Survival of Korean Huntington's Disease Patients

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ABSTRACT

Objective The survival of Huntington's disease (HD) patients is reported to be 15–20 years. However, most studies on the survival of HD have been conducted in patients without genetic confirmation with the possible inclusion of non-HD patients, and all studies have been conducted in Western countries. The survival of patients with HD in East Asia, where its prevalence is 10–50-fold lower compared with Western populations, has not yet been reported.

Methods Forty-seven genetically confirmed Korean HD patients from independent families were included in this retrospective medical record review study.

Results The mean age at onset among the 47 patients was 46.1 ± 14.0 years. At the time of data collection, 25 patients had died, and these patients had a mean age at death of 57.8 ± 13.7 years. The Kaplan-Meier estimate of the median survival from onset in the 47 patients was 14.5 years (95% confidence interval: 12.3–16.6). None of the following factors were associated with the survival time in the univariate Cox regression analysis: gender, age at onset, normal CAG repeat size, mutant CAG repeat size, and the absence or presence of non-motor symptoms at onset.

Conclusion This is the first Asian study on survival in HD patients. Survival in Korean HD patients may be shorter than that reported for Western populations, or at least is in the lower range of expected survival. A larger longitudinal observation study is needed to confirm the results found in this study.

Key Words Huntington's disease; survival; CAG; Korea; Asia.
MATERIALS & METHODS

Forty-seven genetically confirmed HD patients from independent families who visited the neurology department of Seoul National University Hospital (SNUH) from 1994 to 2015 were included in this study. Thirty-six of the 47 (76.6%) patients were included in our previous report. Demographic and clinical information was obtained by retrospective medical record review. Age at onset was defined as the age at which the patient developed motor symptoms or non-motor symptoms attributable to HD. Non-motor symptoms at onset were considered present if unequivocal cognitive decline or psychiatric symptoms developed before the onset of motor symptoms or simultaneously with motor symptoms. The vital status of all patients as of December 2015, as well as the date of death if deceased, was ascertained using data from the Korean National Statistics Office.

Data were expressed as the mean ± SD. Correlations of the age at onset with the CAG repeat size were analyzed with Pearson’s correlation coefficients. Survival was analyzed by the Kaplan-Meier method, and the differences between genders were examined with the log-rank test. The effect of variables on survival was evaluated by Cox proportional hazards modelling. The following variables were evaluated in the Cox proportional hazards model: gender, age at onset, normal CAG repeat size, mutant CAG repeat size, and the absence or presence of non-motor symptoms at onset. All analyses were performed with SPSS 21.0 (SPSS Inc., Chicago, IL, USA). The level of statistical significance was set at p < 0.05. The study protocol was approved by the Seoul National University Hospital Institutional Review Board and conformed to the principles of the Declaration of Helsinki.

RESULTS

The demographic, clinical, and genetic data are presented in Table 1. The year of symptom onset ranged from 1989 to 2011. Motor symptoms including chorea, ataxia, parkinsonism, and dystonia were the initial symptoms of 43 patients as a sole symptom (n = 20) or in combination with other non-motor symptoms including cognitive decline and psychiatric disturbances (n = 23), while four patients only developed non-motor symptoms as an initial symptom. There was no gender difference in the age at onset, symptoms at onset, and CAG repeat size in normal and mutant alleles. The CAG repeat size in the mutant allele showed an inverse correlation with the age at onset (r = -0.674, p < 0.001).

At the time of data collection, 25 patients had died with a mean age at death of 57.8 ± 13.7 (range, 36–80) years (Table 1). The Kaplan-Meier estimate of median survival from onset in the 47 patients was 14.5 years [95% confidence interval (CI): 12.3–16.6] (Figure 1A). No difference in survival was observed between genders in the log-rank test (Figure 1B). In the univariate Cox regression analysis, none of the tested variables were associated with the survival time (Table 2).

DISCUSSION

In this first Asian study on survival in HD patients,
Although a direct comparison is not possible, it appears that the mean survival in our study is shorter than that reported by Rinaldi et al. (20 years, 95% CI: 18.3–21.7). In a study by Pekmezovic et al., the cumulative probabilities of survival in 5, 10, 15, and 20-year periods calculated by the life table method were 91, 63, 10, and 5%, respectively, compared to 88, 49, 26, and 5% in our patients, respectively. Taking into account the studies without a genetic diagnosis which report a survival of 15–20 years as well, the survival in our patients appears to be shorter than that reported for Western populations, or at least is in the lower range of the estimated survival.

A couple of reasons may explain the shorter survival observed in our patients. First, the mean age at onset in our patients was higher by approximately 5 years compared with studies conducted in Western populations, despite a similar mutant CAG repeat size. Specifically, when compared with the results of Rinaldi et al., the mean age at onset was higher by 6 years, despite the fact that the mean age at death was similar. This later onset with a similar age at death may explain the shorter survival in our patients. However, it is not clear whether HD patients in Korea really have a later age of onset or whether this finding is due to a delay in diagnosis. Of note, a recent study from Korea showed an onset age of 44.16 ± 14.08 years, which is similar to our result. Intriguingly, the age at onset of HD patients in Chinese populations was reported to be in the mid-30s. It will be interesting to evaluate survival of HD patients in these populations. Second, differences in the HTT haplotypes and CCG polymorphisms, which are related to the differences in the HD prevalence between populations, might have a role in the difference in survival, although there is no evidence yet that these genetic factors have any effect on the progression or survival of HD patients. It cannot be excluded that yet unknown genetic factors may have an effect on the survival of HD patients. Third, survival among patients with progressive neurodegenerative disorders like HD is influenced not only by the disease itself but also by other sociocultural factors and the prevalence of other disorders affecting the elderly in that population.

In our study, none of the tested variables were associated with the survival time. The lack of an association between the mutant CAG repeat size with survival time is in contrast with recent studies on

| Baseline variable                  | Unadjusted hazard ratio (95% CI) | p-value |
|-----------------------------------|---------------------------------|---------|
| Gender                            | 0.957 (0.408–2.248)             | 0.920   |
| Age at onset                      | 1.027 (0.994–1.061)             | 0.112   |
| Normal CAG repeat size            | 1.077 (0.882–1.317)             | 0.466   |
| Mutant CAG repeat size            | 1.044 (0.961–1.134)             | 0.304   |
| Non-motor symptom at onset        | 0.917 (0.400–2.103)             | 0.839   |

CI: confidence interval.
A clear understanding of survival in HD patients and the factors influencing survival is important for patient care and may help to identify factors related to disease progression in HD patients. Current, ongoing, large longitudinal observational studies will provide a better understanding in this regard.
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