Specific clinical signs and symptoms are predictive of clinical course in sporadic Creutzfeldt−Jakob disease

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Background and purpose: Akinetic mutism is thought to be an appropriate therapeutic end-point in patients with sporadic Creutzfeldt−Jakob disease (sCJD). However, prognostic factors for akinetic mutism are unclear and clinical signs or symptoms that precede this condition have not been defined. The goal of this study was to identify prognostic factors for akinetic mutism and to clarify the order of clinical sign and symptom development prior to its onset.

Methods: The cumulative incidence of akinetic mutism and other clinical signs and symptoms was estimated based on Japanese CJD surveillance data (455 cases) collected from 2003 to 2008. A proportional hazards model was used to identify prognostic factors for the time to onset of akinetic mutism and other clinical signs and symptoms.

Results: Periodic synchronous discharges on electroencephalography were present in the majority of cases (93.5%). The presence of psychiatric symptoms or cerebellar disturbance at sCJD diagnosis was associated with the development of akinetic mutism [hazard ratio (HR) 1.50, 95% confidence interval (CI) 1.14–1.99, and HR 2.15, 95% CI1.61–2.87, respectively]. The clinical course from cerebellar disturbance to myoclonus or akinetic mutism was classified into three types: (i) direct path, (ii) path via pyramidal or extrapyramidal dysfunction and (iii) path via psychiatric symptoms or visual disturbance.

Conclusions: The presence of psychiatric symptoms or cerebellar disturbance increased the risk of akinetic mutism of sCJD cases with probable MM/MV subtypes. Also, there appear to be sequential associations in the development of certain clinical signs and symptoms of this disease.

Introduction

Creutzfeldt−Jakob disease (CJD) is a lethal disorder that is caused by abnormal prion protein (PrP). CJD has a long incubation period but rapidly progresses to serious disability and death. It is categorized into four subtypes: sporadic, genetic/familial, iatrogenic and variant CJD. Sporadic CJD (sCJD) is the most common form of CJD, accounting for 85%–95% of all cases, and has unknown epidemiological factors [1–3]. The median disease duration is approximately 5 months [4]. Because both the genotype at codon 129 of the PrP gene (MM, MV or VV) and PrP type [2,3] act as determinants of the disease phenotype, patients with sCJD can be classified into six groups: MM1, MM2, MV1, MV2, VV1 and VV2 [5,6].

A longer survival of sCJD patients has been associated with female gender, younger age of onset, codon 129 heterozygosity, PrP type 2a, the presence of pseudo-periodic sharp-wave complexes on

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electroencephalography (EEG) and the presence of 14-3-3 proteins in the cerebrospinal fluid (CSF) [4,7,8]. Several other studies have examined the likelihood of longer survival from the perspectives of symptoms alone [9] or of relationships between molecular subtype and phenotype [10]. However, factors that may predict the time from diagnosis to onset of akinetic mutism or other clinical signs and symptoms are unknown.

Several studies have suggested that akinetic mutism is a more suitable end-point than death for evaluating the efficacy of new therapeutic agents [11–14]. Accordingly, the current study aimed to identify prognostic factors for akinetic mutism and to clarify the order of appearance of clinical signs and symptoms prior to its onset.

Methods

Data

This study analyzed data from the annual reports of clinical research submitted to the Specified Disease Treatment Research Program of the Japanese Ministry of Health, Labour and Welfare (MHLW) from 2003 to 2008 [15,16]. A longitudinal dataset was prepared based on cross-sectional data obtained from the annual reports.

Variables

Data were collected on baseline characteristics at diagnosis [gender, time from onset to diagnosis, age at diagnosis, and presence of hyperintense signal on magnetic resonance imaging (MRI) or wave slowing or periodic synchronous discharges (PSDs) on EEG] and dates of diagnosis and onset of clinical signs or symptoms. Clinical signs and symptoms assessed were akinetic mutism, psychiatric symptoms (depression, fretfulness, anxiety, autism, apathy, insomnia, obsession, derangement, excitement, abnormal emotion, character change, abnormal behavior or memory disorder), visual disturbance, cerebellar disturbance, pyramidal dysfunction (excluding progressive dementia or impaired consciousness), extrapyramidal dysfunction and myoclonus. The case report form of this surveillance was created by the experts of medical societies for CJD; it was approved by the expert committee of the MHLW. The case report form was submitted by physicians who diagnosed the CJD patients and was reviewed by an advisory board of neurology experts in each prefecture.

