus but didn't note about their level of intensity. Because pulvinar hyperintensities is less specific [41] and can be found in 7% of sCJD case [42] so, current definition of pulvinar sign is hyperintensity in pulvinar that need to has relatively higher signal than anterior putamen. Our case of vCJD couldn't confirm this definition of pulvinar sign so we diagnosed them with possible vCJD.

Changes in brain metabolism captured by using ^{18}F-fluoro-2-deoxy-d-glucose positron emission tomography (FDG-PET) scan is able to detect abnormalities in patient with CJD [43]. Decreased glucose metabolism in cortical region had been described but their abnormalities couldn't show any area-specific, which limit it utility in clinical practice [44]. There are studies using different tracers, such as amyloid or tau tracers, in patient with prion disease but their number of cases are very small [44–46].

Classic EEG, showing PSWC and triphasic waves, has moderate specificity to Creutzfeldt–Jakob disease and was observed in twelve patients in our case series. EEG of the remaining six patients, five patients showed diffuse slowing of background activity, and one patient showed normal awake EEG. EEG has a sensitivity of 67% and a specificity of 74–86% in the diagnosis of Creutzfeldt–Jakob disease [15,36] but if it was performed in an early stage of the disease, the results can be normal or diffuse general slowing in the background, as in our six cases. Therefore, if the clinical suspicion is high for Creutzfeldt–Jakob disease, repeated EEG should be warranted during the course of the disease to increase the probability of demonstrating characteristic EEG abnormalities [47].

CSF examination was performed in all patients except one patient (case 3) because the patient's family was denied the ability to perform lumbar puncture. In all 17 cases, CSF did not reveal pleocytosis or other abnormalities that explained patient symptoms. The detection of the 14-3-3 protein in CSF has been one of the markers for the diagnosis of Creutzfeldt–Jakob disease [48]; but in our series, the assay was not performed in any patients due to its inaccessibility. So, we used brain magnetic resonance imaging that shows typical findings to support the diagnosis of Creutzfeldt–Jakob disease. According to Zerr et al. [49], MRI findings are equivalent to elevated levels of the 14-3-3 protein in the diagnosis of probable sporadic Creutzfeldt–Jakob disease. The newer technique, RT-QuIC, is an protein aggregation assays in which disease-associated prion protein (PrP^{Sc}) was amplified by using quaking to energize the misfolding of prion protein coupled to fluorescent readout. RT-QuIC is very high specific test for diagnosis of prion disease, specificity 99–100% [14,17,21,50], with sensitivity 92–97% in second generation of this test [50]. This test aids for diagnosis prion disease more accurately but due to inaccessible in our country, none of patient had perform this test.

Over the past year, blood-based biomarkers had getting more interested and had been implement in many research for neurodegenerative disease [51]. For Creutzfeldt–Jakob disease, potential blood-based biomarkers are t-tau and neurofilament light chain (NfL) which their concentration are markedly increased in sporadic Creutzfeldt–Jakob disease compare to healthy control [52]. Even though blood-based biomarker didn't provide higher specificity for diagnosis, comparing to CSF RT-QuIC, its usefulness lies within their easy accessibility.

Our study has limitations. First, a postmortem brain examination to confirm the diagnosis could not be performed in any of the patients. Histological examination and immunostaining for protease resistant protein (PrP^{Sc}) are the gold standard for the diagnosis. As a result, all of our cases were suggestive of prionopathy due to the lack of histological confirmation. Second, the 14-3-3 protein assay could not be performed in all patients due to financial constraints and logistic problems for transfer to a foreign laboratory. Third, MRI brain scan in that period is mostly a film which make information of imaging mainly on the record and contribute to many limitations for reviewing abnormalities. Fourth, due to resource limitation, none of our patients had been evaluated their PRNP genotypes or RT-QuIC test which are drawback of our study. Nevertheless, some other countries may face the same problems, so clinical presentation and correct interpretation of basic tests are still important.

5. Conclusions

Creutzfeldt–Jakob disease is a fatal neurodegenerative disease. It has a wide range of clinical manifestations, including cognitive decline, myoclonus, ataxia, pyramidal and extrapyramidal signs/symptoms, behavioral abnormalities, and psychosis. The diagnosis is based on the constellation of clinical symptoms with the presence of the 14-3-3 protein or high level of total tau in CSF, periodic sharp waves in EEG or signal alterations in brain MRI. Novel technologies, CSF RT-QuIC, is very high specific test and useful in making early diagnosis in the context of suspicious case.

6. Statement of ethics

The protocol for this study was approved by the Siriraj Institutional Review Board (SIRB) of the Siriraj Hospital Faculty of Medicine, Mahidol University, Bangkok, Thailand (COA no.335/2016). Written informed consent was not obtained from study participants due to the retrospective design of our study that preserves anonymity. The ethics committee that waived the need for informed consent was also the Siriraj Institutional Review Board of the Siriraj Hospital of the Faculty of Medicine, Mahidol University, Bangkok, Thailand. All authors confirm that the research was conducted in accordance with the Declaration of Helsinki.

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This was an unfunded study.

8. Data availability statement

All data generated for this study are included in the article. No other data sets were generated during the current study.

CRediT authorship contribution statement

Chaisak Dumrikarnlert: Writing – review & editing, Writing – original draft. **Nuttapong Kanokkawinwong:** Investigation, Formal analysis. **Chatchawan Rattanabannakit:** Conceptualization. **Vorapun Senanarong:** Writing – review & editing, Supervision, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Author contributions

CD was involved in the interpretation of the data and the manuscript writing (first author, co-corresponding author). NK was involved in data collection, data and statistical analysis, data interpretation and manuscript writing (co-author). CR was involved in data collection and review investigation results. VS participated in the design of the study, interpretation of data, and manuscript review (corresponding author). All authors approved the protocol.

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