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SPORADIC CREUTZFELDT-JAKOB DISEASE PRESENTING WITH RAPIDLY PROGRESSING DEMENTIA – A FAMILY MEDICINE PERSPECTIVE OF TWO CASE REPORTS

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ABSTRACT

Dementia is an increasing problem in Singapore's ageing population, with the most common being Alzheimer's disease, vascular dementia, and mixed dementia. Creutzfeldt-Jakob Disease (CJD) is a fatal neurodegenerative condition that causes rapidly progressive dementia. It is a rare human transmissible prion disease with limited literature in Southeast Asia. In this article, we report on two patients diagnosed with CJD who presented to primary care with rapidly progressive dementia, behavioural changes, and rapid functional decline. Deterioration of their clinical condition was relentless, and treatment remained palliative and supportive. It is important for family physicians to be cognisant of the clinical manifestations of CJD. We will outline the role of family physicians in the management of patients with CJD in different healthcare settings – general practice, tertiary hospital, community hospital, and hospice home care.

Keywords: Creutzfeldt-Jakob Disease, rapidly progressive dementia, prion disease, Family Physician

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INTRODUCTION

Dementia (also known as major neurocognitive disorder) as stated in the DSM-5 criteria[1] involves progressive dysfunction in memory and other domains, resulting in a decreased level of function. In Singapore, according to the Well-being of the Singapore Elderly (WiSE) study[2] led by the Institute of Mental Health in 2015, one in 10 people aged 60 and above may have dementia, translating to almost 82,000 people in 2018.

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Unlike Alzheimer's disease and vascular dementia that progress in a gradual or stepwise manner respectively, CJD progresses rapidly, and patients succumb to their illness within 1-2 years. There are several types of CJD, namely, sporadic, genetic, iatrogenic, and variant forms, with sporadic being the most common, accounting for 85 percent of cases.[4,5] There is however limited data of the prevalence of CJD in Singapore and Southeast Asia, with only a handful of published case reports.[6,7,8]

Primary care is the foundation of any healthcare system and often the first point of contact for patients.[16] The initial presentation of CJD is varied and can be subtle. Clinical features include rapidly progressive dementia and any two of the following: myoclonus, visual or cerebellar disturbances, pyramidal/extrapyramidal dysfunction, akinetic mutism, and higher cortical signs. Pertinent history such as family history, prior procedures and exposure are also important (refer to **Figure 1**). Other causes of rapidly progressive dementia can be classified by their aetiology: vascular, infective, toxin mediated, autoimmune, metabolic, intracranial, and neoplastic as summarised in **Figure 2.**

The family physician can perform initial screening tests when encountering patients with suspected dementia and should refer promptly to the neurologists for further workup when suspecting CJD. Definitive diagnosis of CJD requires invasive neuropathological investigations.[6] Other modalities that may be used to support the diagnosis include Electroencephalogram (EEG), Cerebrospinal fluid (CSF) assay, and Magnetic Resonance Imaging (MRI) brain.[9,10,11]

We report two patients, a 75-year-old female and a 61-year-old male who both presented to primary care with rapidly progressive dementia and neuropsychiatric symptoms. They were both promptly referred and diagnosed with CJD in the tertiary hospital. They were also cared for in the community hospital and eventually discharged with home hospice support. They had similar healthcare utilisation patterns. We will review the role of family physicians in the care of these patients.

Figure 1: Presentation and evaluation of different types of CJD[17,18,19]