Times to onset of akinetic mutism and other signs and symptoms were measured from sCJD diagnosis.

Importantly, sCJD diagnosis rather than initial onset was used as the starting point in order to examine the temporal window for potential treatment before akinetic mutism onset.

Sporadic CJD diagnosis

The diagnosis of sCJD had already been performed by the Japanese Surveillance Committee based primarily on the 1998 World Health Organization diagnostic criteria. 'Probable' sCJD was diagnosed in patients with progressive dementia in the absence of an alternative diagnosis based on routine examination; at least two of the four clinical signs or symptoms (myoclonus, visual or cerebellar disturbance, pyramidal or extrapyramidal dysfunction, or akinetic mutism); a typical EEG with generalized triphasic periodic complexes at approximately 1/s, regardless of the duration of the disease; or a positive 14-3-3 assay of the CSF and death in under 2 years. 'Definite' sCJD cases were defined as those with a confirmed pathological diagnosis at autopsy, the presence of PrP protein based on immunocytochemistry or western blotting, or the presence of scrapie-associated fibrils.

Statistical analysis

'Definite' and 'probable' sCJD cases were included in the analysis. Only cases without akinetic mutism at diagnosis were included, because the presence of akinetic mutism precluded the onset of other clinical signs and symptoms. Categorical and continuous data are presented as number of patients (percentage) and mean ± standard deviation, respectively. The cumulative incidence of akinetic mutism was estimated using the Kaplan–Meier method. The Cox proportional hazards model was used to identify prognostic factors for the time from sCJD diagnosis to akinetic mutism onset. The cumulative incidences of other clinical signs and symptoms were calculated adjusting for akinetic mutism as a competing risk [17]. The Fine−Gray proportional hazards model [18], adjusted for akinetic mutism, was used to evaluate relationships between clinical signs and symptoms present at diagnosis and the time to development of other signs or symptoms. Candidate prognostic factors were selected based on $P < 0.05$ in a Wald test and the number of cases in univariate analyses. Prognostic factors were selected using the backward selection method at $P < 0.05$ in multivariate analyses. Hazard ratios (HRs) and 95% confidence intervals (CIs), using the Wald test, were calculated. The median time to onset of each clinical sign or symptom

was calculated. Analyses were performed using SAS version 9.3 (SAS Institute Inc., Cary, NC, USA) and R version 3.0.2 (R Foundation, Vienna, Austria) with the competing risks (cmprsk) library.

Ethics

This study conforms to the ethical guidelines for epidemiological research issued by the MHLW and the Ministry of Education, Culture, Sports, Science and Technology. The ethics committee of the National Institute of Public Health approved this study (No. 218; 10 June 2010). All patients or their proxies gave written informed consent for registration in the Specified Disease Treatment Research Program, and their information was sent to their respective prefectural governors. Following submission of informed consent forms and the approval of a review committee, each patient's information was anonymized and entered into the MHLW database. The anonymized data were provided to us for analysis (Notification of Health Service Bureau, MHLW; No. 0708-1; 8 July 2010).

Results

Demographic data

A total of 717 sCJD case reports ('definite' 52, 'probable' 665) submitted between 2003 and 2008 were included in the analysis. After excluding cases with akinetic mutism at sCJD diagnosis, the dataset comprised 455 cases (Table 1). Genetic testing for genotype at codon 129 of the PrP gene was performed in 108 cases. The majority of cases that included EEG data showed PSDs (93.5%). The number of females was approximately 1.57 times higher than the number of males. The median period from disease onset to diagnosis was 1.2 months (range 0.0–12.5), and the median age at diagnosis was 70 years (range 39–95).

