ORIGINAL CONTRIBUTION

Characteristics of Established and Proposed Sporadic Creutzfeldt-Jakob Disease Variants

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Background: The classic Creutzfeldt-Jakob disease (CJD), Heidenhain, and Oppenheimer-Brownell variants are sporadic CJD (sCJD) phenotypes frequently described in the literature, but many cases present with neuropsychiatric symptoms, suggesting that there may be additional sCJD phenotypes.

Objective: To characterize clinical, diagnostic, and molecular features of 5 sCJD variants.

Design: Retrospective analysis.

Setting: The Johns Hopkins and Veterans Administration health care systems.

Participants: Eighty-eight patients with definite or probable sCJD.

Main Outcome Measures: Differences in age at onset, illness progression, diagnostic test results, and molecular subtype.

Results: The age at onset differed among sCJD variants ($P=.03$); the affective variant had the youngest mean age at onset (59.7 years). Survival time ($P<.001$) and the time to clinical presentation ($P=.003$) differed among groups. Patients with the classic CJD phenotype had the shortest median survival time from symptom onset (66 days) and those who met criteria for the affective sCJD variant had the longest (421 days) and presented to clinicians significantly later (median time from onset to presentation, 92 days; $P=.004$). Cerebrospinal fluid analyses were positive for 14-3-3 protein in all of the affective variants, regardless of illness duration. Periodic sharp-wave complexes were not detected on any of the electroencephalography tracings in the Oppenheimer-Brownell group; basal ganglia hyperintensity was not detected on brain magnetic resonance imaging in this group either. All of the Heidenhain variants were of the methionine/methionine type 1 molecular subtype.

Conclusions: The classic CJD phenotype and the Heidenhain, Oppenheimer-Brownell, cognitive, and affective sCJD variants differ by age at disease onset, survival time, and diagnostic test results. Characteristics of these 5 phenotypes are provided to facilitate further clinicopathologic investigation that may lead to more reliable and timely diagnoses of sCJD.

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Creutzfeldt-Jakob disease (CJD) is the most prevalent human prion disease, with an estimated worldwide incidence of 1 case per million people per year.[1] Eighty-five percent of human prion diseases are sporadic CJD (sCJD). There is a considerable amount of variability in the presenting symptoms of sCJD, but several studies support the existence of distinct clinical phenotypes that differ from the classic CJD presentation. The often described sCJD variants include the Heidenhain variant, which presents with visual disturbances, and the Oppenheimer-Brownell variant, which solely presents with ataxia.[2-4] In a prior meta-analytic review,[5] we confirmed an earlier observation made by Wall and colleagues,[6] that neuropsychiatric symptoms are among the most common symptoms of sCJD, particularly in its early stages, which suggests the possible existence of neuropsychiatric sCJD variants. A top-down approach that examines molecular, pathologic, and diagnostic correlates among cases that share similar clinical phenotypes may identify important molecular subtypes and could enhance diagnostic accuracy by providing information that may lead to the identification of different pathogenic mechanisms or disease-modifying factors of prion diseases.

METHODS

All cases that received a clinical or neuropathologic diagnosis of sCJD between 1995 and 2007 were obtained from the Johns Hopkins and US Veterans Administration health care systems using billing and pathology records after in-

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Table 1. Demographic Characteristics of sCJD Variants

Characteristic	No. (%)						
	sCJD Variant						
	Cognitive (n=28)	Heidenhain (n=15)	Affective (n=13)	Classic CJD (n=11)	Oppenheimer-Brownell (n=8)	Indeterminate (n=13)	Total (N=88)
Center							
Johns Hopkins	18 (64.3)	9 (60)	6 (46.2)	7 (63.6)	3 (37.5)	7 (53.8)	50 (56.8)
Veterans Administration	10 (35.7)	6 (40)	7 (53.8)	4 (36.4)	5 (62.5)	6 (46.2)	38 (43.2)
Sex							
M	19 (67.9)	10 (66.7)	8 (61.5)	6 (54.5)	7 (87.5)	12 (92.3)[a]	62 (70.5)
F	9 (32.1)	5 (33.3)	5 (38.5)	5 (45.5)	1 (12.5)	1 (7.7)	26 (29.5)
Race							
White	18 (64.3)	13 (86.6)	8 (61.5)	9 (81.8)	5 (62.5)	8 (61.5)	61 (69.3)
Black	2 (7.1)	1 (6.7)	0	0	0	0	3 (3.4)
Hispanic	2 (7.1)	0	2 (15.4)	0	1 (12.5)	1 (6.7)	6 (6.8)
Other	1 (3.6)	0	0	0	0	1 (6.7)	2 (2.3)
Unknown	5 (17.9)	1 (6.7)	3 (23.1)	2 (18.2)	2 (25)	3 (23.1)	16 (18.2)
Diagnostic criteria							
Definite CJD[b,7]	15 (53.6)	11 (73.3)	9 (69.2)	5 (45.5)	4 (50)	8 (61.5)	52 (59.1)
Probable CJD, WHO criteria[7]	11 (39.3)	4 (26.7)	3 (23.1)	6 (54.5)	3 (37.5)	3 (23.1)	30 (34.1)
Probable CJD, UCSF criteria[8]	2 (7.1)	0	1 (7.7)	0	1 (12.5)	2 (15.4)	6 (6.8)

Abbreviations: CJD, Creutzfeldt-Jakob disease; sCJD, sporadic Creutzfeldt-Jakob disease; UCSF, University of California–San Francisco; WHO, World Health Organization.

