Long-Term Disability and Prognosis in Dentatorubral-Pallidoluysian Atrophy: a Correlation with CAG Repeat Length

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Abstract: Dentatorubral-pallidoluysian atrophy (DRPLA) is a rare autosomal dominant neurodegenerative disorder caused by CAG repeat expansion. Previous studies demonstrated that the onset of DRPLA is closely associated with CAG repeat length. However, the natural history of DRPLA has not yet been evaluated. We here retrospectively investigated the factors that determine the disease milestones and prognosis in 183 Japanese patients genetically diagnosed with DRPLA. We determined the age at onset, age at which each of the subsequent clinical manifestations appeared, age at becoming wheelchair-bound, and age at death. Kaplan-Meier analysis revealed that the patients with CAG repeats larger than the median length of 65 repeats developed each of the clinical features of DRPLA at a younger age than those with <65 repeats. The patients became wheelchair-bound at a median age of 33 years (n = 61; range, 3–77 years) and died at a median age of 49 years (n = 23; range, 18–80 years). The ages at becoming wheelchair-bound and at death strongly correlated with the expanded CAG repeat length. Moreover, the patients with ≥65 CAG repeats showed a more severe long-term disability and a poorer prognosis. In contrast, the rate of progression after the onset did not correlate with CAG repeat length. The CAG repeat length may have a considerable effect on not only the disease onset but also the disease milestones and prognosis in DRPLA patients. These effects of CAG repeat length may be relevant in designing future clinical therapeutic trials. © 2010 Movement Disorder Society

Key words: DRPLA; CAG repeat expansion; prognosis

Dentatorubral-pallidoluysian atrophy (DRPLA) (OMIM 125370) is an autosomal dominant neurodegenerative disorder that is clinically characterized by various combinations of clinical features including ataxia, chorea, epilepsy, myoclonus, cognitive impairment, and psychiatric symptoms.1 DRPLA is caused by a CAG repeat expansion that encodes a polyglutamine tract.2,3 Although most DRPLA patients were initially reported in the Japanese population, it is now recognized that DRPLA is not geographically or ethnically restricted, but is distributed worldwide.4–6 Numerous studies have demonstrated that the age at onset in patients with DRPLA inversely correlates with the length of expanded CAG repeats.7,8 Moreover, variable clinical phenotypes have been shown to be associated with CAG repeat length.9,10 However, it remains unclear which factors determine the long-term progression of disability and prognosis of DRPLA patients. It is necessary to determine the natural history of patients with DRPLA for designing therapeutic trials and preventive interventions. In this study, we investigated the possible contribution of CAG repeat length...
in the DRPLA gene and other factors to the disease milestones and prognosis in a large and consecutive series of 183 Japanese DRPLA patients.

METHODS

Patients

We diagnosed a total of 185 Japanese patients as having DRPLA by genetic analysis at our center. Two patients were excluded because of insufficient information on the disease progression. We reviewed the age at onset, the initial symptoms, and the age at which each of the subsequent clinical manifestations including epilepsy, myoclonus, chorea, ataxia, cognitive impairment, and psychiatric symptoms appeared after the onset. The age at disease onset was defined as the age at which the first symptoms considered to be attributable to DRPLA appeared. Patients were considered to have cognitive impairment when they exhibited mental retardation during childhood or dementia in adults. Mental retardation was defined as a disability developing before the age of 18 years and characterized by significant limitations both in intellectual functioning and adaptive behavior as expressed in conceptual, social, and practical adaptive skills. Dementia in adults was defined as loss of cognitive abilities sufficient to produce substantial and apparently permanent impairment in social and daily activities and cognitive decline as determined by Mini-Mental State Examination or the revised Hasegawa Dementia Scale. Psychiatric symptoms of DRPLA patients were defined as hallucination, delusion, psychosis, character change, or euphoria. The age at death and cause of death were also investigated in 23 DRPLA patients. Seventeen out of 23 deceased patients were neuropathologically examined. We examined the age at which the use of a wheelchair was required as a milestone of long-term disability, which can be assessed easily by the patients, their caregivers, or a neurologist. Assessment of clinical information was based on a systemic review of the patients’ clinical records obtained from direct interview, examination of the patients, and family interviews. Symptoms were recorded as absent if not reported. When the onset was not clearly shown, we used the age when the symptom was first mentioned in the clinical records. Where conflicting clinical information was reported, the findings described by the neurologists in the clinical records were used. Genetic investigation was conducted with written informed consent, and the study protocol was approved by the ethics committee of Niigata University School of Medicine.