Incidence of clinical signs or symptoms prior to onset of akinetic mutism

The cumulative incidences of clinical signs and symptoms are shown in Fig. 1. The cumulative incidence (95% CI) of akinetic mutism at 3, 6 and 12 months after diagnosis of sCJD was 67.8% (62.7%–72.9%), 78.6% (73.3%–82.8%) and 85.7% (80.7%–89.4%), respectively (Fig. 1a). The median times to onset of akinetic mutism, myoclonus, pyramidal dysfunction, extrapyramidal dysfunction, psychiatric symptoms, cerebellar disturbance and visual disturbance were
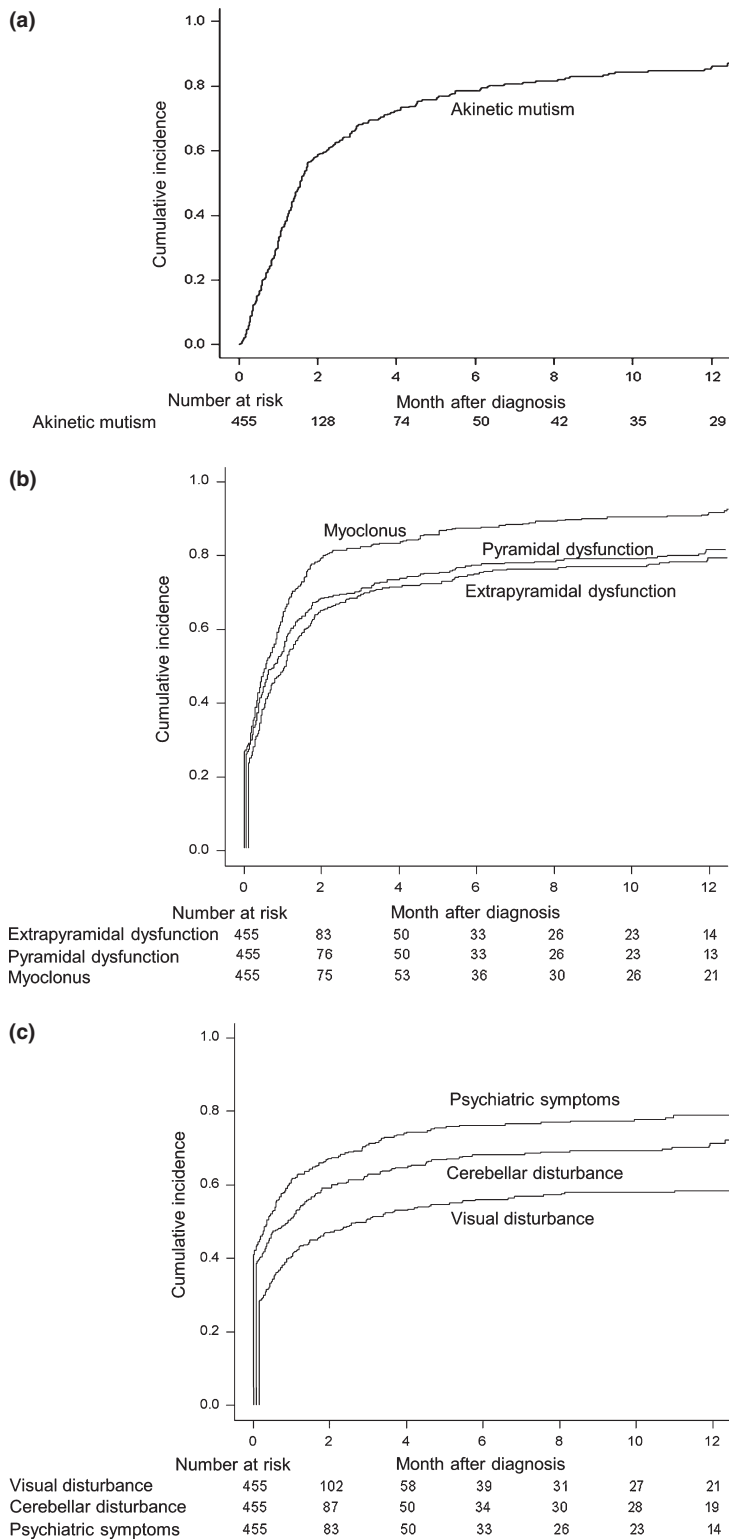
Table 1 Baseline characteristics of sCJD patients

