Case Series of Probable Creutzfeldt- Jacob Disease Admitted in a Tertiary Hospital in Metro Manila

Myleene F. Erola-Fuentes, MD*, Jo Ann R. Soliven, MD, FPNA

ABSTRACT

Background

Creutzfeldt–Jakob disease is a rapidly progressive, fatal, transmissible neurodegenerative disorder caused by a prion protein. It is characterized by cognitive decline, motor dysfunction, and eventually, death. It occurs globally with 1 case per one million population/year. And It is still considered rare in countries like the Philippines due to challenges in its diagnosis and the under recognition of its clinical features. As of now, the local prevalence or incidence of this disease in our country remains unknown, as only a single case report has been documented. As of now, the local prevalence or incidence of this disease in our country remains unknown, as only a single case report has been documented.

Objective

To report a series of patients with probable sporadic CJD from a tertiary hospital in the Philippines.

Materials and Methods

Patients with rapidly developing dementia fulfilling the diagnostic criteria for sCJD were included. All were investigated in detail to find out any possible treatable cause, including electroencephalography (EEG), magnetic resonance imaging (MRI) of the brain, and cerebrospinal fluid analysis.

Results

A total of 3 patients with probable sCJD were diagnosed using the European diagnostic criterion from January 2022 to April 2023. The clinical features are consistent with other reported series. All 3 patients had the classical EEG findings, typical MRI features, and positive for 14-3-3 assay, and one was positive for RT-QuIC. Two patients died within 13 months from the disease onset.

Conclusion

This is the first reported case series of probable sCJD in the Philippines from a tertiary hospital in Metro Manila. Like in our patients, this disease should be considered in individuals with rapidly progressive dementia associated with myoclonus, neuropsychiatric symptoms, akinetic mutism, visual abnormality, and ataxia with signs of pyramidal and extra-pyramidal dysfunction. Although a definitive diagnosis must be histopathological, there are ancillary tests that are currently available that allow us to make a probable diagnosis of sCJD possible. Our study raises question about the prevalence of this disease in the Philippines which needs more validated studies from other parts of the country.

Keywords: *Creutzfeld- Jacob Disease; Prion Disease*

INTRODUCTION

Creutzfeldt-Jakob disease (CJD) is a fatal neurodegenerative disorder that affects humans. The pathophysiological mechanism of the disease consists of the formation of an abnormal isoform of the prion protein (PrP) called scrapie (PrPSc) which accumulates in the gray matter of the brain and is partially resistant to the action of proteases[1–4]. Prions

The Medical City, Ortigas Avenue, Pasig City
*Email address: angelmyles_19@yahoo.com

are infectious, protein-containing particles (PrP^{Sc}) that replicate by auto-catalytic templating, replacing normal prion proteins (PrP^{C}) and leading to neurotoxicity, as the accumulation of this protein or fragments of it in neurons leads to apoptosis and cell death[5].

The estimated annual incidence of the disease worldwide is 1 to 2 cases per million of population. The age of onset is between 55 and 75 years, both sexes are equally affected[6]. There are 4 subtypes of CJD: sporadic, genetic, iatrogenic and variant. Sporadic CJD (sCJD) is the most common form of the disease, accounting for 85–90% of all CJD cases. The prognosis of the disease is fatal because 90% of patients die within the first year of symptom onset[7]. The cause of death is usually infection, heart failure, or respiratory failure[8].

The clinical presentation of CJD is highly variable. Most cases have a subacute course. Frequent manifestations include: rapidly progressive dementia associated with neuropsychiatric manifestations, cerebellar ataxia, visual abnormality, myoclonus, akinetic mutism, and pyramidal and/or extrapyramidal signs[9–10]. Atypical manifestations have also been described, which at their onset, resemble cerebrovascular disease, depression or supranuclear palsy[11].

Pre-mortem diagnosis is based on 5 types of paraclinical tests: electroencephalogram (EEG), cerebrospinal fluid (CSF) biomarkers, brain magnetic resonance imaging (MRI), positive real-time quaking-induced conversion (RT-QuIC) in CSF or other tissues and brain biopsy[11–14]. The gold standard for definitive diagnosis Of CJD is a histopathological confirmation through a brain biopsy or autopsy[12–16].

The disease neuropathologic features include accumulation of protease-resistant prion protein, neuronal loss, proliferation of glial cells, absence of a classic inflammatory response, and presence of small vacuoles within the neuropil, which produces a spongiform appearance[17].