Genetic Analysis

Genomic DNA was extracted from peripheral blood leukocytes of the patients by standard procedures. The CAG repeat in the DRPLA gene was amplified by PCR as previously described. Aliquots of PCR products were separated by electrophoresis with an automated sequencer. The length of the CAG repeat was determined with Fragment Manager software (Applied Biosystems, Foster City, CA) using PCR standards containing known repeat sizes.

Data Analysis

The Mann–Whitney U test for nonparametric statistics was used as appropriate. The correlations between the age at onset for each factor and the length of the CAG repeat of the DRPLA gene were analyzed using Pearson’s correlation coefficient. Kaplan-Meier analyses were used to estimate the disease milestones and prognosis. Log-rank test statistics were used to determine whether the Kaplan-Meier curves differ between subgroups. Cox multiple stepwise regression analysis was performed for gender as a categorical covariate, and CAG repeat length, ages at onset and examination, and duration as continuous variables. Statistical significance was defined as a probability (P) value of <0.05. Calculations were performed using the statistical software package SPSS version 12.0J (SPSS Japan, Tokyo, Japan).

RESULTS

Clinical and Genetic Characteristics

We identified 183 patients with DRPLA consisting of 82 men and 101 women (Table 1). All the patients were of Japanese descent. Ages at onset ranged from 0 to 72 years with an average of 31.5 years. The mean age at the time of data collection was 41.1 ± 19.7 years (mean ± standard deviation; range, 5–80 years). The mean duration from the onset was 9.5 ± 6.8 years (range, 0–35 years). Ataxia was the most frequent initial symptom (n = 94), followed by epilepsy (n = 62) and cognitive impairment (n = 55). The mean length of the expanded CAG repeats in the DRPLA gene was 64.8 ± 4.4 repeats (range, 56–82 repeats). The age at onset inversely correlated with the size of the expanded CAG repeats, as previously reported (r = −0.795, P < 0.001).2,3

Correlation of Age at which Each of the Clinical Manifestations Appeared with CAG Repeat Length

The distribution of age at which each of the clinical manifestations (i.e., epilepsy, myoclonus, chorea, cognitive impairment, ataxia, or psychiatric symptoms) appeared is summarized in Table 1. Epilepsy and myo-
Table 1 presents the patient subgroups above and below the median CAG repeat length of 65 repeats. The table includes columns for all patients, <65 CAG repeats, and ≥65 repeats, with data for age at onset, age at death, age at wheelchair requirement, age at onset of various clinical manifestations, and disease duration. The data indicate that patients with ≥65 CAG repeats had earlier age at onset of various clinical manifestations compared to those with <65 repeats, and the disease duration was longer. Significant correlations were observed between CAG repeat length and age at becoming wheelchair-bound (r = −0.87, P < 0.001) (Fig. 2A). In contrast, the interval between the onset of the disease and the age at becoming wheelchair-bound did not correlate with CAG repeat length (Fig. 2B). Kaplan-Meier estimate for age at requirement of wheelchair-bound in all the patients is shown in Supporting Information Figure 3A.

We divided the patients into two groups, those carrying repeats above and below the median CAG length of 65 repeats (Table 1). Kaplan-Meier estimates for age at which the clinical manifestations appeared during the disease course of the total DRPLA patients are shown in Supporting Information Figure 2. The age at onset of myoclonus and myoclonus were significantly younger than those of chorea, ataxia, psychiatric symptoms, and cognitive decline. The age at which each of the clinical manifestations appeared during the disease course significantly correlated with expanded CAG repeat length (Supporting Information Fig. 1). Kaplan-Meier estimates for age at which each of the clinical manifestations appeared during the disease course of the total DRPLA patients are shown in Supporting Information Figure 2.