Variable at diagnosis	$n = 455$
sCJD diagnosis (definite:probable)	38:417
Male gender	177 (38.9%)
Time from onset to diagnosis (months)	2.9 ± 2.1 ($n = 437$)
Age at diagnosis (years)	68.9 ± 9.1 ($n = 433$)
31–40	3 (0.7%)
41–50	12 (2.8%)
51–60	60 (13.9%)
61–70	157 (36.3%)
71–80	168 (38.8%)
81–90	31 (7.2%)
91–100	2 (0.5%)
Codon 129 genotype (MM:MV, total percentage of 455 cases)	98:10 (23.7%)
EEG and MRI findings	
PSD on EEG	417/446 (93.5%)
Wave slowing on EEG	367/407 (90.2%)
Hyperintensity on MRI	377/402 (93.8%)
Cerebrospinal fluid analysis	
Increase in proteins	107/348 (30.7%)
Increase in cells	17/335 (5.1%)
Increase in NSE	132/156 (84.6%)
Increase in 14-3-3 proteins	96/118 (81.4%)
Clinical signs and symptoms	
Psychiatric symptoms	195/387 (50.4%)
Visual disturbance	138/308 (44.8%)
Cerebellar disturbance	183/360 (50.8%)
Pyramidal dysfunction	134/418 (32.1%)
Extrapyramidal dysfunction	116/397 (29.2%)
Myoclonus	127/443 (28.7%)

EEG, electroencephalography; MRI, magnetic resonance imaging; NSE, neuron-specific enolase; PSD, periodic synchronous discharge; sCJD, sporadic Creutzfeldt–Jakob disease. The denominator for calculating the proportion on cerebrospinal fluid analysis was the total of normal and increase.

1.51, 0.56, 0.56, 0.86, 0.36, 0.53 and 2.17 months, respectively (Fig. 1).

Relationships between clinical signs and symptoms and time to akinetic mutism onset

Significant factors identified by a univariate Cox regression analysis were considered candidate prognostic factors for akinetic mutism (Table 2). A multivariate Cox regression analysis demonstrated that the presence of psychiatric symptoms or cerebellar disturbance at diagnosis was predictive of akinetic mutism (HR 1.50, 95% CI 1.14–1.99, $P = 0.004$, and HR 2.15, 95% CI 1.61–2.87, $P < 0.001$, respectively; Table 2). The stratified cumulative incidence of akinetic mutism is shown in Fig. 2. The median times to akinetic mutism onset in patients with psychiatric symptoms and cerebellar disturbance, cerebellar disturbance only, psychiatric symptoms only, and neither condition were 0.99, 1.51, 1.88 and 2.93 months, respectively (Fig. 2).

(a)

Number at risk

Akinetic mutism	455	128	74	50	42	35	29

(b)

Number at risk

Extrapyramidal dysfunction	455	83	50	33	26	23	14
Pyramidal dysfunction	455	76	50	33	26	23	13
Myoclonus	455	75	53	36	30	26	21

(c)

Number at risk

|						
Visual disturbance	455	102	58	39	31	27	21
Cerebellar disturbance	455	87	50	34	30	28	19
Psychiatric symptoms	455	83	50	33	26	23	14

Figure 1 Cumulative incidences of clinical signs and symptoms. Cumulative incidence plots of (a) akinetic mutism; (b) myoclonus, pyramidal dysfunction and extrapyramidal dysfunction; and (c) psychiatric symptoms, cerebellar disturbance and visual disturbance.

Table 2 Univariate and multivariate regression analyses of time to akinetic mutism onset

Variable at diagnosis (reference or unit)	Univariate regression			Multivariate regression		
	HR	95% CI	P	HR	95% CI	P
Gender: male (female)	0.95	0.75–1.20	0.676			
Time from onset to diagnosis (1 month)	1.04	0.91–1.02	0.169			
Age at diagnosis (1 year)	0.99	0.98–1.01	0.425			
Codon 129 genotype: MM (MV)	3.45	1.39–9.09	0.007			
EEG and MRI findings						
PSD on EEG	1.77	1.07–2.93	0.028			
Wave slowing on EEG	0.69	0.42–1.11	0.126			
Hyperintensity on MRI	1.10	0.67–1.81	0.700			
Cerebrospinal fluid analysis						
Increase in proteins	1.29	0.98–1.70	0.067			
Increase in cells	1.88	1.13–3.14	0.016			
Increase in NSE	2.11	1.21–3.66	0.008			
Increase in 14-3-3 proteins	2.69	1.45–4.97	0.002			
Clinical signs and symptoms						
Myoclonus	1.57	1.20–2.06	0.001			
Pyramidal dysfunction	1.24	0.95–1.60	0.115			
Extrapyramidal dysfunction	1.27	0.97–1.66	0.085			
Psychiatric symptoms	1.78	1.38–2.29	<0.001	1.50	1.14–1.99	0.004
Cerebellar disturbance	2.30	1.75–3.01	<0.001	2.15	1.61–2.87	<0.001
Visual disturbance	1.83	1.36–2.47	<0.001			