CJD	Sporadic (sCJD)	Genetic	Acquired	
			Iatrogenic (iCJD)	Variant (vCJD)
% of CJD	85%	10-15% Subtypes: • Familial CJD • Fatal familial insomnia. • Gerstmann-Schausler-Scheinker syndrome	<1%	<1 %
Epidemiology	Incidence: 1-2 cases per million population			
	• Median duration of illness: 4-5 months • Age of occurrence: 60-80 years old • Median age of death: 68 years old			• Age of onset: 26 • Longer disease duration (Median 14 months) • Median age of death: 28
Modes of transmission	• Origins remain unclear • Believed to be spontaneous transformation of prion protein from its normal form PrP^{C} (referring to its normal cellular form) to PrP^{Sc} (Scrapie, referring to a prion disease in sheep)	• PRNP Gene mutation • Person-to-person transmission by blood, milk saliva, urine or faeces has not been reported • CJD has not been reported in infants born to infected mothers	• Most of the cases recorded following procedures for dura mater grafts, growth hormone treatment, electroencephalography needles, neurosurgery, receipt of corneal grafts, gonadotrophin, or packed red blood cells.	• Unclear transmission • Postulated to be transmitted to humans by eating food contaminated with bovine spongiform encephalopathy infected cattle
Clinical presentations	Two or more clinical features: • Rapidly progressive dementia • Disease duration <2 years • Myoclonus • Visual disturbances • Pyramidal or extrapyramidal features • Akinetic mutism • Cerebellar dysfunction (ataxia) • Higher cortical signs (neglect, aphasia, apraxia, acalculia)	• Clinical features as per sCJD • Progressive neuropsychiatric disorder • May have definite or probable prion disease in a first-degree relative • Variations dependent on subtypes and specific mutations	• Clinical features as per sCJD • Rapidly progressive dementia • Recognised risk factor for iatrogenic transmission (Refer to modes of transmission)	• Progressive neuropsychiatric disorder <6 months with no evidence of genetic prion disease or iatrogenic exposure • Commonly starts with psychiatric symptoms (Dysphoria, anxiety, withdrawal, irritability, insomnia, lack of interest) • Hallucinations, delusions • Neurological signs happen later (ataxia, global cognitive impairment, involuntary movement)

Investigations	• EEG: Periodic triphasic sharp wave complexes at 1-2 Hz • MRI: Restricted diffusion in basal ganglia or cortical ribboning on MRI-DWI One or more of the following: • CSF: 14-3-3 protein, tau protein, Quaking-induced Conversion (QuIC) assay	• As per sCJD. Plus • PRNP gene mutation	• As per sCJD	• EEG: Generally, does not have typical features seen in EEG. Might sometimes occur in late stages of vCJD. • MRI: Pulvinar sign present in >75%
Pathological findings	One or more of the following: • Spongiform encephalopathy in cerebral and/or cerebellar cortex and/or subcortical grey matter • Prion protein (PrP) immunoreactivity in plaque like and/or diffuse synaptic and/or patchy/perivacuolar patterns • Presence of protease resistant PrP by Western blot	One or more of the following: • Spongiform encephalopathy in cerebral and/or cerebellar cortex and/or subcortical grey matter • Prion protein (PrP) immunoreactivity in plaque like and/or diffuse synaptic and/or patchy/perivacuolar patterns • Presence of protease resistant PrP by Western blot • Multicentric PrP-immunoreactive plaques in cerebral and/or cerebral cortex, with neuron loss and spongiform change (GSS neuropathologic phenotype).	One or more of the following: • Spongiform encephalopathy in cerebral and/or cerebellar cortex and/or subcortical grey matter • Prion protein (PrP) immunoreactivity in plaque like and/or diffuse synaptic and/or patchy/perivacuolar patterns • Presence of protease resistant PrP by Western blot.	• Extensive lymphoreticular deposition of prion protein • Spongiform change • Extensive PrP deposition • Florid plaques throughout cerebrum and cerebellum

Figure 2: Differential diagnoses of rapidly progressive dementia[3]

Vascular • Multi infarcts • Thalamic or callosum infarcts • Central Nervous System (CNS) vasculitis • Venous thrombosis • Posterior Reversible Encephalopathy Syndrome	**Toxin-mediated** • Uraemia • Portosystemic encephalopathy • Bismuth • Lithium • Mercury • Arsenic
Infections ***Bacterial*** • Syphilis • Whipple's Disease • Lyme disease ***Viral*** • Viral encephalitis, (e.g., Herpes Simplex Virus) • Human Immunodeficiency Virus dementia • Progressive Multifocal Leukoencephalopathy • Subacute sclerosing panencephalitis ***Others*** • Fungal infections (e.g., CNS aspergillosis) • Parasites (e.g., Balamuthia)	**Autoimmune** • Hashimoto's Encephalopathy • Paraneoplastic (autoimmune) limbic encephalopathy • Non-paraneoplastic autoimmune (e.g., anti-VGKC mediated) • Lupus cerebritis • CNS Vasculitis • Sarcoidosis
Metabolic/Endocrine • Vitamin B12 (Cyanocobalamin) deficiency • Vitamin B1 (Thiamine) deficiency • Vitamin B3 (Niacin) deficiency • Folate deficiencyWilson's disease • Porphyria • Thyroid disturbances • Parathyroid abnormalities • Non-autoimmune paraneoplastic conditions	**Neurodegenerative** • Creutzfeldt-Jakob disease (sporadic, iatrogenic, familial) • Dementia with Lewy Bodies • Frontotemporal dementia • Corticobasal degeneration • Progressive Supranuclear Palsy
	Intracranial • Primary CNS lymphoma • Intravascular lymphoma • Lymphomatoid granulomatosis • Gliomatosis cerebri