In the Philippines, there are no studies of the prevalence or incidence of CJD so far, and only one clinical case report of CJD has been published. In this case series, I presented 3 cases of CJD admitted in a tertiary hospital in Metro Manila from January 2022 to April 2023.

CASE PRESENTATION

Case 1

The patient was a 61-year-old male who came in due to rapidly progressive behavioral changes such as paranoia, confusions, hallucinations and disorientations associated with memory lapses, abdominal discomfort, numbness of extremities and ataxia. He later developed changes in gait, akinetic mutism, involuntary movements of his extremities and startle myoclonus.

Laboratory work ups included an electroencephalogram demonstrating the presence of periodic sharp wave complexes. Diffusion-weighted imaging (DWI) showed bilateral restricted diffusion on the bilateral fronto-parietal regions, right more than the left and in the fluid attenuated inversion recovery (FLAIR) MRI showed hyperintensities on the same cortical areas as well as in the deep gray matter. His cerebrospinal fluid was positive for 14-3-3 assay. The patient died of nosocomial pneumonia after 6 months from the time of diagnosis.

Case 2

A 76-year-old female, known hypertensive, dyslipidemic, a case of hypothyroidism who came in due to loss of appetite. She was noted initially to have behavioral changes described as depressed mood, apathy, disorientation associated with hallucinations, memory impairment, and later akinetic mutism. She also had slowness in gait, tremors of extremities and startle myoclonus.

Laboratory studies including EEG showed occasional sharp waves with a triphasic morphology seen in the frontopolar and frontal regions. Cranial imaging had

Fig. 1. DWI (left) and T2/FLAIR (right) MRI imaging of the patient in Case 1, showing restricted diffusion in the right fronto- parietal regions and hyperintensities in the bilateral cortical and deep gray pattern areas.

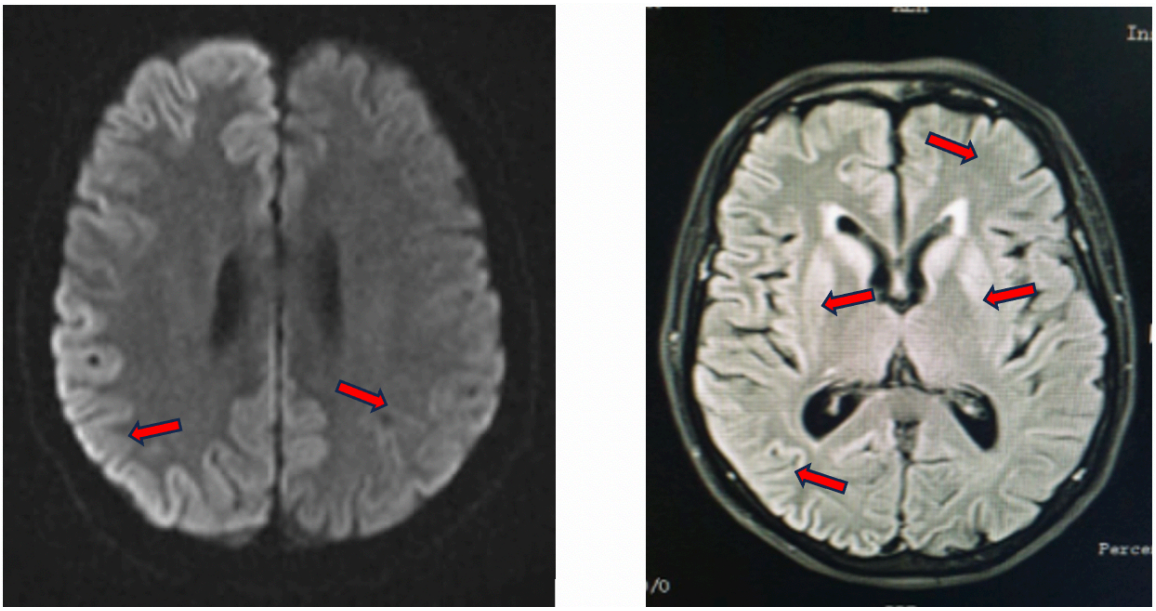


Fig 2. Electroencephalography of the patient in case 1, 2 months after the onset of symptoms showing periodic sharp wave complexes.