CI, confidence interval; HR, hazard ratio; other abbreviations as in Table 1. The reference for estimating HRs for clinical signs and symptoms and EEG and MRI findings is absence against presence. The reference for estimating HRs for cerebrospinal fluid analysis is normal against increase.
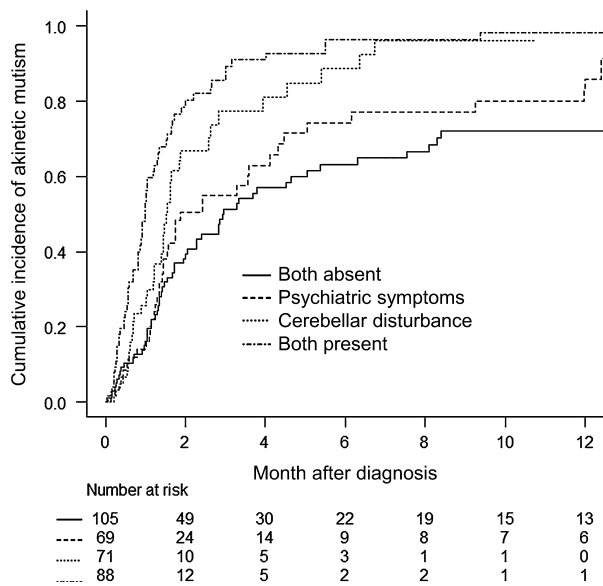
Figure 2 Stratified cumulative incidence of akinetic mutism based on prognostic factors. Stratified cumulative incidence of akinetic mutism based on the presence of cerebellar disturbance and/or psychiatric symptoms at diagnosis.

Relationships between clinical signs and symptoms

The results of a Fine−Gray regression analysis of clinical signs and symptoms are shown in Table 3.

Notably, the presence of cerebellar disturbance at diagnosis was predictive of subsequent development of myoclonus, pyramidal and extrapyramidal dysfunction, and visual disturbance. A schematic description of the order of development of signs and symptoms is presented in Fig. 3. Clinical courses from cerebellar disturbance to myoclonus or akinetic mutism were classified into three types: (i) direct path (Fig. 3, center), (ii) path via pyramidal or extrapyramidal dysfunction (Fig. 3, left) and (iii) path via psychiatric symptoms or visual disturbance (Fig. 3, right).

Discussion

The presence of psychiatric symptoms or cerebellar disturbance at sCJD diagnosis was associated with a risk for akinetic mutism. A similar result was obtained from analysis of 717 cases including those with akinetic mutism at the time of diagnosis (data not shown). In contrast, the prognostic factors for death, which are assumed to be similar to those for akinetic mutism, are not consistent across genders or ages of onset [4]. These differences from our study might be explained by the previous study's use of clinical signs or symptoms at diagnosis as covariates in multivariate regression analyses, differences in the baseline data and outcomes examined, and the inclusion of patients with codon 129 type VV. Thus, clinical signs and