CASE REPORT 1

The first patient is a 75-year-old Chinese female with a past medical history of dyslipidaemia, hepatitis B carrier, gastric ulcer, diverticular disease, and coronary artery disease.

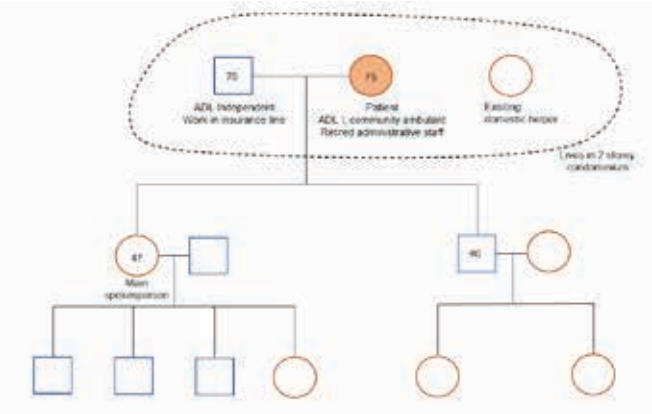
Initial Presentation

She first presented to a family physician in private practice with amnesia and repetitive behaviour (e.g., making up to 20 phone calls to her husband in a day). She was noted to have word-finding difficulties and apraxia affecting her gait and dressing (e.g., wearing her clothes inside out). Her family reported an acute change in her mood and behaviour over the previous month, characterised by sleep-wake reversal, anxiety, and a pervasive fear of deaths in the family. She was promptly referred to the tertiary hospital in Singapore for further evaluation in October 2018.

Social History

Prior to presentation, she was ADL-independent, and community ambulant. She had no family history of rapidly progressive dementia and no prior surgical interventions. The patient shared a close and supportive relationship with her spouse and children. **Figure 3** depicts her genogram.

Figure 3: Case 1 Genogram



Investigation

Initial investigations such as full blood count, electrolytes, vitamin B levels, liver function, thyroid function, and autoimmune panel were unremarkable.

Lumbar puncture was done, and CSF was evaluated for the RT-QuIC test – a sensitive and specific marker for CJD,[10,11] which returned positive. The rest of the CSF studies including cytology, encephalitis panel, virology studies, and cultures were negative.

EEG showed triphasic sharp wave complexes and MRI brain showed Type 2 weighted hyperintensity of bilateral caudate and bilateral cerebral hemispheres. Repeat MRI brain a month later showed diffused signal change involving bilateral cerebral hemispheres, cortices, and basal ganglia.

Progression of Disease

During her admission to the tertiary hospital, she deteriorated further, developing frequent tantrums and myoclonic jerks. She was started on fluvoxamine and sodium valproate. She was discharged home but was readmitted within a week to the tertiary hospital for functional decline. She became more lethargic, had decreased appetite, and developed muscle weakness. Repeated investigations did not reveal any acute cause for her deterioration.

She was subsequently discharged to the community hospital. The team in the community hospital included family physicians, visiting consultants, physiotherapists, nurses, occupational therapists, music therapists, art therapists, dietitians, speech therapists, pastoral care team, and medical social workers. She continued to decline rapidly. Two months into her diagnosis, she was minimally communicative and bedbound. Speech therapists reviewed her regularly and diagnosed her with moderate oropharyngeal dysphagia. A nasogastric tube (NGT) was inserted for feeding. The physiotherapists and occupational therapists provided rehabilitation and caregiver training. The family physician continued to oversee the care of the patient, pace with her family, and manage acute medical issues. The patient had an episode of aspiration pneumonia and was treated with a course of antibiotics.

