Clinical Features of Sporadic Fatal Insomnia

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Recent advances in neuropathology, genotyping, and physiochemical characterization of proteins have allowed for the classification and verification of MM2-thalamic Creutzfeldt-Jakob disease (CJD). CJD is a fatal neurodegenerative illness belonging to the transmissible spongiform encephalopathies, also known as prion diseases. *Sporadic CJD is generally classified by the genotype at codon 129 of the prion protein gene and the distinct physiochemical features of the pathologic prion protein (PrP^{sc}). The entity is characterized by methionine homozygosity at codon 129, type 2 PrP^{sc}, and, primarily, thalamic pathology (MM2-thalamic CJD). It shares clinical and pathologic similarities with the genetic prion disorder fatal familial insomnia; the MM2-thalamic phenotype has therefore been called* sporadic fatal insomnia *(SFI). SFI may also present like other neurodegenerative diseases, and common diagnostic findings that are seen in other forms of sporadic CJD may be absent.*
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Creutzfeldt-Jakob disease (CJD) is a fatal neurodegenerative illness belonging to a group of disorders known as the *transmissible spongiform encephalopathies*. Sporadic CJD (sCJD) represents 80% to 90% of all CJD cases[1] and is widely classified by 2 characteristics: the genotype at codon 129 of the prion protein gene (*PRNP*) and the distinct physiochemical features of the pathologic prion protein (PrP^{sc}). Although polymorphic codon 129 may show methionine homozygosity (MM), valine homozygosity (VV), or methionine-valine heterozygosity (MV), the relative molecular mass of the PrP^{sc} fragment after proteinase digestion and deglycosylation may be 21 kd (type 1) or 19 kd (type 2).[2] Therefore, at least 6 distinct phenotypes of sCJD have been associated

with these properties: MM1, MM2, VV1, VV2, MV1, and MV2.[3] (Of note, *both* PrP^{sc} types 1 and 2 have been isolated in single patients, and so some authors have included MM1/2, VV1/2, and MV1/2 as additional phenotypes.[4])

In one major study, MM2-type sCJD was found in only 12 of 300 patients; 6 of these were noted to have predominantly cortical pathology (MM2-C), and the remainder had a lesion profile primarily localized to the thalamic and olivary regions (MM2-T).[3] The most common clinical features of the latter entity included cognitive loss, insomnia, dysautonomia, psychiatric symptoms, and motor signs, including ataxia and myoclonus.[3,5,6] Given these clinical and pathologic similarities to the genetic disorder fatal familial insomnia ([FFI] associated with a substitution of asparagine for aspartic acid at *PRNP* codon 178, allelic to methionine at codon 129), the MM2 thalamic phenotype was called *sporadic fatal insomnia* (SFI).[5,6] However, other diseases may present in a similar fashion, and the differential diagnosis has included progressive supranuclear palsy, spinocerebellar degeneration, and Alzheimer's disease.[7] Additionally, common diagnostic findings seen in other forms of sCJD, including elevated levels of cerebrospinal fluid (CSF) 14-3-3 protein, periodic discharges on an electroencephalogram (EEG), and distinctive hyperintensities on magnetic resonance imaging (MRI), may all be absent in SFI.[7] Given the rarity of this condition and the difficulty in diagnosis, a systematic review of the literature was performed to better characterize the clinical features of confirmed cases.

Methods

PubMed was used to identify case reports and case series of SFI (MM2-thalamic CJD). The search phrases "sporadic fatal insomnia" and "MM2 Creutzfeldt-Jakob disease" were used to find all such studies published through November 2008. The references, bibliographies, and other sources mentioned in these articles were also reviewed. All publication types in the English language were considered for inclusion.

To be considered for this review, each case required evidence of a wild-type *PRNP* sequence by genetic analysis; MM at *PRNP* codon 129; the isolation of type 2 PrP^{sc} in brain tissue; and histopathologic confirmation of the diagnosis, similar to that described by Parchi and colleagues.[3] Articles that did not detail the MM2 subtype (cortical or thalamic) or describe the clinical features of each patient were excluded. The epidemiologic characteristics (age, sex, and duration), signs, symptoms, and key diagnostic testing for the cases were reviewed and summarized. In each instance in which the completion of relevant diagnostic testing was not explicitly specified, the authors were contacted when possible, to clarify the tests that were (or were not) performed.