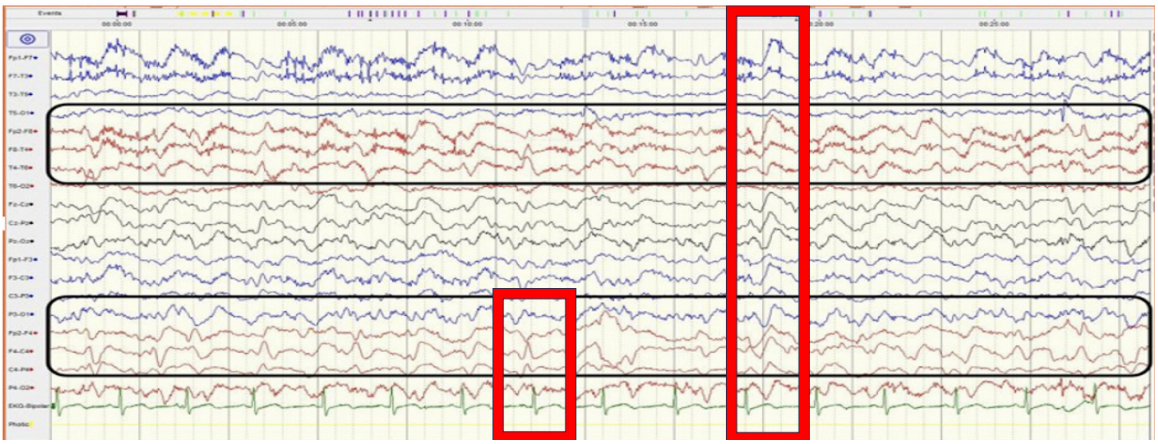


Fig. 3. DWI and T2/FLAIR imaging of the patient in case 2 showing restricted diffusion and hyperintensities in the bilateral frontoparietal subcortices.

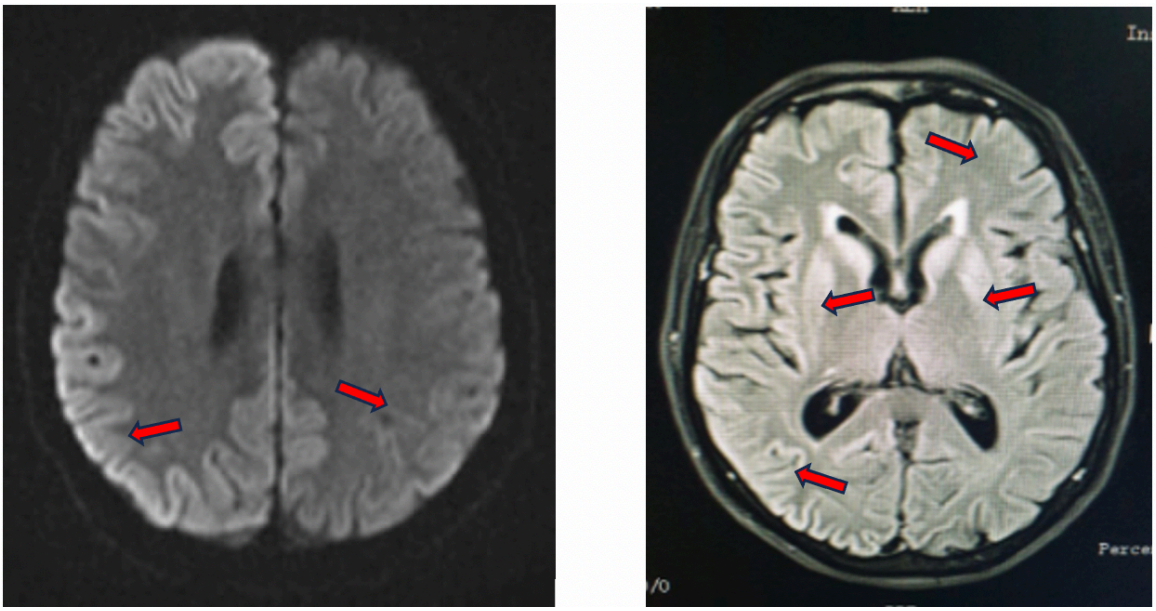


Fig 4. Electroencephalography of the patient in case 2 showing bilateral periodic sharp wave complexes.