In view of lethargy, the dose of sodium valproate was down titrated. Unfortunately, the patient developed new onset seizures on 8 January 2019. She was administered rectal diazepam. However, she developed another episode of seizure soon after and a top-up dose of sodium valproate was administered. In view of recurrent seizures, a decision was made to transfer her back to the tertiary hospital for further evaluation and management. Nonetheless, in light of her poor prognosis, the goals of care and advance care planning could have been initiated earlier by the family physician in the community hospital.

The patient was reviewed in the tertiary hospital and started on levetiracetam and clonazepam with good response. The inpatient team in the tertiary hospital made the necessary arrangements and she was discharged with home hospice support. She passed away on November 2019, 13 months from her initial presentation. **Figure 4** illustrates her clinical condition and transition within the healthcare institutions, and summarises the roles family physicians played in this case.

Figure 4: Transition of care for Cases 1 and 2

Timeline	September 2018	October 2018	November 2018	December 2018	January 2019	November 2019
Clinical Manifestations (Case 1)	• Well	• Amnesia, repetitive speech • Aphasia • Apraxia, affecting gait • Anxious	• Myoclonic jerks – started on sodium valproate and fluvoxamine • Loss of appetite • Muscle weakness • Sleep-wake reversal	• NGT inserted • Developed aspiration pneumonia • Uncommunicative • Bedbound • Developed seizures	• Started on leviraticam and clonazepam	• Demise
Clinical Manifestations (Case 2)	• Well	• Amnesia • Agnosia • Apraxia • Behavioural change	• ADL-dependent • Loss of appetite • Myoclonic jerks – started on sodium valproate, levetiracetam, and clonazepam	• NGT inserted • Uncommunicative • Bedbound	• Uncommunicative • Bedbound	• Demise
Setting of care	• Home	• Tertiary hospital	• Discharged home • Readmitted to tertiary hospital	• Community hospital	• Tertiary hospital (Case 1) • Home with hospice home care (Case 2)	• Home with hospice home care
Role of family physician	• Early recognition and referral to tertiary institution for evaluation • Follow-up with family and provision of support		• In view of expected deterioration of patient and high care needs, family physician can work with internists from tertiary institutions for discharge planning	• Management of acute condition • Goals of care • ACP discussion	• End-of-life care • Coordination of community resources • Work with hospice home care	• Part of hospice home care team • May be called upon to do house calls in acute events • Possible to work with palliative team to certify death

CASE REPORT 2

The second patient is a 61-year-old Malay male with a past medical history of diabetes mellitus and hyperlipidaemia.

Initial Presentation

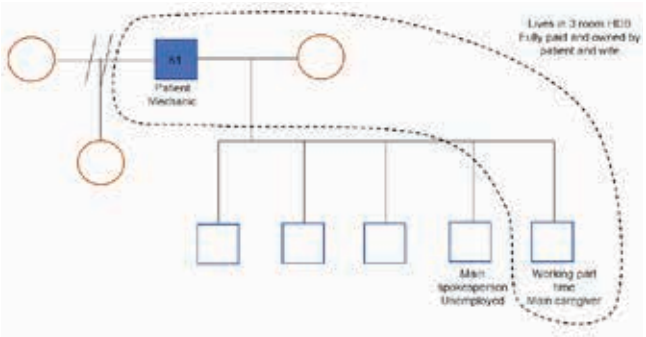
He first presented to a family physician in an outpatient clinic in October 2018 for concerns of dementia and abnormal behaviour for one month. He had agnosia and was unable to recognise his family members. He was also noted to have amnesia (e.g., repetitive speech, and repeatedly forgetting to bring his staff pass), and aphasia with word-finding difficulties.

His family reported abnormal behaviours such as jumping on his bed and talking to himself. Initial investigations done in the outpatient clinic returned normal and he was promptly referred on to a tertiary institution for further evaluation.

Social History

Prior to presentation, he was ADL independent and community ambulant without aid. He worked as a technician. There was no family history of rapidly progressive dementia or prior surgical interventions. The patient was married and had five sons and a stepdaughter. He lived with his wife and his youngest son in a 3-room HDB flat. His family appeared close-knit and visited him frequently. **Figure 5** depicts his genogram.

Figure 5: Case 2 Genogram



Investigation

Full blood count, electrolytes, vitamin B levels, liver function, and thyroid function tests done in the outpatient clinic were normal. Autoimmune panel done in the specialist clinic also returned normal.