[a] $P \leq .05$.

[b] Neuropathologic examination.

stitutional review board approval at each site. Cases were classified as definite sCJD according to World Health Organization (WHO) criteria[7] if neuropathologic examination revealed spongiform changes and/or the presence of pathologic prion proteins (PrP^{Sc}) via immunocytochemistry or Western blot analysis. Two criteria were used to determine a clinical diagnosis of sCJD in cases that did not have neuropathologic material available for analysis. Cases were diagnosed as probable sCJD using the 1998 WHO criteria[7] if there was evidence of progressive dementia and at least 2 of the following symptoms: myoclonus, visual or cerebellar disturbance, pyramidal or extrapyramidal dysfunction, and akinetic mutism. Probable sCJD cases (by WHO criteria) also had either triphasic periodic complexes on electroencephalography (EEG) or a cerebrospinal fluid (CSF) assay positive for 14-3-3 protein with a survival time shorter than 2 years. Cases that met the mentioned symptom criteria for probable sCJD but that did not demonstrate a positive 14-3-3 protein analysis or triphasic period complexes on EEG or did not undergo these studies were classified as probable sCJD according to the University of California–San Francisco criteria[8] if they had subcortical hyperdensity or cortical ribboning on diffusion-weighted imaging.

Medical records were reviewed by a neuropsychiatrist (B.S.A.) and a neurologist (K.K.A.), and data were abstracted for demographic characteristics and illness chronology. Results of CSF 14-3-3 protein assay, EEG, and brain magnetic resonance imaging studies were collected as well. Data were abstracted from medical records using the same abstraction instrument for all cases. The PrP^{Sc} type and *PRNP* genotype data that were not included in medical records were obtained through collaboration with the National Prion Disease Pathology Surveillance Center.

Based on prior research that examined symptom chronology through factor analyses,[5,9,10] case histories were reviewed and classified into 5 predetermined sCJD variants and an indeterminate group following the consensus of the reviewing physician and an additional physician who was masked to clinical data (B.S.A. and K.K.A.). Initial symptoms were ascertained by including all symptoms that were documented to have occurred within the first week of illness. Cases that did not have this information were excluded from analysis. Cases were classified as the Heidenhain variant if visual disturbances such as cortical blindness, oculomotor impairment, and/or visual hallucinations were documented within the first week of illness. The Oppenheimer-Brownell variant included cases that had ataxia within the first week of illness in the absence of cognitive and visual impairments. Cases presenting with dementia, memory impairment, executive dysfunction, language impairment, and/or confusion in the absence of visual, cerebellar, and mood symptoms within the first week of illness were classified as the cognitive variant. Patients with cognitive symptoms and ataxia, without visual impairments and affective symptoms during the first week of illness, were classified as having classic CJD. Patients who were reported to have symptoms of depression, mood lability, mania, hypomania, and/or anxiety within the first week of illness were classified as having the affective variant if they did not meet inclusion criteria for the Heidenhain group. Cases that could not be classified into 1 of the aforementioned groups were designated indeterminate.

We used SPSS, version 15.0 (SPSS Inc, Chicago, Illinois), to perform the statistical analyses. Survival data were calculated using Kaplan-Meier analyses, and Cox proportional hazard regression models were used to adjust for age, illness duration, sex, medical center, and diagnostic criteria. Analysis of variance was used for continuous variables, and χ^2 analysis was used for categorical variables.

RESULTS

Eighty-eight cases of definite or probable sCJD were included in the study (**Table 1**). Seventy-five cases (85%) met criteria for 1 of the predefined sCJD variants and 13 cases (15%) were classified as indeterminate. The phenotype with the largest percentage of cases was the cog-

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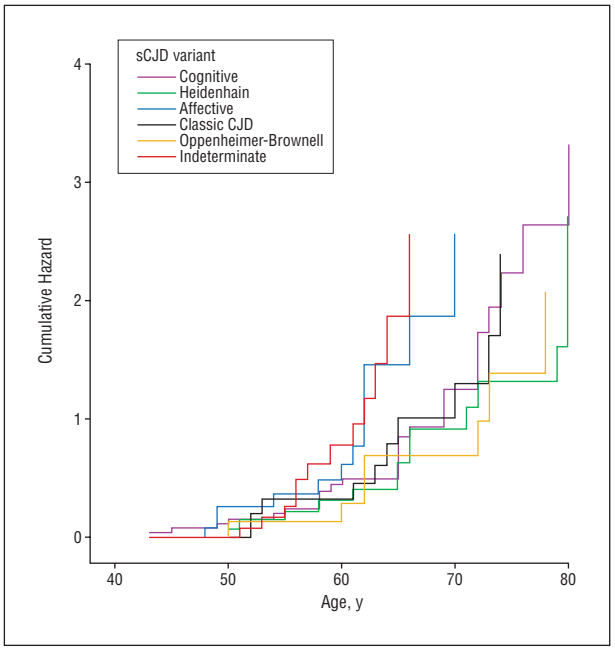

