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

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

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 dysfuntion | 134/418 (32.1%) |
| Extrapyramidal dysfuntion | 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, 0.86, 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).
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.
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 symptoms at diagnosis were associated with a risk for akinetic mutism.

### 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.

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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.

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.
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.

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.

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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