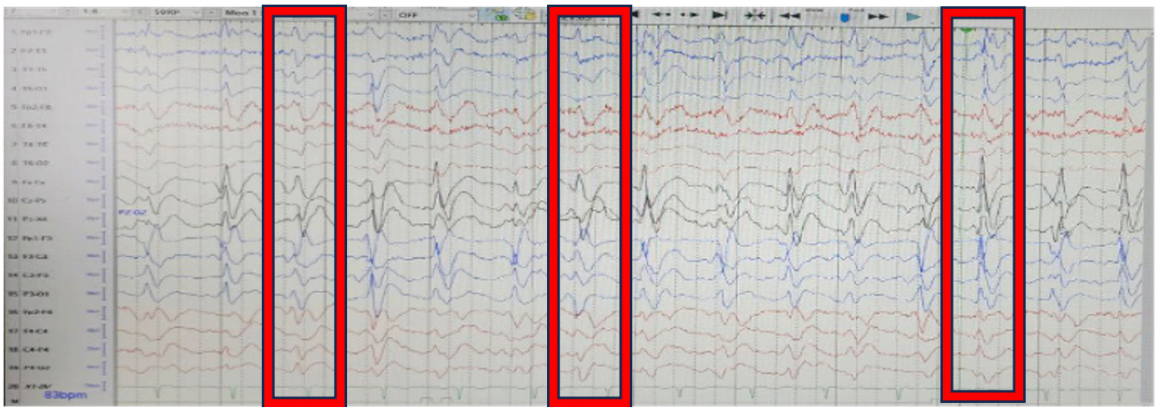


Fig. 5. DWI and T2/FLAIR imaging of the patient in case 3 showed restricted diffusion and hyperintensities in the bilateral superior frontal, middle frontal, superior parietal lobule respectively

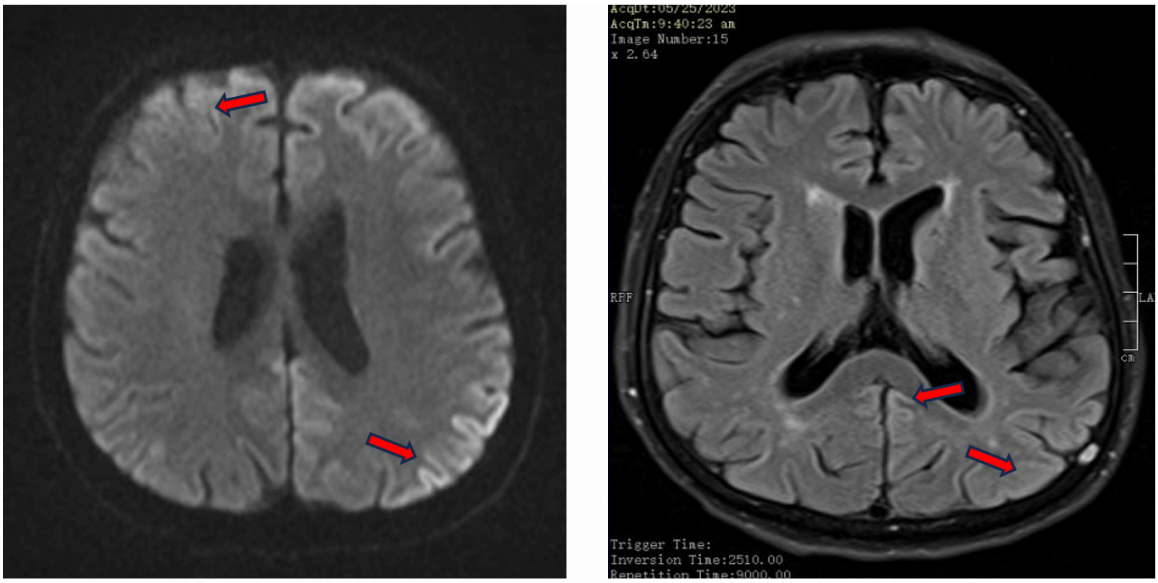
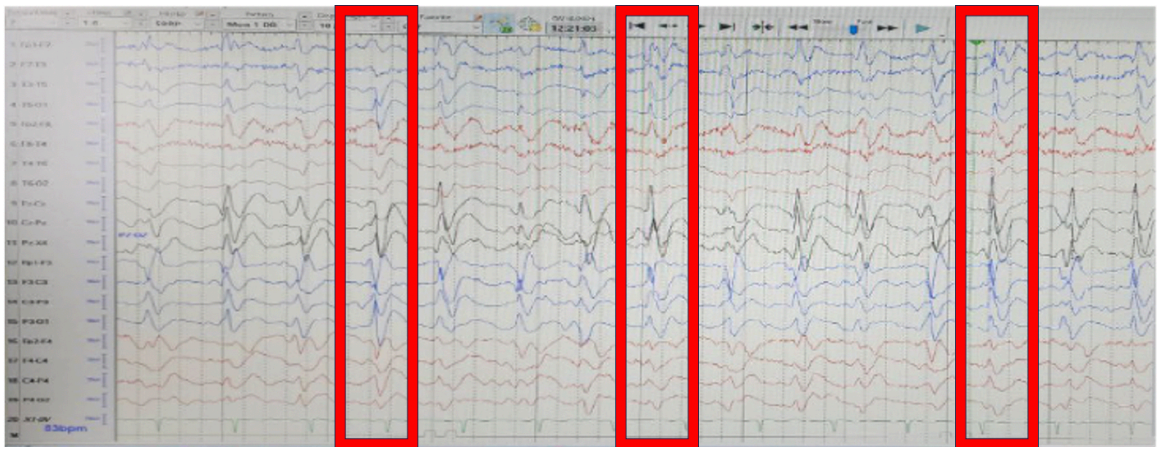