Figure 1. Age at disease onset (log-rank test, χ^2=12.7, *P*=.03). CJD indicates Creutzfeldt-Jakob disease; sCJD, sporadic Creutzfeldt-Jakob disease.

nitive variant (n=28 [32%]); 15 cases (17%) were classified as the Heidenhain variant; 13 cases (15%) were categorized as the affective variant; and 11 were classic CJD (13%). The Oppenheimer-Brownell phenotype group had the fewest number of cases (n=8 [9%]). There were significantly more men in the indeterminate group (n=12 [92.3%]; Exp[B]=0.104; 95% confidence interval, 0.011-0.97; *P*=.047), as demonstrated by a logistic regression model that included the evaluation center (*P*=.39), age at onset (*P*=.07), and diagnostic criteria (*P*=.26). Most were neuropathologically proven cases of sCJD (n=52 [59.1%]); there were no significant differences in diagnostic criteria between groups.

No significant differences in race or center were observed between groups. The mean age at the onset of illness across the entire sample was 63.5 years (**Figure 1**). Age significantly differed between groups (log-rank test, χ^2_5=12.07, *P*=.03); those with the affective variant (59.7 years) and the indeterminate group (59.6 years) had the youngest mean ages at onset compared with those in the Heidenhain (66.7 years) and Oppenheimer-Brownell (67.1 years) groups. Patients with classic CJD had a mean age of 63.9 years.

The initial symptoms of each group are presented in **Table 2**. Thirteen patients (86.7%) within the Heidenhain group presented with cortical blindness or oculomotor dysfunction and 2 patients (13.3%) presented with visual hallucinations. Memory impairment was the primary presenting symptom in those with the cognitive variant of sCJD (n=15 [53.6%]; Pearson test, χ^2_1=3.86, *P*=.049), and depression was the most common presenting symptom in affective variant cases (n=7 [53.8%]; Fisher exact test [2-sided], *P*<.001). Sleep disorders were also more prevalent in the affective variants (n=5 [38.5%]; Fisher exact test [2-sided], *P*<.001). Patients with indeterminate cases presented with symptoms of myoclonus (n=2 [15.4%]), speech impairment (n=1 [7.7%]), abnormal sensations (n=1 [7.7%]), headache (n=1 [7.7%]), vertigo (n=2 [15.4%]), apathy (n=1 [7.7%]), behavioral/personality changes (n=3 [23.1%]), and paranoid delusions (n=1 [7.7%]). The most frequently documented neuropsychological instrument that was used was the Mini-Mental State Examination (14 cases [15.9%]).[11] The Mini-Mental State Examination was more frequently administered to the cognitive (n=7 [25%]) and Oppenheimer-Brownell (n=2 [25%]) groups in contrast to the indeterminate (n=1 [7.7%]), classic CJD (n=2 [18.2%]), and affective (n=2 [15.4%]) groups. Use of the Mini-Mental State Examination was not documented in any of the Heidenhain cases.

Clinical characteristics were further characterized by variations in survival time (log-rank test, χ^2_5=25.3, *P*<.001) (**Figure 2**). Using a Cox proportional hazards regression model, we found classic CJD cases to have the shortest median survival time from symptom onset (66 days; *P*=.002), while the affective (421 days; Exp[B]=0.320, *P*=.02) and cognitive (214 days; Exp[B]=0.406, *P*=.03) groups had the longest median survival times. The Heidenhain, Oppenheimer-Brownell, and indeterminate groups had median survival times of 104 days, 147 days, and 119 days, respectively.

Patients with sCJD presented to clinicians at different illness durations (log-rank test, χ^2=18.345, *P*=.003) (**Figure 3**). Those in the affective (median, 92 days; Exp[B]=0.265, *P*=.006) and cognitive groups (median time, 67 days; Exp[B]=0.359, *P*=.01) presented to clinicians further into their illnesses, while patients with classic CJD presented to clinicians shortly after symptom onset (median time, 21 days; *P*=.007). The median time to presentation was between 3 to 4 weeks in the remaining groups (Heidenhain, Oppenheimer-Brownell, and indeterminate) (*P*>.05).

Most patients (n=57 [68.7%]) underwent a lumbar puncture for 14-3-3 protein analysis, the results of which did not significantly vary between groups (*P*>.05). However, there was a difference in the interval between illness onset and 14-3-3 protein analysis (log-rank test, χ^2_5=14.841, *P*=.01) (**Figure 4**). The median time to 14-3-3 protein analysis was shortest in the classic CJD group (47 days; *P*=.02) and longest in the affective (222 days; Exp[B]=0.120, *P*=.004) and cognitive (95 days; Exp[B]=0.343, *P*=.03) groups regardless of center, age, sex, and diagnostic criteria (*P*>.05). All of the known CSF 14-3-3 protein analysis results were positive in the affective group (n=5) group. No statistically significant differences were found between the 14-3-3 results of each group when controlling for time via logistic regression analysis (*P*>.05).