Results

The PubMed search strategy yielded 12 potentially relevant studies.[4-15] Seven additional studies were identified through bibliographic review.[2,3,16-20] Two reports included only cases of the MM2-cortical phenotype,[2,19] and these studies failed to meet the inclusion criteria. One study that did not specify MM2 subtypes[4] and 3 other investigations that did not individually describe the clinical features of MM2-thalamic patients[3,14,18] were excluded. One patient initially considered as MM2-thalamic[15] was excluded when the pathology was later reclassified as having both thalamic and cortical features.[21] Therefore, 8 studies met all the inclusion criteria and were included in our analysis.[5-7,9-13] Of note, the case series of Hamaguchi and colleagues[7] included 3 MM2-thalamic cases discussed elsewhere.[8,16,20] Furthermore, the case of a young Japanese man fully described by Hirose and coworkers[11] has been included in multiple case series.[15,17]

A total of 16 cases were included for review. The group included 10 men and 6 women who presented at a mean age of 51.4 ± 13.6 years (range, 30-72 years) (Table 1). The mean duration of symptoms was 26.7 ± 15.7 months (range, 13-73 months). Cognitive impairment (100%), ataxia or gait disorder (81.3%), insomnia (68.8%), dysautonomia (62.5%), and myoclonus (62.5%) were most often described during the course of the illness (Table 2). Psychiatric features, pyramidal and extrapyramidal findings, visual abnormalities, dysarthria, and dysphagia were also reported.

Among the 7 patients tested for 14-3-3 protein in the CSF, just 1 patient had a positive result, and 1 was indeterminate (Table 3). Only 1 patient had characteristic periodic discharges on EEG. No patient had typical hyperintensities on MRI. However, 6 patients underwent nuclear imaging; all showed reduced metabolism (1 by positron emission tomography [PET]) or blood flow (5 by single photon emission computed tomography [SPECT]) in the thalamic region. All 5 SPECT studies also showed reduced blood flow to the cortical areas. Both patients who underwent polysomnography (PSG) had insomnia objectively verified.

Discussion

Although the earliest descriptions of "thalamic dementia" were published 70 years ago,[22] more recent advances in neuropathology, genotyping, and

Table 1
Demographic Characteristics of Sporadic Fatal Insomnia Patients

Study	Patient #	Sex	Age at Onset/ Presentation (y)	Disease Duration (mo)
Mastrianni et al[5]	1	M	44	16
Parchi et al[6]	2	M	53	18
	3	F	46	15
	4	M	70	24
	5	F	40	15
	6	M	36	17
Hamaguchi et al[7]	7	F	49	30
	8	M	64	53
	9	F	30	73
	10	M	71	25
	11	M	58	13
Scaravilli et al[9]	12	M	58	27
Piao et al[10]	13	M	72	29
Hirose et al[11]	14	M	32	30
Capellari et al[12]	15	F	43	24
Mehta et al[13]	16	F	56	18
Total		10 M; 6 F		
Median			51	24
Mean			51.4	26.7
Standard Deviation			13.6	15.7
Range			30-72	13-73

F, female; M, male.

physiochemical characterization of proteins have allowed for the classification and verification of MM2-thalamic CJD (SFI). Our review of patients, all autopsy-confirmed, showed that sporadic and familial fatal insomnia share many clinical features. In our series, the mean age of onset was 51 years, which was also found in a previous review of FFI. Moreover, the range and average duration of symptoms of patients in this review (range, 13-73 months; mean, 26.7 months) are comparable with those patients who had a longer disease course in the original FFI pedigrees (range, 11-72 months; mean, 30.8 months).[23] Insomnia and dysautonomia, 2 of the cardinal features of FFI,[23] were each noted in more than 60% of the SFI patients, and in more than 80% of patients when combined. Cognitive deficits and at least 1 motor disturbance (myoclonus, dysarthria, dysphagia, pyramidal, and extrapyramidal findings, as well as ataxia and gait disorder) were each reported during the course of all 16 cases.

Because SFI may initially present like other neurodegenerative diseases,[7] there has been a search for findings that might accurately aid in premortem diagnosis. This review confirmed the paucity of diagnostic findings that are commonly associated with other forms of sCJD, including elevated levels of CSF 14-3-3 protein, periodic discharges on EEG, and distinctive hyperintense signals on MRI. Even brain biopsy, performed on 3 patients (2 cerebellar and 1 temporal),[5,6] was nondiagnostic in all instances. Given that the thalamus and olives represent primary sites of pathology in SFI, the yield of these biopsies might have been limited, at least in part, due to the neuroanatomical location in which they were performed.

In contrast to the lack of findings on MRI, reduced tracer uptake in the thalamus was found in all 6 patients who had nuclear imaging; the finding was also noted in cortical regions in all 5 SPECT scans. Scintigraphic changes in the thalamus, with or without associated cortical findings (and without involvement of other regions of the brain), have been reported in FFI (Figure 1),[24,25] although not in other dementing illnesses such as Alzheimer's disease or dementia with Lewy bodies.[26,27] Given that these changes have been observed relatively early in the course of the SFI,[7] SPECT and PET might be of particular value in the diagnosis of this condition. However, further studies are needed to clarify the significance of the findings in this small sample, particularly with PET, which was performed in only 1 patient.

