Journal of the Neurological Sciences 357 (2015) 63–68

Contents lists available at ScienceDirect

Journal of the Neurological Sciences

journal homepage: www.elsevier.com/locate/jns

Factors influencing the survival period in Japanese patients with sporadic Creutzfeldt–Jakob disease

Yasushi Iwasaki [a,*], Akio Akagi [a], Maya Mimuro [a], Tetsuyuki Kitamoto [b], Mari Yoshida [a]

[a] Department of Neuropathology, Institute for Medical Science of Aging, Aichi Medical University, 1-1 Yazakokarimata, Nagakute 480-1195, Japan
[b] Department of Neurological Science, Tohoku University Graduate School of Medicine, 2-1 Seiryo-machi, Aoba-ku, Sendai 980-8575, Japan

ARTICLE INFO

Article history:
Received 27 December 2014
Received in revised form 13 June 2015
Accepted 28 June 2015
Available online 30 June 2015

Keywords:
Creutzfeldt–Jakob disease
Akinetic mutism state
Total disease duration
Tube feeding
Gastrostomy
Tracheotomy

ABSTRACT

Although Japanese cases of sporadic Creutzfeldt–Jakob disease (sCJD) generally involve longer survival periods compared to those from other countries, details regarding the factors influencing survival are unclear. To determine the influence of certain factors on survival, we retrospectively assessed 51 Japanese MM1-type sCJD patients with respect to background, clinical course, and disease management. No significant differences were found between men and women, tracheotomy and nontracheotomy patients, or patients treated in public and other types of hospitals. Although the survival period of tube-fed patients was significantly longer than that of patients who were not tube fed, survival of patients fed via a nasal tube did not differ significantly from that of gastrostomy-fed patients. The proportion of tube-fed patients was 68.6% (35/51). Disease duration was not significantly associated with age or year of onset. However, it was associated with time from onset to first recognition of myoclonus, first recognition of periodic sharp-wave complexes on electroencephalogram, and progression to the akinetic mutism state. Mechanical ventilation was not performed for any patient. Because the total disease duration increased in cases with a slowly progressive clinical course as a natural outcome, we concluded that the most crucial factor contributing to the prolonged survival of Japanese sCJD patients was tube feeding once the akinetic mutism state had been reached.

1. Introduction

In general, Japanese sporadic Creutzfeldt–Jakob disease (sCJD) cases involve considerably longer total disease duration relative to North American and European cases [3,6,7]; however, the factors that influence the survival period remain unknown. In an international multicenter study involving a series of 300 North American and European cases, Parchi et al. [10] showed that a polymorphism at codon 129 of the prion protein (PrP) gene and two protease-resistant PrP types are major determinants of the phenotypic heterogeneity of clinicopathological findings concerning sCJD. Based on combinations of the codon 129 polymorphism involving methionine (Met) or valine (Val) (Met/Met, Met/Val, or Val/Val) and PrP type (1 or 2), they proposed six subtypes of sCJD: MM1, MM2, MV1, MV2, VV1, and VV2. According to their examination of the clinicopathological findings regarding the respective subtypes, MM1-type represents the typical clinical features of sCJD, namely, myoclonus and periodic sharp-wave complexes (PSWCs) on electroencephalogram (EEG) and rapidly progressive cognitive impairment, referred to as "classic-type CJD" [10]. Because the clinical course and total disease duration differ among sCJD subtypes [10], it is necessary to examine the factors influencing the survival period separately in cases of each subtype. Therefore, we investigated the factors potentially influencing survival in the Japanese MM1-type sCJD series, including patient background, clinical course, and disease management, using statistical analysis.

2. Materials and methods

2.1. Subjects

Fifty-one autopsy-confirmed MM1-type sCJD cases, examined with respect to clinical and pathological findings at the Institute for Medical Science of Aging, Aichi Medical University, were included in the present study. Autopsy was performed after receiving informed consent from the patients' relatives for research use. Protocols for the analysis of the PrP gene and western blot of protease-resistant PrP were conducted as previously described [7]. PrP gene mutation was not found in any of the cases, and there was no clinicopathological evidence of iatrogenic CJD. The polymorphic codon 129 demonstrated Met homozygosity, and the polymorphic codon 219 showed glutamic acid homozygosity in all cases. PrP typing via western blot analysis was performed

Abbreviations: EEG, electroencephalogram; sCJD, sporadic Creutzfeldt–Jakob disease; PSWC, periodic sharp-wave complex.

* Corresponding author.
E-mail addresses: iwasaki@sc4.so-net.ne.jp (Y. Iwasaki), akio.akagi@gmail.com (A. Akagi), mimuro@aichi-med-u.ac.jp (M. Mimuro), kitamoto@med.tohoku.ac.jp (T. Kitamoto), myoshida@aichi-med-u.ac.jp (M. Yoshida).

http://dx.doi.org/10.1016/j.jns.2015.06.065
0022-510X/

according to the classification proposed by Parchi et al. [10]. Although all patients showed type 1 PrP^{Sc} (scrapie) according to western blot analysis, we analyzed the PrP type in one region, using frozen cerebral cortical samples in the majority of cases. We ruled out the coexistence of type 2 PrP^{Sc} on the basis of the pathology findings (large confluent vacuoles/perivacuolar type PrP deposits; [5,7,10]). However, in a similar manner to our previous investigation [5], we included cases in which type 2 PrP^{Sc} pathology was only partially mixed; even if mixed pathology was present, it was limited to a few partial cerebral cortical regions. All patients were Japanese. The majority of the patients had lived in Aichi prefecture, but some had lived in the Mie, Gifu, or Shiga prefectures. One case (patient 3) had a history of cerebral subcortical hemorrhage, for which conservative treatment was administered, and two cases (patients 25 and 43) involved clinicopathological Parkinson's disease with dementia. The remaining cases did not have any clinical or pathological complications with respect to other neurological disorders. None of the cases was treated with quinacrine or pentosan polysulfate in prion disease clinical trials. There were no patients with fatal non-neurological disorders at CJD onset.