Lumbar puncture was done. CSF was evaluated for RT-QuIC test and 14-3-3 protein, which returned positive. The rest of CSF studies including cytology, encephalitis panel, virology studies, and cultures returned negative.

Initial EEG done in November showed diffuse encephalopathy with no epileptiform abnormalities. Subsequent EEG repeated in December showed multifocal generalised sharp waves consistent with that of sCJD. MRI brain showed bilateral symmetrical widespread cortical signal abnormalities including the caudate nuclei.

Progress of Disease

Following workup, the patient was discharged with a neurology appointment. However, in view of the rapid functional decline and caregiver stress, the patient was soon readmitted. One month into his diagnosis, he became uncommunicative and lost his ability to walk independently. He had swallowing impairment and poor appetite, necessitating insertion of an NGT. He developed myoclonic jerks, occasional eye deviation, and repetitive lip-smacking movements, and was started on sodium valproate, levetiracetam, and clonazepam.

In December 2018, he was transferred to an inpatient hospice in a community hospital. The patient and his family were supported by the multidisciplinary team in the community hospital involving family physicians, visiting consultants from the palliative department, nurses, physiotherapists, occupational therapists, speech therapists, dietitians, pastoral counsellors, medical social workers, and the infection control team. Several family conferences were held in the tertiary institution and in the community hospital. The diagnosis and disease trajectory were shared with the patient's family and a prognosis of one year from his diagnosis was given. The patient's family was shocked by the acute deterioration of his condition and were grieving.

The multidisciplinary team helmed by the family physicians continued to oversee the medical care and titration of medications for the patient. Along with the medical social worker, the family physician paced with the family. The physiotherapists, occupational therapists, and nurses also provided caregiver training for the family and ensured that the home was set up with the necessary equipment. The home hospice team was engaged to care for the patient upon discharge.

Discharge Planning

After completion of caregiver training and procurement of the necessary equipment, the patient was eventually discharged with hospice home support.

The infectious disease team was consulted regarding the management of patients with prion disease. The family was counselled and trained regarding infection control measures to take while caring for the patient. A memo was also written to alert the home hospice team of his medical condition.

As with Case Report 1, the patient passed away on November 2019, 13 months from his initial presentation. **Figure 4** illustrates his clinical condition, transition within the healthcare institutions and how the family physician can add value to patient care.

DISCUSSION

We reported two patients who presented with rapidly progressive dementia associated with varied neuropsychiatric and behavioural manifestations. They were both evaluated with blood tests, lumbar puncture, MRI brain and EEG in the tertiary hospital, and diagnosed with CJD. Their decline was relentless with several complications including aspiration pneumonia and seizures. The goals of care remained supportive and palliative. They both lost their independence within two months of diagnosis and demised 13 months from onset.

Both patients had similar patterns of healthcare utilisation as shown in **Figure 4**. We will review how family physicians can contribute and add value to the care of patients diagnosed with CJD in the different settings. These pointers can also be adapted to caring for patients with different types of dementia.

Primary Care/Outpatient Setting

Both patients presented to the family physician in the outpatient setting with rapidly progressive dementia and behavioural changes. When faced with patients with suspected dementia, preliminary blood tests may be done to evaluate the causes of dementia as mentioned in **Figure 2**. However, in view of atypical presentation of rapidly progressive dementia and features as mentioned in **Figure 1**, both patients were promptly referred to the tertiary hospital for further work-up. Raising the awareness of CJD and other rapidly progressive dementias can help doctors recognise and refer patients promptly for evaluation.

Tertiary Setting

Both patients were discharged from the respective hospitals but quickly readmitted in view of functional decline and caregiver stress. Family physicians can work with internists in discharge planning and optimise patient care in the community. Post-discharge house visits, coordination of community resources, review of home setup, and caregiver training are examples of where family physicians can add value in supporting patients and their families in the community.