Fig 6. Electroencephalography of the patient in case 3 showing bilateral periodic sharp wave complexes.



multiple DWI restricted diffusion and T2/ FLAIR hyperintense foci scattered in the bilateral frontoparietal subcortices and periventricular white matter regions, as well as the corpus callosum. CSF studies showed an elevated protein with normal glucose, differential count and culture studies. CSF 14-3-3 testing had a positive result. The patient died of pneumonia after 8 months.

Case 3

The patient is a 72-year-old, male, known case of Alzheimer's Dementia for 20 years, who was brought in due to a remarkably decreasing verbal output and activity of 2 weeks duration. He presented rapidly progressing behavioral change described as apathy, disorientation and visual hallucinations associated with worsening of his memory lapses, ataxia and constipation.

His Cranial MRI showed multiple areas of cerebral cortical restricted diffusion with no magnetic susceptibility artifacts in the bilateral superior frontal, middle frontal, superior temporal, middle temporal, superior parietal lobule, cuneus and precuneus, more extensive in the left. His video EEG displayed moderate to severe generalized slowing of the background activity with almost continuous triphasic sharp discharges bilaterally. He was noted to have myoclonic jerks on the video. CSF studies revealed positive for 14-3-3, gamma protein, Tau- protein and RT-QulC.

All patients received a symptomatic treatment which included the empiric use of selective serotonin reuptake inhibitors for the treatment of depression, atypical antipsychotics to treat agitation and psychosis, an NMDA receptor antagonist for dementia and Clonazepam to treat severe myoclonus. A nasogastric tube were inserted to all patients as access for nutrition and medication administration. Genetic analysis was not done in our patients because, molecular genetic tests are not available in the Philippines.

RESULTS

A total of 3 cases of probable sCJD were admitted in a tertiary hospital in Metro Manila from January 2022 to April 2023. Table 1 shows the demographic profile of the patients, their clinical presentations, EEG and MRI findings. All of them were residents of Metro Manila. The mean age of patients at the time of diagnosis was 70.3 years old. All patients had behavioral abnormalities, extrapyramidal symptoms and spontaneous myoclonus. All became bedbound within 1- 3 months from the onset of their illness and developed akinetic mutism. Two had ataxia, visual hallucinations and had recent history of travel outside the country. No history of head trauma, blood transfusion, intracranial surgery, hormonal replacement nor any family history of rapidly progressive dementia noted on all patients. All patients had periodic spike wave complexes on EEG and their CSF showed normal or have mildly elevated protein. Their Cranial MRI showed features suggestive of CJD that include bilateral asymmetrical hyperintensities in the frontoparietal cortices as well as in the temporal lobe, corpus callosum and deep gray matter. Two of them died of pneumonia. The 2 patients who died did not undergo autopsy.

DISCUSSION

This case series consists of 3 cases of probable sCJD diagnosed on the basis of current European diagnostic criteria as shown on Table 2. All of our patients had clinical features of rapidly progressive dementia, akinetic mutism and myoclonus. The other clinical features include neuropsychiatric abnormalities such as apathy, disorientation abdominal discomfort, ataxia, and extrapyramidal manifestations. All of them were evaluated with detailed investigations to exclude other treatable causes; like metabolic, infectious, and autoimmune diseases. All patients showed a positive MRI finding fulfilling the criteria. Their EEG were all positive for periodic sharp waves and showed diffuse slowing of background activity. Thus, all of our patients fulfilled the criteria for the diagnosis of a probable sCJD.