Only 2 of 11 patients with reported insomnia in this sample underwent a formal sleep study. In both patients, PSG verified disturbances of sleep architecture characteristic of the fatal insomnia phenotype, including loss of sleep spindles and slow wave sleep.[9,12] Although sleep studies served to support clinical suspicions in these patients, PSG might be beneficial in illuminating scenarios that might be less clear. In cases of FFI, for example, some patients are sleepy during the day due to sleep deprivation; these patients are often inaccurately labeled as hypersomnolent until disrupted nocturnal sleep is finally observed.[23]

Table 2
Symptoms and Signs Reported in Sporadic Fatal Insomnia Patients Throughout the Course of Illness

Study	Patient #	Insomnia	Dysautonomia*	Ataxia/Gait Disorder	Dysarthria	Cognitive†	Myoclonus	Psychiatric‡	Dysphagia§	Pyramidal‖	Extrapyramidal¶	Visual**
Mastrianni et a1[5]	1	X	X	X	X	X	X	X	X			
Parchi et al[6]	2	X	X	X	X	X			X			
	3	X	X	X		X	X	X		X	X	X
	4	X	X	X		X			X		X	
	5			X		X		X		X		X
	6	X	X	X	X	X	X	X				
Hamaguchi et al[7]	7	X	X			X	X	X		X	X	
	8		X	X	X	X	X	X	X		X	X
	9			X	X	X	X	X		X	X	X
	10		X	X		X						
	11			X		X	X	X		X		
Scaravilli et al[9]	12	X		X	X	X	X			X	X	
Piao et al[10]	13	X				X	X					
Hirose et al[11]	14	X	X			X		X			X	
Capellari et al[12]	15	X	X	X		X	X					X
Mehta et al[13]	16	X		X	X	X				X		X
Total (of 16)		11	10	13	7	16	10	9	4	7	7	6
Percentage (%)		68.8	62.5	81.3	43.8	100	62.5	56.3	25.0	43.8	43.8	

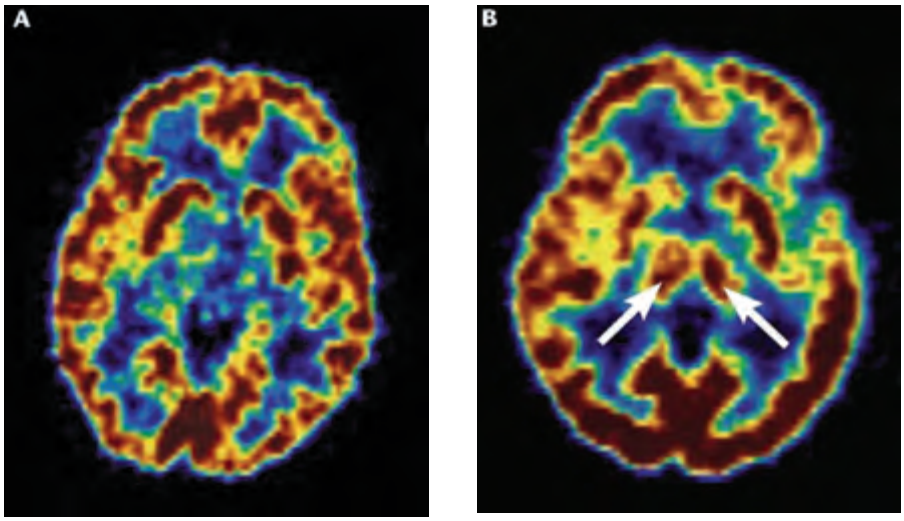
*Dysautonomia includes excessive lacrimation, impotence, incontinence, and hyperhidrosis.
†Cognitive includes memory loss, disorientation, and dementia.
‡Psychiatric includes hallucinations, delusions, depression, emotional lability, and withdrawal.
§Dysphagia includes aspiration.
‖Pyramidal includes hyperreflexia, hypertonia, and present Babinski sign.
¶Extrapyramidal symptoms (Parkinsonism) include cogwheeling, asymmetric rigidity, bradykinesia, resting tremor, and hypomimia.
**Visual includes diplopia.