Electroencephalography was performed in most cases (n=79 [91.9%]), but was not sensitive in detecting prion disease, as only 23 cases (30.7%) had periodic sharp-wave complexes on the initial EEG. The time from disease onset to EEG varied between groups (log-rank test, χ^2_5=26.523, *P*<.001) (**Figure 5**) but was not found to affect the presence of periodic sharp-wave complexes when a multinomial logistic regression model was used (*P*>.05). Although the presence of periodic sharp-wave complexes was not statistically different between

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Table 2. Symptoms of sCJD Reported Within the First Week of Illness

	No. (%)						
	sCJD Variant						
Initial Symptom	Cognitive (n=28)	Heidenhain (n=15)	Affective (n=13)	Classic CJD (n=11)	Oppenheimer-Brownell (n=8)	Indeterminate[a] (n=13)	Total (N=88)
Memory impairment	15 (53.6)[b]	6 (40)	6 (46.2)	7 (63.6)	0[b]	0[c]	34 (38.6)
Ataxia	0[d]	8 (53.3)	4 (30.8)	11 (100)[d]	8 (100)[c]	0[c]	31 (35.2)
Unspecified cognitive decline	13 (46.4)[c]	1 (6.7)	5 (38.5)	5 (45.5)	0	0[b]	24 (27.3)
Disorientation	9 (32.1)	4 (26.7)	4 (30.8)	7 (63.6)[c]	0	0[b]	24 (27.3)
Visual/oculomotor	0	13 (86.7)	0	0	0	0	13 (14.8)
Depression	0	2 (13.3)	7 (53.8)[d]	0	0	0	9 (10.2)
Sleep disorder	1 (3.6)	0	5 (38.5)[d]	0	0	0	6 (6.8)
Executive dysfunction	4 (14.3)	0	2 (15.4)	0	0	0	6 (6.8)
Anxiety	0	0	5 (38.5)[d]	0	0	0	5 (5.7)
Language impairment	3 (10.7)	1 (6.7)	1 (7.7)	0	0	0	5 (5.7)
Mood lability	0	0	2 (15.4)	0	0	0	2 (2.3)
Visual hallucinations	0	2 (13.3)	0	0	0	0	2 (2.3)

Abbreviations: CJD, Creutzfeldt-Jakob disease; sCJD, sporadic Creutzfeldt-Jakob disease.
[a] Indeterminate cases presented with myoclonus (n=2 [15.4%]), speech impairments (n=1 [7.7%]), abnormal sensations (n=1 [7.7%]), headache (n=1 [7.7%]), vertigo (n=2 [15.4%]), apathy (n=1 [7.7%]), behavioral/personality changes (n=3 [23.1%]), agitation, (n=2 [15.4%]), and paranoid delusions (n=1 [7.7%]).
[b] $P<.05$.
[c] $P<.01$.
[d] $P<.001$.

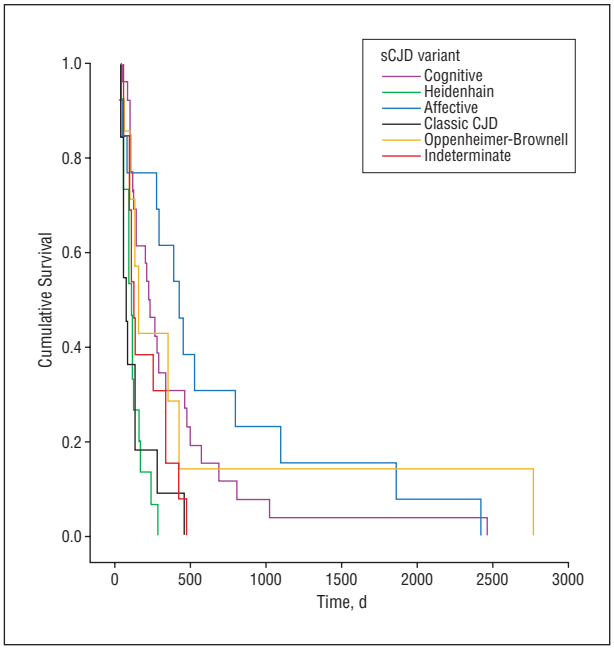

Figure 2. Survival analysis of sporadic Creutzfeldt-Jakob disease (sCJD) variants (log-rank test, χ^2_5=25.3, $P<.001$). CJD indicates Creutzfeldt-Jakob disease.

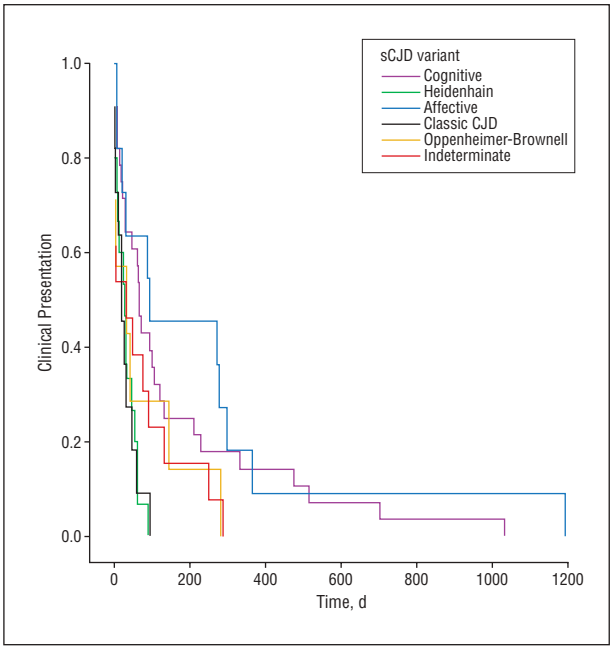

Figure 3. Time from symptom onset to clinical presentation of sporadic Creutzfeldt-Jakob disease (sCJD) variants (log-rank test, χ^2_5=18.35, P=.003). CJD indicates Creutzfeldt-Jakob disease.