The mean age of patients at the time of diagnosis was 70.3 years with a male to female ratio of 2:1. In the 10 cases of

Table 1. Patient Characteristics

Age/ Sex	Clinical presentation	Duration of the disease (months)	Periodic sharp waves in EEG	MRI Findings	CSF 14-3-3	Autopsy	Age of death (Years)
61/M	Abdominal discomfort, paranoia, confusion, hallucination, disorientation, memory lapses, numbness, ataxia,change in gait, akinetic mutism, extrapyramidal symptoms, myoclonus	8 months	Present	DWI bilateral restricted diffusion on the bilateral fronto-parietal regions, right more than the left and FLAIR hyperintensities on the same cortical areas as well as in the deep gray matter	Positive	Not done	61
78/F	Depression, disorientation, confusion, apathy, akinetic mutism, hallucinations, gait disturbance, tremors, myoclonus	18 months	Present	DWI restricted diffusion and T2/FLAIR hyperintensities in the bilateral frontoparietal subcortices and periventricular white matter regions, as well as the corpus callosum	Positive	Not done	79
72/M	Behavior changes, apathy, disorientation, visual hallucinations, Rapid deterioration of memory lapses, ataxia, constipation, myoclonic jerks	1 month	Present	Multiple areas of cerebral cortical restricted diffusion and hyperintensities in the bilateral superior frontal, middle frontal, superior temporal, middle temporal, superior parietal lobule, cuneus, and precuneus, more extensive in the left.	14-3-3: Positive RT-QuIC: Positive Elecvated Tau protein	Not done	Still alive

Table 2. The University of Edinburgh 2017 criteria for diagnosis of sCJD.

Diagnostic Certainty	Characteristic
Definite	Progressive neurological syndrome AND Neuropathologically or immunocytochemically or biochemically confirmed
Probable	Rapidly progressive cognitive impairment Two or more of A – B – C – D and Typical EEG (Generalised periodic complexes)
OR	Rapidly progressive cognitive impairment Two or more of A – B – C – D and Typical MRI brain scan (High signal in caudate/ putamen on MRI brain scan or at least two cortical regions temporal, parietal, occipital, either on DWI or FLAIR
OR	Rapidly progressive cognitive impairment Two or more of A – B – C – D and Positive 14–3-3
OR	Progressive neurological syndrome and positive RT-QuIC in CSF or other tissues
Possible	Rapidly progressive cognitive impairment two or more of A – B – C – D And duration < 2 years
	Clinical Criteria A. Myoclonus B. Visual or cerebellar problems C. Pyramidal or extrapyramidal features D kinetic mutism EEG electroencephalogram, MRI magnetic resonance imaging, DWI diffusion- weighted imaging, FLAIR fluid attenuated inversion recovery, RT-QuIc positive real-time quaking-induced conversión, CSF cerebrospinal fluid

Mehndiratta et al., the mean age was more younger with 53.80 years with a M:F of 1:1[14].

It is known that 30% of sCJD cases begin with cognitive or behavioral changes, and 30% begin with focal neurological signs, such as vision loss, cerebellar ataxia, aphasia and motor deficit[18]. In our patients, the presenting symptoms are cognitive impairment, behavioral changes, ataxia, and extrapyramidal features. They all became bedbound, developed akinetic mutism and had myoclonus, findings similar to the report of Mehndiratta et al[14]. Myoclonus is considered as the most characteristic and constant sign in CJD. Depression in patients with CJD has also been described in the literature[19]. One of our patients had depression.

All of our patients had classical EEG changes like periodic sharp wave complexes and diffuse slowing of the background activity. PSWCs in EEG give a sensitivity of 67% and specificity of 86% for detection of CJD.[20] More than 90% of patients may show periodic complexes if repeated EEG records are taken. One of our patients had a repeat EEG where the PSWCs were then noted which were not initially seen on the first EEG which only showed slowing of the background activity. PSWCs, either lateralized (in earlier stages) or generalized, occur in about two-thirds of patients with sCJD, with a positive predictive value of 95%[16].

MRI with DWI and FLAIR sequences is an invaluable modality in supporting the diagnosis of CJD. The detection of the specified high signal abnormalities in FLAIR or DWI MRI is considered to have similar diagnostic importance as PSWCs on the EEG or 14-3-3 protein detection in the CSF[17]. The study of Shiga et al. concluded that diffusion-weighted MRI had higher sensitivity (92%) in the detection of CJD than FLAIR (41-59%), T2 sequences (36-50%), EEG (50-78%), CSF protein 14-3-3 (84%), or neuron-specific enolase (73%)[18]. Matoba et al., noted that the hyperintensity in the basal ganglia and cortex during the early stages was more extensive and conspicuous while in the later stages there was disappearance of the abnormal signals in the cortex[19]. The combination of DWI and FLAIR has a sensitivity, specificity, and accuracy of over 90% in differentiating CJD from other dementias[20]. It is argued that the multifocal cortical and subcortical hyperintensities in the grey matter showing restricted diffusion on MRI may be more useful than the CSF protein 14-3-3 analysis[21]. In another recent study, Fujita et al., argued that FLAIR without DWI is unreliable for the diagnosis of sCJD[22].