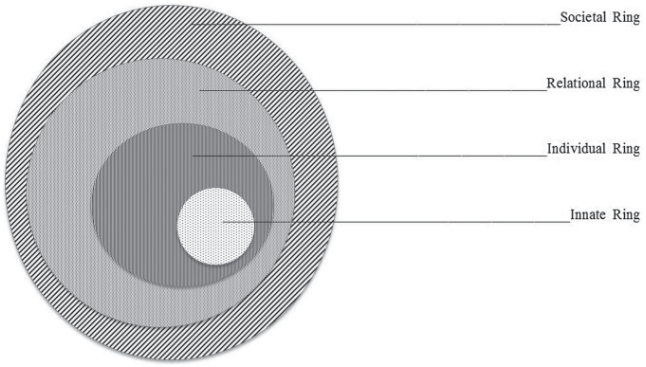
Community Hospital/Inpatient Hospice

Both patients were discharged to the community hospital from the tertiary hospital in view of high care needs and were managed by the multidisciplinary team. Family physicians coordinate care amongst team members and manage the patients' medical condition. Acute problems faced by the patients include aspiration pneumonia, functional decline, agitation, drowsiness, and seizure. Family physicians need to be knowledgeable and well equipped to titrate the relevant medications and pre-empt complications. Family physicians can help to pace with the family through the course of the patient's illness.

End of Life Care/Hospice Home Care

In neurodegenerative diseases, patients lose their autonomy and capacity as the disease progresses. The Krishna's Ring Theory as represented in **Figure 6** suggests that a patient's personhood is represented by four interrelated ring domains – innate, individual, relational, and societal.[14]

Figure 6: The Krishna's Ring Theory of Personhood



The innate ring embodies the belief that personhood begins from the moment of conception. It also encompasses the person's religious beliefs and connection with God. Encapsulating the innate ring is the individual ring that pivots on the patient's ability to maintain the innate ring, conscious function, cognition, and interaction with others. It also embodies autonomy and competence. However, with neurodegenerative diseases such as CJD, the individual ring is compromised by the disease process. The patient's family who shares strong personal bonds with them form the relational rings, preserving the individuality of the incapacitated patients. Family physicians can be represented in the societal ring to provide care, maintain a patient's dignity, support the family, and be an advocate for the patient.[14]

Both reported patients required insertion of NGT for feeding and were discharged with home hospice services. These were some of the tough decisions their families had to make. Advance Care Planning (ACP) is a process of planning one's future health and personal care through a series of discussions with the healthcare team. It is recommended for all patients, especially those with life-limiting conditions. A study done in Singapore showed that amongst Singaporeans, there was low awareness but high willingness to participate in ACP discussions.[15] Hence, family physicians are in a good position within the community to encourage and facilitate the ACP discussions. This can help both the family and healthcare team understand the values and beliefs of the patients.

Family physicians may also play an integral role as part of the home hospice team or home medical services and may be called upon to care for these patients as part of house calls when they are discharged from the hospital. Family

physicians would also need to be confident in managing deceased patients in accordance with MOH and World Health Organization (WHO) infection control guidelines for transmissible spongiform encephalitis.

Standard precautions that should be taken include appropriate hand hygiene, use of personal protective equipment (such as gloves and masks), safe injection practices, and safe handling of potentially contaminated equipment. Disposal of body substances with no detectable infectivity such as blood, urine, secretions, vomitus, and stools can be carried out as usual at home with precautions to limit splash.[12] No special precautions are required for personal equipment such as feeding utensils, tubes, suction tubes, wound care products, and bed linens.

With regards to funeral matters, in Singapore, only undertakers approved by the Ministry of Health (MOH) can manage the body of patients with CJD upon demise. The body should be placed on an impermeable sheet or body pouch. Embalming an autopsied or traumatised body is discouraged.[12]

Clinical Practice Pointers

a. Family physicians will be seeing more patients with dementia as the population ages and need to be able to pick up on atypical features such as rapidly progressive dementia, myoclonus, and early behavioural changes. Prompt referral to the tertiary institution for evaluation will allow earlier diagnosis and management.

b. Family physicians may be involved in the care of patients with CJD in various settings from diagnosis to death. Family physicians play a significant role in early identification of suspected cases, performing initial investigations and making prompt referrals to specialists where indicated. A sound knowledge of CJD will allow family physicians to pre-empt certain manifestations such as myoclonus and complications such as immobility and swallowing impairment. Family physicians can also collaborate with the inpatient team for discharge planning. With good understanding of the disease trajectory, family physicians can help to pace with the family and coordinate patient care in both the hospital and community.

c. Family physicians play a vital role in being advocates for their patients towards the end of life as represented in the Krishna's ring theory. ACP is one such tool that can be used.

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