groups, none of the Oppenheimer-Brownell variants had periodic sharp-wave complexes on EEG tracings (n=5 [0%]).

The sCJD variants also varied in the interval between disease onset and brain magnetic resonance imaging (log-rank test, χ^2_5=29.122, $P<.001$) (**Figure 6**). Patients with affective (median time, 232 [SE, 129.4] days) and cognitive (median, 122 [SE, 41.9] days) variants underwent brain magnetic resonance imaging much later than the overall sample (median, 83 [SE, 10.4] days). The most notable difference was the lack of basal ganglia hyperintensity in all of the Oppenheimer-Brownell variants (Fisher exact test [2-sided], P=.05).

Of the total sample, 36 patients (41.4%) underwent autopsy: 22 from the Veterans Administration (61%) and 14 from Johns Hopkins (39%) (**Table 3**). Nineteen cases (21.8%) had brain biopsies: 17 from Johns Hopkins (90%) and 2 from the Veterans Administration (10%). Results of Western blot analysis of PrP^{Sc} proteins were positive in all cases that underwent autopsy (n=26) and biopsy

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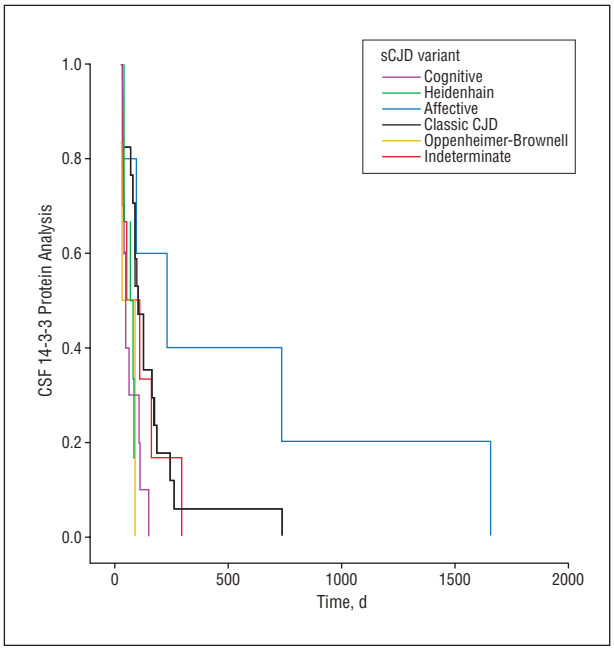

Figure 4. Time from illness onset to cerebrospinal fluid (CSF) 14-3-3 protein analysis. CJD indicates Creutzfeldt-Jakob disease; sCJD, sporadic Creutzfeldt-Jakob disease.

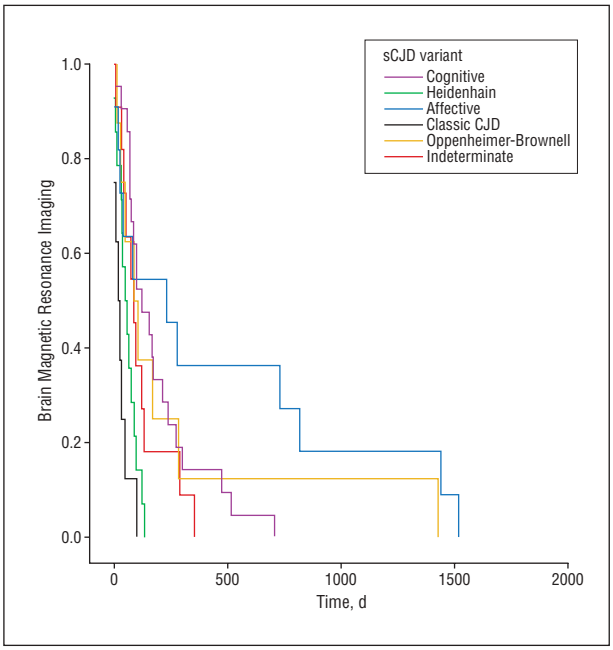

Figure 6. Time from disease onset to brain magnetic resonance imaging (log-rank test, χ^2_5=29.1, P<.001). CJD indicates Creutzfeldt-Jakob disease; sCJD, sporadic Creutzfeldt-Jakob disease.