RT-QuIC is a recently described laboratory technique that provides definitive diagnosis of CJD from CSF samples by detecting PrPSc[23]. Orru et al., used RT- QuIC with nasal brushings and showed a sensitivity of 97% and a specificity of 100%. This method is even less invasive than lumbar puncture, which only had 77% sensitivity but 100% specificity when the CSF was tested in the same patients[24]. One of our patients who was diagnosed with dementia for 10 years, turned out to be positive for CSF RT-QuIC. This became the basis of attributing the rapid decline of his neurocognitive function to CJD. This patient was also noted to have an elevated level of tau protein level in the CSF. The tau protein is released after neuronal damage. Its presence reaches a sensitivity of 81% and a specificity of 85% for the diagnosis of CJD. However, the presence of tau protein, together with the 14–3-3 protein has a positive predictive value of 91%[25]. Hamlin et al., studied 420 patients with CJD. They demonstrated that tau protein was superior to 14–3-3 protein as a marker in the diagnosis of CJD[26]. All of our patients had positive 14–3-3 protein in their CSF.

Ninety percent of patients with prion disease die within the first year of disease onset[27]. In our patients, two died within a mean period of 13 months from the disease onset, which is almost 3 times longer as compared to the result of 4.56 months of Biswas et al.[28] and similar to the findings of Herran et al.[29] The mainstay of treatment is symptomatic and supportive.

This case series is a single center experience over a period of 1.5 years. The disease is still considered a rare entity in the Philippines. And only one clinical case report of CJD has been described in the country[30]. The observation of so many patients within a 1.5-year period is an important observation. This demands rethinking about the disease prevalence in our country. The availability of new diagnostic criteria, readily accessible MRI and sophisticated tests such as 14-3-3, tau protein and RT QuIC assay in recent years made a probable diagnosis of CJD possible even without autopsy.

CONCLUSION

In conclusion, this is the first reported case series of probable sporadic CJD in the Philippines from a tertiary hospital in Metro Manila. Like in our patients, this disease should be considered in individuals with a rapidly progressive dementia associated with myoclonus, neuropsychiatric symptoms, akinetic mutism, visual abnormality, ataxia with signs of pyramidal and extra- pyramidal dysfunction. Although definitive diagnosis must be histopathological, there are ancillary tests that are currently available that allows us make a probable diagnosis of sCJD possible. Our study raises question about the prevalence of this disease in the Philippines which needs more validated studies from other parts of the country.