Table 3
Diagnostic Test Results in Sporadic Fatal Insomnia Patients

Study	Patient #	CSF 14-3-3 Protein	Periodic Discharges on EEG	Insomnia on PSG	CJD-Associated MRI Changes*	Thalamic/Cortical Reduced Update on Nuclear Imaging†
Mastrianni et al[5]	1	NA	–	NA	–	+/–
Parchi et al[6]	2	–	–	NA	–	NA
	3	NA	–	NA	–	NA
	4	NA	–	NA	–	NA
	5	NA	–	NA	–	NA
	6	–	–	NA	–	NA
Hamaguchi et al[7]	7	NA	–	NA	NA	+/+
	8	NA	–	NA	NA	+/+
	9	NA	+	NA	–	+/+
	10	+	–	NA	–	NA
	11	E	–	NA	–	+/+
Scaravilli et al[9]	12	–	–	+	–	NA
Piao et al[10]	13	NA	–	NA	NA	NA
Hirose et al[11]	14	–	–	NA	–	+/+
Capellari et al[12]	15	NA	NA	+	NA	NA
Mehta et al[13]	16	–	–	NA	–	NA
Total (+ of total tested)		1/7	1/15	2/2	0/12	6/6; 5/6
Percentage (%)		14.2	6.7	100	0	100; 83.3

*Such as basal ganglia hyperintensity, ribbon, and pulvinar signs.
†All studies were single photon emission computed tomography except for positron emission tomography performed in patient 1.
CJD, Creutzfeldt-Jakob disease; CSF, cerebrospinal fluid; EEG, electroencephalogram; E, equivocal; MRI, magnetic resonance imaging; NA, not available; –, negative; +, positive; PSG, polysomnography.

Figure 1. *This [^{18}F]fluorodeoxyglucose positron-emission tomogram of a patient with sporadic fatal insomnia* **(A)** *is paired with that of an age-matched control subject* **(B)**. *Metabolic activity within the thalamus of the patient with sporadic fatal insomnia is almost completely absent (yellow and blue signals), as compared with the normal intense activity (red signal) in the control subject (arrows). Reprinted with permission from Mastrianni JA et al.*[5]



Like insomnia, dysautonomia represents a key feature of SFI. In this review, 10 of 16 patients had evidence of an autonomic disturbance, including excessive lacrimation, impotence, incontinence, and hyperhidrosis. A relative elevation of blood pressure and heart rate on continuous monitoring and a reduction in the circadian variation of these cardiovascular properties have been previously described in FFI.[28,29] Unfortunately, no SFI patient included here was reported to have undergone a formal autonomic evaluation. Given the paucity of reliable diagnostic testing for this condition, autonomic studies could be especially significant, potentially

revealing patterns characteristic of SFI and even "subclinical" evidence of dysautonomia not otherwise reported in the history or observed on routine examination.

Based on this review, MM2-thalamic CJD represents a neurodegenerative illness that can be diagnosed ante mortem by the following clinical features: presence of cognitive impairment *and* a motor disturbance (including myoclonus, dysarthria, dysphagia, pyramidal and extrapyramidal findings, ataxia, and gait disorder), prolonged disease course (> 12 months), an isolated scintigraphic pattern of reduced tracer uptake in the thalamus with or without associated cortical involvement, and genotyping that excludes a known *PRNP* mutation (including substitution of asparagine for aspartic acid at codon 178) and confirms MM at *PRNP* codon 129. Insomnia and dysautonomia are reported findings in most, though not all, patients; given the potential subtleties of these features, PSG and formal autonomic testing should be strongly considered for confirmation in each patient in whom MM2-thalamic CJD is suspected. This point is reinforced by the paucity of diagnostic MRI, EEG, and CSF findings commonly associated with other forms of sCJD. ■

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Main Points

- MM2-thalamic Creutzfeldt-Jakob disease (CJD) is a relatively rare form of sporadic CJD, and is known as *sporadic fatal insomnia* (SFI) for its clinical and pathologic similarities to the genetic prion disease, fatal familial insomnia (FFI).
- The mean age of onset of SFI cases is 51 years, similar to that previously reported for FFI. The average duration of illness is 26.7 months (range: 13-73 months), similar to those patients who experienced a longer duration of illness in the original FFI pedigrees.
- In this case series, cognitive deficits and at least 1 motor disturbance were reported for each patient. Insomnia and dysautonomia, cardinal features of FFI, were each observed in more than 60% of the SFI patients, and in more than 80% of cases when combined.
- Scintigraphic changes in the thalamus, with or without associated cortical findings (and without involvement of other regions of the brain), were seen in all 6 SFI patients who underwent nuclear imaging. Two patients with reported insomnia underwent polysomnography; both showed disturbances in sleep architecture consistent with the fatal insomnia phenotype.
- The following features may help to clinically diagnose MM2-thalamic CJD: presence of cognitive impairment *and* a motor disturbance, disease course greater than 12 months, an isolated scintigraphic pattern of reduced tracer uptake in the thalamus with or without associated cortical involvement, and genotyping that excludes a known prion protein gene (*PRNP*) mutation and confirms methionine homozygosity at *PRNP* codon 129.

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