We divided the patients into two groups of those carrying repeats above and below the median CAG length of 65 repeats (Table 1). Kaplan-Meier estimates for age at which each of the clinical manifestations appeared during the disease course between the two groups are shown in Figure 1. The patient group with ≥65 CAG repeats developed each of the clinical manifestations at a younger age than the group with <65 repeats (log-rank test, P < 0.001). Notably, the patient group with <65 repeats exhibited epilepsy, myoclonus, or chorea less frequently than the group with ≥65 repeats (Fig. 1A–C). On the other hand, cognitive impairment and ataxia were commonly observed during the disease course in both groups (Fig. 1E,F).

Correlation of Disease Milestones and Prognosis with CAG Repeat Length

The median age of becoming wheelchair-bound was 33 years (n = 61; range, 3–77 years) and the median duration after the disease onset was 10 years (range, 3–25 years). Expanded CAG repeat length significantly correlated with the age of becoming wheelchair-bound (r = −0.87, P < 0.001) (Fig. 2A). In contrast, the interval between the onset of the disease and the age at becoming wheelchair-bound did not correlate with CAG repeat length (Fig. 2B). Kaplan-Meier estimate for age at requirement of wheelchair-bound in all the patients is shown in Supporting Information Figure 3A.

We compared the age at becoming wheelchair-bound and the interval from age at onset to age at becoming wheelchair-bound between the patient group with ≥65 CAG repeats and that with <65 repeats (Table 1). Although the group with ≥65 CAG repeats became wheelchair-bound statistically significantly earlier than the group with <65 repeats, there was no significant difference in the interval from age at onset to age at becoming wheelchair-bound between the groups. Kaplan-Meier estimates for age at requirement of wheelchair between the group with ≥65 CAG repeats and that with <65 repeats are shown in Figure 3A. The patient group with ≥65 repeats became wheelchair-bound at a younger age than those with <65 repeats (log-rank test, P < 0.001).

The median age at death was 49 years (n = 23; range, 18–80 years) and the median interval between the onset and death was 15 years (range, 7–34 years). We were able to determine the cause of death in 17 patients; the most common cause of death was respiratory failure associated with pneumonia (n = 12), followed by status epilepticus (n = 3) and sudden death (n = 2). There was a significant correlation between CAG repeat length and age at death (r = −0.89, P < 0.001) (Fig. 2C). By contrast, the interval between the onset of disease and the age at death did not correlate with expanded CAG repeat length (Fig. 2D). Kaplan-Meier analysis for mortality rate of all patients is shown in Supporting Information Figure 3B.
The relationship between CAG repeat length and death was examined by comparing groups below and above the median length of 65 CAG repeats. The patient group with ≥65 CAG repeat died statistically significantly earlier than the group with <65 repeats (Table 1). In contrast, the interval from age at onset to age at death was comparable between the two groups (Table 1). Kaplan-Meier analysis for death between the two groups revealed that the patients with ≥65 repeats died earlier than those with <65 repeats (log-rank test, \( P < 0.05 \)) (Fig. 3B).

The risk of being wheelchair-bound or death was assessed using the Cox proportional hazards model adjusted for sex, the normal and expanded CAG repeat lengths, ages at onset and examination, and duration after the onset. The analysis revealed that the expanded CAG repeat length was only associated with earlier age of wheelchair requirement (hazard ratio, 1.34; 95% confidence interval, 1.18–1.52; \( P < 0.001 \)). Neither factor showed a significant association with age at death, as determined using Cox proportional hazards models.

**DISCUSSION**

It has been well recognized that age at onset in patients with DRPLA closely correlates with expanded CAG repeat length in the DRPLA gene.\(^7,8\) However, the long-term progression of disability and prognosis of DRPLA has not been assessed; hence, there was no information on which factors determine the natural history of DRPLA. To our knowledge, the present study is the first description of the progression of subsequent clinical manifestations after the onset, disease milestones, and prognosis in a large and consecutive series of DRPLA patients with genetic diagnosis.