REFERENCES

1. Ironside JW. Creutzfeldt-Jakob disease. Brain Pathol. 1996;6:379–88.

2. Prusiner SB. Prions. Proc Natl Acad Sci U S A. 1998;95:13363–83.
3. Prusiner SB. Neurodegenerative diseases and prions. N Engl J Med. 2001; 344:1516–26.
3. Forloni G, Angeretti N, Chiesa R, et al. Neurotoxicity of a prion protein fragment. Nature 1993; 362:543.
4. Will RG. The transmission of prions to humans. Acta Paediatr Suppl. 1999;88: 28–32.
5. Johnson RT. Prion diseases. Lancet Neurol. 2005;4:635–42.
6. Tee BL, Geschwind MD. Prion diseases. In: Jankovic J, Mazziotta JC, Pomeroy SL, Newman NJ, eds. Bradley and Daroff's Neurology in Clinical Practice. 8th ed. Philadelphia, PA: Elsevier; 2022:chap 94
7. Eggenberger E. Prion disease. Neurol Clin. 2007;25:833–42.
8. Johnson RT. Prion diseases. Lancet Neurol. 2005;4:635–42.
9. Panagariya A, Jain RS, Sharma AK. Stroke like presentation of Creutzfeldt-Jakob disease: an unusual variant. J Assoc Physicians India. 1999;47:548–50.
10. Puoti G, Bizzi A, Forloni G, Safar JG, Tagliavini F, Gambetti P. Sporadic human prion diseases: molecular insights and diagnosis. Lancet Neurol. 2012;11:618–28.
11. Brown K, Mastrianni JA. The prion diseases. J Geriatr Psychiatry Neurol. 2010; 23:277–98.
12. Mehndiratta MM, Bajaj BK, Gupta M, Anand R, Tatke M, Seryam S, et al. Creutzfeldt-Jakob disease: Report of 10 cases from North India. Neurol India 2001;49:338-41.
13. Steinhoff BJ, Racker S, Herrendorf G, Poser S, Grosche S, Zerr I, et al. Accuracy and reliability of periodic sharp wave complexes in Creutzfeldt-Jakob disease. Arch Neurol 1996;53:162-6.
14. Zerr I, Pocchiari M, Collins S, Brandel JP, de Pedro Cuesta J, Knight RS, et al. Analysis of EEG and CSF 14-3-3 proteins as aids to the diagnosis of Creutzfeldt-Jakob disease. Neurology 2000;55:811-5.
15. Prusiner SB. The prion hypothesis. In: Prions, Prusiner SB, McKinley MP (Eds), Academic Press, San Diego 1987. p.17.
16. Eggenberger E. Prion disease. Neurol Clin. 2007;25:833–42.; 2. Johnson RT. Prion diseases. Lancet Neurol. 2005;4:635–42.
17. Gao C, Shi Q, Tian C, Chen C, Han J, Zhou W, et al. The epidemiological, clinical, and laboratory features of sporadic Creutzfeldt-Jakob disease patients
18. Steinhoff BJ, Racker S, Herrendorf G, Poser S, Grosche S, Zerr I, et al. Accuracy and reliability of periodic sharp wave complexes in Creutzfeldt-Jakob disease. Arch Neurol 1996;53:162-6.
19. Shiga Y, Miyazawak 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;63:443-9.
20. 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.
21. Young GS, Geschwind DM, Fischbein NJ, Martindale LJ, Henry RG, Liu S, et al. Diffusion–weighted and fluid–attenuated inversion recovery imaging in Creutzfeldt–Jakob disease: High sensitivity and specificity for diagnosis. AJNR Am J Neuroradiol 2005;26:1551-62.
22. Mendez OE, Shang J, Jungreis CA, Kaufer DI. Diffusion-weighted MRI in Creutzfeldt-Jackob disease: A better diagnostic marker than CSF protein 14-3-3? J Neuroimaging 2003;13:147-51.
23. Fujita K, Harada M, Sasaki M, Yuasa T, Sakai K, Hamaguchi T, et al. Multicentre multi-observer study of

diffusion-weighted and fluid–attenuated inversion recovery MRI for the diagnosis of sporadic Creutzfeldt–Jakob disease: A reliability and agreement study. BMJ Open 2012;2:e000649

24. Safar JG, Geschwind MD, Deering C, Didorenko S, Sattavat M, Sanchez H, et al. Diagnosis of human prion disease. Proc Natl Acad Sci U S A. 2005;102: 3501–6.
25. Orrú CD, Bongianni M, Tonoli G, Ferrari S, Hughson AG, Groveman BR, et al. A test for Creutzfeldt–Jakob disease using nasal brushings. N Engl J Med. 2014;371:519–29].
26. Castellani RJ, Colucci M, Xie Z, Zou W, Li C, Parchi P, et al. Sensitivity of 14-3-3 protein test varies in subtypes of sporadic Creutzfeldt-Jakob disease. Neurology. 2004;63:436–42.
27. Hamlin C, Puoti G, Berri S, Sting E, Harris C, Cohen M, et al. A comparison of tau and 14-3-3 protein in the diagnosis of Creutzfeldt-Jakob disease.Neurology. 2012;79:547–52. Johnson RT. Prion diseases. Lancet Neurol. 2005;4:635–42.
28. Atanu Biswas, Namrata Khandelwal, Alak Pandit et al. Case Series of Probable Sporadic Creutzfeldt- Jacob Disease from Eastern India. Ann Indian Acad Neurol. 2013 Oct-Dec; 16(4): 659–663]
29. Germaine Eleanor Torres Herrán1, Andrés Damián Ortega Herrera1, Braulio Martinez Burbano et al. Case series of Creutzfeldt-Jakob disease in a third-level hospital in Quito BMC Neurology (2018) 18:55]
30. Cuanang, Joven R, , & Dayrit, Greg David V, (0000).Creutzfeldt-Jakob in a 78 year old Filipina: Is it a variant-CJD or a "mad cow disease"? A case report. Philippine Journal of Neurology