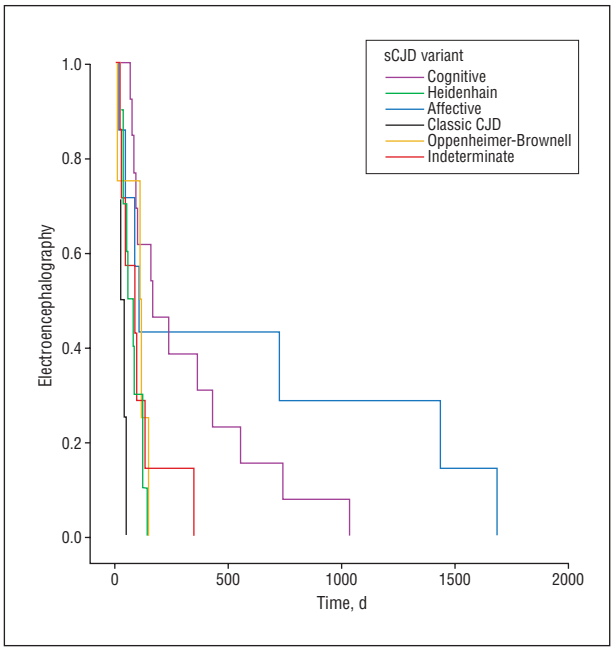

Figure 5. Time from disease onset to electroencephalography (log-rank test, χ^2_5=26.5, P<.001). CJD indicates Creutzfeldt-Jakob disease; sCJD, sporadic Creutzfeldt-Jakob disease.

(n=10); the remaining cases had spongiform changes but were not tested for PrP^{Sc} for unknown reasons. Genotyping of *PRNP* was performed in 32 cases (36.4%), and none had known pathologic *PRNP* mutations. There was no evidence of familial prion disease or iatrogenic exposure that would indicate a nonsporadic etiology in any of the cases. Of the 33 cases that underwent PrP^{Sc} analysis, 19 cases (63.3%) had type 1 protein, 7 cases (23.3%) had type 2, 2 cases (6.7%) had type 1 and type 2 proteins, 2 cases (6.7%) had protease-sensitive PrP (PSPr),[12] and 1 previously reported case[14] had PrP^{Sc} 7-8 without a *PRNP* mutation or a family history of dementia. *PRNP* codon 129 polymorphisms were identified in 32 cases (36%): 16 were homozygous for methionine (Met) (50%), 10 were Met/valine (Met/Val) heterozygous (31.3%), and 6 were Val/Val homozygous (n=6). All 4 Heidenhain variant cases with known molecular data were homozygous for Met, and all 3 cases with known PrP^{Sc} type were of the Met/Met type 1 molecular subtype. Given these findings, we propose characteristics for 5 sCJD phenotypes (**Table 4**) to aid in interpreting test results and diagnosing cases.

COMMENT

The findings of this study provide support for the existence of 5 sCJD variants that differ by clinical presentation, disease course, and diagnostic test results. We have confirmed the existence of 3 previously reported clinical subtypes (classic CJD, Heidenhain, and Oppenheimer-Brownell variants) and offer support for the existence of 2 neuropsychiatric variants that are characterized by cognitive impairment and disturbances in mood.

Although sCJD is known to have a range of clinical symptoms, our findings indicate that clinical clusters of cases may be delineated by differences in initial symptoms. It is also significant that the sCJD variants differ with respect to age at symptom onset and survival time, indicating a difference in disease pathology and/or expression. Differences in survival time not only imply differences in the natural history of the illness but also suggest the possibility of differences in the underlying pathologic process of the illness. Clinical sCJD variants may be a reflection of PrP^{Sc} type and *PRNP* codon 129

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Table 3. Neuropathologic and Molecular Characteristics of sCJD Variants

	No. (%)						
	sCJD Variant						
Characteristic	Cognitive (n=28)	Heidenhain (n=15)	Affective (n=13)	Classic CJD (n=11)	Oppenheimer-Brownell (n=8)	Indeterminate (n=13)	Total (N=88)
Autopsy	8 (28)	7 (46)	5 (38)	4 (36)	5 (62)	7 (53)	36 (41)
Cortical spongiosis	4/4 (100)	4/4 (100)	2/2 (100)	2/2 (100)	3/4 (75)	2/2 (100)	17/18 (94)
Striatal spongiosis	4/4 (100)	2/2 (100)		2/2 (100)	3/3 (100)	2/2 (100)	13/13 (100)
Thalamic spongiosis				3/3 (100)	1/1 (100)	1/1 (100)	5/5 (100)
Cerebellar spongiosis	2/4 (50) (100)	2/2 (100)	1/1 (100)	1/2 (50)	3/3 (100)	1/1 (100)	10/13 (77)
Western blot analysis for PrP^{Sc}	7/7 (100)	2/2 (100)	4/4 (100)	4/4 (100)	3/3 (100)	6/6 (100)	26/26 (100)
Mean brain weight, g	1255	1191.7	1190	1452.5	1180	1235	1247.8
Brain biopsy	7 (25)	5 (33)	4 (30)	1 (9.1)	0	2 (15)	19 (21)
Spongiosis	5/7 (71)	5/5 (100)	3/4 (75)	1/1 (100)		0/2	14/19 (74)
Western blot analysis for PrP^{Sc}	4/4 (100)	2/2 (100)	1/1 (100)	1/1 (100)		2/2 (100)	10/10 (100)
PrP^{Sc}[12]							
Type 1	4 (57)	3 (100)	3 (50)	4 (100)	1 (33)	4 (57)	19 (63)
Type 2	1 (14)	0	3 (50)	0	0	3 (43)	7 (23)
Type 1 and 2	1 (14)	0	0	0	1 (33)	0	2 (7)
PSPr	1 (14)	0	0	0	1 (33)	0	2 (7)
PRNP codon 129 polymorphism							
Met/Met	3 (37.5)	4 (100)	2 (33)	2 (50)	1 (33)	4 (57)	16 (50)
Met/Val	2 (25)	0	3 (50)	2 (50)	2 (67)	1 (14)	10 (31)
Val/Val	3 (37.5)	0	1 (17)	0	0	2 (29)	6 (19)
Molecular subtype[13]							
Met/Met type 1	2 (29)	3 (100)	1 (17)	2 (50)	1 (50)	3 (43)	12 (40)
Met/Met type 2			1 (17)			1 (14)	2 (7)
Met/Val type 1	1 (14)		1 (17)	2 (50)		1 (14)	5 (17)
Met/Val type 2			2 (33)				2 (7)
Met/Val type 1 and 2					1 (50)		1 (3)
Val/Val type 1	1 (14)		1 (17)				2 (7)
Val/Val type 2	1 (14)					2 (29)	3 (10)
Val/Val type 1 and 2	1 (14)						1 (3)
Met/Val PSPr	1 (14)				1 (33)		2 (7)