The ages at which the subsequent clinical manifestations of DRPLA appeared after the onset extremely varied; however, these ages correlated well with expanded CAG repeat length. Myoclonus and epilepsy...
appeared in an early phase of the disease, which probably corresponds to the phenotype of progressive myoclonus epilepsy. On the other hand, ataxia, chorea, and psychiatric symptoms are noted in the late phase of the disease. Importantly, our study revealed that patients with CAG repeats larger than the median length of 65 repeats exhibited each of the clinical manifestations at an earlier age than those with <65 CAG repeats. These findings suggest that CAG repeat length has an effect on not only the age at onset of an initial symptom but also the development of subsequent clinical symptoms during the disease course after the onset.

In this study, the age at becoming wheelchair-bound and age at death strongly correlated with CAG repeat length. In contrast, the intervals between the age of disease onset and these parameters did not correlate with expanded CAG repeat length. Moreover, the disease intervals between the age at disease onset and the age at reaching the disease milestones were comparable between the group with ≥65 CAG repeats and that with <65 repeats. These findings suggest that the length of the CAG repeat expansion is relevant to the disease milestones and prognosis, but not to the rate of progression after the disease onset. These results may be explained as follows. Firstly, an abnormal protein product encoded by the CAG repeat expansion may exert a continuous toxic effect after the birth of patients, reaching critical thresholds throughout the life span including disease onset, wheelchair-bound state, and death; hence, both CAG repeat length and patient age are important determinants of each of these parameters. In this regard, we and others previously reported that CAG repeat length and patient age upon MRI examination correlated well with the degree of brain atrophy in patients with DRPLA and Machado-Joseph disease. An alternative explanation is that there

**FIG. 2.** Correlations of CAG repeat length with age at becoming wheelchair-bound (A) and age at death (C) were analyzed using Pearson’s coefficient. Intervals from the disease onset to age at becoming wheelchair-bound (B) and age at death (D) were also examined with the expanded CAG repeat length.
could be imprecision in determining the exact onset of the disease owing to the insidious onset, or that the aging process may accelerate the disease progression in patients with the elderly onset with a relatively small CAG expansion.

The correlation between CAG repeat length and natural history was previously examined in other polyglutamine diseases including Huntington’s disease (HD), spinal and bulbar muscular atrophy (SBMA), and spinocerebellar ataxia (SCA). In HD, the reported factors that determine the rate of progression have been controversial; studies of disease progression after the onset have not consistently shown an association between either age at onset or CAG repeat length. However, it has been reported that the ages at late-stage milestones such as nursing home admission, percutaneous endoscopic gastrostomy, and death in patients with HD correlated with expanded CAG repeat length. In SBMA, Atsuta et al. reported that the CAG repeat length in the androgen receptor gene correlates with the age at each ADL milestone such as dysphagia, use of a cane, use of a wheelchair, and death. Similarly to our study, they failed to show a significant correlation between the interval from the onset of weakness to each milestone and CAG repeat length. In SCA3, a larger number of expanded CAG repeats were reported to significantly increase the risk of becoming dependent early on walking aids and wheelchair-bound. Taken together, polyglutamine diseases may share a common phenomenon, that is, the ages at milestones including the onset, ADL status, and death correlate with expanded CAG repeat length; however, the association between the rate of progression after the onset and CAG repeat length is not as clear.

The limitations of this study are that it is a retrospective data collection in terms of design and that functional decline was not prospectively assessed in each patient. For instance, not all the patients underwent neuropsychological examination, and we performed the test only on patients who were clinically suspected to have apparent cognitive decline. Therefore, we might underestimate the frequency of cognitive impairment in patients who did not undergo neuropsychological examination. However, the strength of this study lies in its study design, that is, a large number of consecutive patients were genetically diagnosed at a single institute. Nonetheless, this study provides useful information on the natural history in DRPLA patients, although a prospective study that follows each patient in assessing the ADL milestones and prognosis is required to ascertain more accurately the validity of this natural history of DRPLA.

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REFERENCES