Table 3 Univariate and multivariate regression analyses of time to onset of other clinical signs and symptoms

| Clinical sign or symptom as outcome	Clinical signs and symptoms at diagnosis	Univariate regression			Multivariate regression		
		HR	95% CI	P	HR	95% CI	P
Myoclonus	Pyramidal dysfunction	1.56	1.24–1.97	<0.001	1.67	1.25–2.23	<0.001
	Extrapyramidal dysfunction	1.52	1.18–1.94	0.001			
	Psychiatric symptoms	1.36	1.11–1.67	0.003	1.54	1.20–1.97	0.001
	Cerebellar disturbance	1.98	1.56–2.52	<0.001	1.45	1.08–1.96	0.013
	Visual disturbance	1.65	1.31–2.08	<0.001	1.40	1.08–1.81	0.011
Pyramidal dysfunction	Myoclonus	1.64	1.27–2.11	<0.001	1.59	1.17–2.15	0.003
	Extrapyramidal dysfunction	3.66	2.43–5.50	<0.001			
	Psychiatric symptoms	1.14	0.92–1.41	0.250			
	Cerebellar disturbance	1.55	1.23–1.96	<0.001	1.40	1.11–1.78	0.005
	Visual disturbance	1.10	0.85–1.41	0.470			
Extrapyramidal dysfunction	Myoclonus	1.43	1.09–1.87	0.009	1.59	1.17–2.18	0.003
	Pyramidal dysfunction	1.02	0.79–1.32	0.860			
	Psychiatric symptoms	1.09	0.88–1.36	0.430			
	Cerebellar disturbance	1.50	1.19–1.88	0.001	1.36	1.08–1.71	0.009
	Visual disturbance	1.05	0.82–1.34	0.720			
Psychiatric symptoms	Myoclonus	0.97	0.77–1.22	0.770			
	Pyramidal dysfunction	1.07	0.86–1.33	0.550			
	Extrapyramidal dysfunction	1.03	0.82–1.29	0.820			
	Cerebellar disturbance	1.04	0.84–1.28	0.720			
	Visual disturbance	1.40	1.11–1.77	0.005	1.40	1.11–1.77	0.005
Cerebellar disturbance	Myoclonus	1.04	0.84–1.28	0.720			
	Pyramidal dysfunction	1.09	0.87–1.36	0.440			
	Extrapyramidal dysfunction	1.22	0.98–1.51	0.078			
	Psychiatric symptoms	0.99	0.81–1.22	0.950			
	Visual disturbance	1.18	0.93–1.48	0.170			
Visual disturbance	Myoclonus	1.51	1.16–1.96	0.002			
	Pyramidal dysfunction	0.80	0.61–1.05	0.110			
	Extrapyramidal dysfunction	0.80	0.61–1.05	0.110			
	Psychiatric symptoms	1.12	0.89–1.41	0.340			
	Cerebellar disturbance	1.28	1.01–1.64	0.044	1.28	1.01–1.64	0.044

Abbreviations as used in Tables 1 and 2. The reference for estimating HRs of clinical signs and symptoms at diagnosis is absence against presence.

symptoms at diagnosis were strong prognostic factors in our study and can be used as alternatives to gender and age of onset as predictors of future outcomes. In future studies, clinical signs and symptoms at the time of diagnosis should be used as covariates to predict time to onset of akinetic mutism. Although treatment in the early stage of sCJD is essential, the progression of sCJD is rapid and there is little time for effective treatment. However, it was found that cases without cerebellar disturbance or psychiatric symptoms at diagnosis may have a window for therapy of approximately 0.5–2.0 months. Further studies are required to identify clinical signs or symptoms that are useful in the prediction of prognosis and thereby expand the therapeutic period.

The order of onset of clinical signs and symptoms after sCJD diagnosis is described schematically in Fig. 3. Previous studies have examined sCJD signs or symptoms regardless of their time of appearance after diagnosis. A better understanding of the clinical course of sCJD may be useful for the selection of

therapeutic strategies and planning of supportive care. Future studies are needed to investigate the development of clinical signs and symptoms after disease onset, which is typically indicated by progressive dementia, and to further explore sCJD etiology. Furthermore, if the presence of symptoms before CJD diagnosis is assessed, there is a possibility that a specific constellation of symptoms in the prodromal period before diagnosis may be found.