Abbreviations: CJD, Creutzfeldt-Jakob disease; Met, methionine; PrP^{Sc}, pathologic prion protein; *PRNP*, prion protein gene; PSPr, protease-sensitive prionopathy; sCJD, sporadic Creutzfeldt-Jakob disease; Val, valine.

genotype as previously reported.[13,15,16] Individuals who display features of an sCJD variant may also have unique genetic or other disease-altering variables (eg, age) that modulate illness characteristics. Our data may help to provide a basis for developing clinicopathologic associations to facilitate the clinical identification of sCJD variants, which would aid in clinical detection and diagnosis.

The formalization of sCJD phenotypes is valuable for a number of reasons. The heterogeneity of clinical presentations observed in sCJD frequently results in the delayed diagnosis or misdiagnosis of prion diseases.[9,17-19] Thus, it is reasonable to conclude that the delineation of various sCJD subtypes can be used to educate clinicians about the variability of clinical symptoms that are commonly observed in sCJD in addition to the disease's propensity to be misdiagnosed. An example of this would be considering prion disease in the differential diagnosis of a patient with suspected posterior cortical atrophy (ie, owing to knowledge of the Heidenhain variant). Furthermore, patients with neuropsychiatric variants presented to clinicians later in the course of their illness, which is pertinent, as disease duration has been found to affect EEG findings.[20] Likewise, prior reports have suggested that 14-3-3 protein is most likely detected in CSF shortly after the onset of symptoms.[21] However, our results suggest that clinical subtypes themselves may also be associated with diagnostic test results, as demonstrated by assays positive for the 14-3-3 protein in all of the affective phenotypes despite CSF samples being obtained significantly later in the illness. The lack of classic periodic sharp-wave complexes and hyperintensity in the basal ganglia on brain magnetic resonance imaging in the Oppenheimer-Brownell variant may also reflect an independent phenotype-related feature. Knowledge of this diagnostic test pattern can influence the physician's clinical judgment and hence contribute to the continued consideration of prion disease despite negative findings of these tests in a patient who presents with pure ataxia of unknown etiology. As a result, the predictive value and utility of diagnostic tests may vary by clinical phenotype as well as by illness duration. Additional studies are needed to clarify the proper interpretation of these diagnostic test results in relation to sCJD variants and the stage of illness.

The association between molecular subtypes and phenotypes confirms prior findings by Parchi and colleagues.[13] Classic CJD and the Heidenhain variant were associated with the Met/Met type 1 and Met/Val type 1

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Table 4. Characteristics of 5 sCJD Variants

sCJD Phenotype	Characteristics
Classic CJD	Onset of cognitive symptoms (cognitive decline, amnesia, language impairment, executive dysfunction, and/or disorientation) and ataxia at illness onset, without visual disturbances Clinical presentation within 1 mo of illness onset Short interval between symptom onset and diagnostic testing (CSF 14-3-3 protein, EEG, and brain MRI) Survival time ≤3 mo Predominance of PrP^{Sc} type 1
Heidenhain	Onset of diplopia, blurred vision, cortical blindness, and/or visual hallucinations at illness onset Survival time ≤4 mo Predominance of the Met/Met type 1 molecular subtype
Oppenheimer-Brownell	Ataxia in the absence of other presenting symptoms at illness onset Older age at illness onset (median, 67 y) Lack of PSWCs on EEG and basal ganglia hyperintensity on brain MRI
Cognitive	Onset of dementia, memory impairment, language impairment, executive dysfunction, and/or disorientation at illness onset in the absence of ataxia and visual disturbances Clinical presentation 2 mo after symptom onset Prolonged interval between illness onset and diagnostic testing Survival time >4 mo
Affective	Depression, mood lability, and/or anxiety at illness onset Age at onset ≤65 y Prolonged time to clinical presentation Prolonged time to diagnostic testing High rate of positive CSF analyses for 14-3-3 protein despite duration of illness Survival time >6 mo