2.2. Data collection

The following clinical data were collected from clinical summaries and autopsy records for each case: (1) sex, (2) age at disease onset, (3) year of disease onset, (4-1) time from disease onset to first observation of myoclonus, (4-2) time from disease onset to first observation of PSWCs on EEG, (4-3) time from disease onset to progression to the akinetic mutism state, (5) whether tube feeding was performed (including gastrostomy tube feeding) during the course of the disease, (6) whether tracheotomy was performed or a respirator (mechanical ventilator) used during the course of the disease, and (7) the type of hospital that treated the patient at death. Total disease duration (time from disease onset to death) was also collected. Disease onset was considered to have occurred with the first presentation of neurological signs or symptoms suggestive of organic brain involvement. The akinetic mutism state was defined as a state in which patients lacked voluntary movement or the ability to produce meaningful words [3,5,6]. In this state, involuntary movements such as myoclonus, startle reaction, and convulsions might have been present, and the patients may have been able to produce nonsensical sounds such as groans [3,5,6].

2.3. Statistical analysis

Statistical analyses were performed using a two-sided Mann–Whitney's U test or the Spearman rank correlation coefficient. These analyses were performed using Excel 2010 (Microsoft; Redmond, WA, USA) and the add-in software, Statcel 2 (OMS; Tokyo, Japan). Statistical significance was set at a p-value of <0.05. Data are expressed as means ± standard deviations (median, range).

3. Results

The clinical data obtained for 51 MM1-type sCJD cases, arranged according to total disease duration and brain weight, are shown in Table 1. The average total disease duration was 12.3 ± 9.6 months (median: 9 months, range: 1–32 months). The results of the respective statistical analyses are shown in Table 2.

3.1. Comparison of total disease duration between men and women

The average total disease duration was 12.8 ± 11.1 months (median: 5.5 months, range: 1–32 months) for men ($n = 26$) and 11.9 ± 8.0 months (median: 11 months, range: 2–30 months) for women ($n = 25$). Men and women did not differ significantly with respect to total disease duration ($p = 0.62$).

3.2. Relationship between age at disease onset and total disease duration

The average age at disease onset in the present series was 69.5 ± 7.6 years (median: 69 years, range: 57–89 years). Age at disease onset and total disease duration were not significantly correlated ($p = 0.86$, $rs = -0.02$).

3.3. Relationship between year of disease onset and total disease duration

Year of disease onset in the present series ranged from 1996 to 2013. There was no significant correlation between year of disease onset and total disease duration ($p = 0.60$, $rs = -0.07$).

3.4. Relationship between clinical manifestations and total disease duration

Myoclonus was found in all but one case (patient 5), PSWCs on EEG were found in all but 3 cases (patients 1 [EEG was not performed], 4, and 17), and akinetic mutism state was found in all but one case (patient 1).

The average time from disease onset to first observation of myoclonus was 2.0 ± 1.0 months (median: 2 months, range: 0.5–6 months). Time from disease onset to first observation of myoclonus was significantly associated with total disease duration ($p = 0.04$, $rs = 0.30$).

The average time from disease onset to first observation of PSWCs on EEG was 2.0 ± 1.3 months (median: 2 months, range: 0.75–7 months). Time from disease onset to first observation of PSWCs on EEG was significantly associated with total disease duration ($p = 0.01$, $rs = 0.36$).

The average time from disease onset to progression to the akinetic mutism state was 3.0 ± 1.4 months (median: 2.75 months, range: 1–8 months). Time from disease onset to progression to the akinetic mutism state was significantly associated with total disease duration ($p < 0.001$, $rs = 0.55$).

3.5. Comparison of total disease duration between tube-fed and non tube-fed patients

Thirty-five cases involved tube feeding (nasal tube feeding or gastrostomy tube feeding) during the course of the disease. The average total disease duration was 4.0 ± 1.6 months (median: 4 months, range: 1–6 months) in patients who were not tube fed and 16.1 ± 9.4 months (median: 16 months, range: 2–32 months) in tube-fed patients. Total disease duration differed significantly between the two groups ($p < 0.0001$).

The time from onset to akinetic mutism was 2.8 ± 0.9 months (median: 3 months, range: 2–4.5 months) in patients who were not tube fed and 3.1 ± 1.5 months (median: 2.5 months, range: 1–8 months) in tube-fed patients. The groups did not differ significantly with respect to time from onset to akinetic mutism ($p = 0.80$).

Of the 35 tube-fed patients, 32 involved nasal tube feeding and 3 involved gastrostomy tube feeding. The average total disease duration was 15.5 ± 9.2 months (median: 15.5 months, range: 2–31 months) in cases involving nasal tube feeding and 23.0 ± 9.5 months (median: 24 months, range: 13–32 months) in those involving gastrostomy tube feeding. The groups did not differ significantly with respect to total disease duration ($p = 0.18$).

3.6. Comparison of total disease duration according to respiratory support

With respect to respiratory support, 3 cases involved tracheotomy, but mechanical ventilation was not performed in any of the 51 cases.

The average total disease duration was 11.9 ± 9.4 months (median: 7.5 months, range: 1–32 months) in the 48 cases that did not involve tracheotomy, and 20.0 ± 12.5 months (median: 24 months, range: 6–30 months) in the 3 cases involving tracheotomy. The groups did not differ significantly with respect to total disease duration ($p = 0.13$).