The presence of cerebellar disturbance at diagnosis increased the risks of akinetic mutism (Table 2) and four other clinical signs and symptoms (Table 3). Thus, cerebellar disturbance may be a key predictive factor for the clinical course of sCJD. Consistent with this finding, patients with cerebellar disturbance showed survival rates of 55.8% and 29.4% for less than or greater than 10 months after diagnosis, respectively [19]. This finding may be attributable to the transmission speed of PrP from certain brain regions or accumulation of PrP in specific structures.
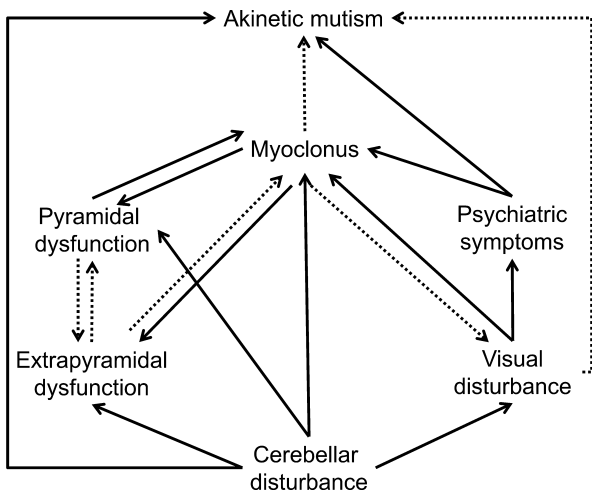
Figure 3 Schematic description of regression analysis results showing typical sequences of sign and symptom development. For signs or symptoms A (e.g. cerebellar disturbance) and B (e.g. myoclonus), solid arrows from A to B indicate that the A at diagnosis was identified as a prognostic factor by multivariate regression analyses for the time to onset of B. Dashed arrows from C (e.g. myoclonus) to D (e.g. akinetic mutism) indicate that the C at diagnosis was identified as a potential prognostic factor by univariate regression analyses for the time to onset of D.

MM1 and MV1 are the most common subtypes of sCJD, accounting for 60%–70% of all cases [5,6]. Our data may be affected by a high prevalence of MM1 and MV1 subtypes. As only a quarter of patients underwent genetic tests in this study, it is unclear whether CJD patients with VV type were included. However, the number of CJD patients with VV type would have been limited, given the sample size and a low rate of VV type in Japan [20]. PSDs, cerebellar disturbance and myoclonus are typically not observed in patients with V108I mutations or the MM2 cortical subtype, which are often categorized as sCJD [6,21–25]. Thus, because most sCJD patients included in our study experienced cerebellar disturbance or myoclonus, our dataset may consist mainly of patients with the MM1 and MV1 subtypes. Hence, our conclusions may be applicable only to these molecular subtypes of sCJD.

There are several limitations to this study. First, our data did not include information on PrP types or genotypes as prognostic factors for survival, although different genotypes are known to be associated with different symptoms and disease time course. However, it was found that clinical signs and symptoms, which reflect disease progression, can be strong prognostic factors for akinetic mutism even in a cohort presumed to be largely MM1 or MV1. Secondly, our analysis was performed without correcting for missing data. However, akinetic mutism onset typically did not have

the same incidence date as other clinical signs and symptoms, and further clinical signs and symptoms would not be observed in cases of akinetic mutism or death. Further, to prevent overestimation of the cumulative incidences of other clinical signs and symptoms, akinetic mutism was used as a competing risk in our calculations. Thirdly, because this was a retrospective analysis, our data did not assess conditions related to akinetic mutism. Akinetic mutism involves severely diminished neurological drive and is diagnosed based on markedly diminished movement and speech; however, some patients with akinetic mutism show involuntary movements or vocalizations, including grunts, myoclonus, dystonia and generalized convulsions [11,14]. Thus, future prospective studies applying standardized clinical assessments are needed to validate the predictive factors for akinetic mutism found in our study. Finally, because the autopsy rate in Japan was generally low [20], diagnostic confirmation was not available for most cases in this study and our data are based on clinical diagnosis, allowing for the absence of pathological confirmation in many cases. Despite these limitations, our findings suggest that clinical signs or symptoms may be used as indicators of sCJD progression.

In conclusion, our study demonstrates that the presence of psychiatric symptoms or cerebellar disturbance at the time of sCJD diagnosis increases the likelihood of future onset of akinetic mutism in sCJD cases with probable MM/MV subtypes. Evidence of temporal relationships between specific sCJD signs and symptoms is also provided.

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Disclosure of conflicts of interest

The authors declare no financial or other conflicts of interest.

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