Abbreviations: CJD, Creutzfeldt-Jakob disease; CSF, cerebrospinal fluid; EEG, electroencephalography; Met, methionine; MRI, magnetic resonance imaging; PrP^{Sc}, pathologic prion protein; PSWC, periodic sharp-wave complex; sCJD, sporadic Creutzfeldt-Jakob disease.

subtypes described in their article. In our study, the longest survival time was observed in the affective group, of whom 2 cases had the only Met/Val type 2 molecular subtypes; this subtype is associated with a prolonged survival time (>2 years). On the other hand, patients with the Oppenheimer-Brownell phenotype initially presented with ataxia and did not have periodic sharp-wave complexes on EEG tracings. In our sample, the Oppenheimer-Brownell phenotype was not associated with the Val/Val type 2 molecular subtype, as described by Parchi and colleagues.[22]

There are several limitations to this study. Because retrospective analysis only captures the reported findings of a case, it is possible that symptoms were overlooked or inaccurately recorded. It is difficult to ascertain what the impact or direction of such information biases may be, but it is reasonable to conclude that predominant symptoms are unlikely overlooked. Thus, we argue that information bias unlikely results in the delineation of sCJD variants that do not exist but may result in uncommon phenotypes being overlooked or unclassified. It may be argued that initial neuropsychiatric symptoms of sCJD are prodromal; however, differences in age at onset, survival times, diagnostic test results, and possibly molecular subtypes among these 5 sCJD phenotypes make this possibility unlikely. Not all patients with definite sCJD underwent *PRNP* genotyping, which raises the possibility that some cases may have been of genetic etiology, which would influence the age at onset, survival time, clinical presentation, and diagnostic test results. We also note that the size of the sample is limited, especially given its stratification across 5 sCJD phenotypes and an indeterminate group. It is also possible that additional phenotypes exist and that indeterminate cases within this analysis represent other phenotypes.

The sample in this study is difficult to classify according to Parchi and colleagues' system.[13] The inclusion of a newly reported prionopathy[12] with a novel codon 129 polymorphism and recent findings by Notari and colleagues[23] make our molecular data particularly difficult to categorize and interpret. Although PrP^{Sc} types 1 and 2 differ in size and glycosylation,[22] both are protease-resistant. In contrast, PSPr is characterized by a predominance of protease-sensitive prion proteins.[12] All of the 11 cases reported to date have been homozygous for Val at codon 129 of the *PRNP* gene,[12] but we now report 2 PSPr cases that were heterozygous (Met/Val) at codon 129, implying that Val/Val homozygosity is not required for protease-sensitive prion disease. The report of PSPr heterozygotes in this study is significant, as these 2 cases had longer survival times (7.7 years and 2.8 years) than the Val/Val homozygous PSPr cases described by Gambetti and colleagues (mean, 1.7 years).[12] This is consistent with the study by Pocchiari and colleagues,[24] which demonstrated longer survival times in heterozygous cases (Met/Val) compared with homozygous cases (Met/Met and Val/Val) in typical sCJD. This strengthens the position that prion protein isoforms (eg, types 1, 2, and PSPr) and codon 129 polymorphisms (ie, Met/Met, Val/Val, and Met/Val) demonstrate clinical variability that may be used for clinicopathologic association studies. As such, findings from this study and Gambetti and colleagues' article[12] suggest that ascertainment rates of PSPr cases may be low owing to their atypical presentation in terms of survival time and nonclassic CJD phenotype. The 2 heterozygous PSPr cases in our article were classified as cognitive and Oppenheimer-Brownell variants, whereas Gambetti and colleagues' cohort contained 6 cases that presented with mood and/or sleep disturbances and 4 cases that presented with cognitive decline in the absence of mood, sleep, and motor disturbances. Further investigation is necessary to characterize PSPr disease and to develop further clinicopathologic associations. Our findings suggest that neuropsychiatric symptoms should not be overlooked in these investigations, as they are prominent in prion diseases and also require phenomenological distinction (eg, cognitive symptoms, mood symptoms, psychosis) owing to clinical, neuropathologic, and molecular differences.

In conclusion, results from this study suggest that there are 2 neuropsychiatric sCJD variants that present with cognitive impairment and disturbances in mood and affect. These proposed variants, in addition to the 3 previously established sCJD phenotypes, vary in important illness characteristics and diagnostic investigations, indicating

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that the detection of distinct clinical syndromes may be profitably used for the clinical evaluation and possibly clinicopathologic correlation studies of prion diseases. Findings from this study provide support for a top-down approach in the investigation of genotype-phenotype relationships, especially given the complexity of molecular and neuropathologic factors inherent within the spectrum of prion diseases. Based on the findings of this and prior studies, we propose preliminary characteristics for the classification of the 5 sCJD phenotypes listed in Table 4, with the intent to facilitate additional studies focused on early diagnosis, treatment, and clinicopathologic correlations. Additional studies are needed to replicate these findings and to identify whether there are other characteristics of these proposed subtypes or additional sCJD variants.

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