TRINUCLEOTIDE REPEAT LENGTH AND CLINICAL PROGRESSION IN HUNTINGTON'S DISEASE

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ABSTRACT

Objective: Huntington's Disease is a progressive degenerative disorder having an expanded triplicate repeat in the gene IT-15 on chromosome 4. The interrelation between the trinucleotide repeat length and disease progression was studied.

Methods: Five patients included in the study were evaluated by "Quantified staging of functional capacity for Huntington's Disease patients" and age of disease onsets were determined. Progression rate was calculated and interrelationship between age of disease onset and repeat length; progression rate and repeat length were studied.

Results: We found a statistically significant negative correlation between age of disease onset and trinucleotide repeat length (pearson $r=-0.9514$ $p<0.05$). There was a statistically significant positive correlation between CAG repeat length and progression rate (pearson $r=0.8809$, $p<0.05$).

Conclusion: Our study, conducted with a very limited number of patients, revealed the correlation between trinucleotide repeat length and disease progression. It like few similar studies in the literature, gave an impression of the important pathophysiological role of expanded CAG repeat during the entire course of the disease.

Key Words: Huntington's Disease, progression rate, trinucleotide repeat, prognosis.

INTRODUCTION

Huntington's Disease (HD) is a dominantly inherited neurodegenerative disorder usually presenting in adult life with progressive chorea, affective disorder and dementia (1). The genetic defect causing HD has been mapped to the short arm of chromosome 4 (2). In 1993, gene IT-15 containing a highly polymorphic CAG repeat in the 5' region, which is expanded and unstable in HD, was described (3).

The discovery of the genetic mutation for HD allows the examination of the relationship between the etiology of the disease and its clinical characteristics. The number of repeats on normal chromosomes ranges from 12-31. On HD chromosomes it ranges from 37-80. Because the number of trinucleotide repeat varies among patients, we are able to determine the correlation between inter-individual variability in clinical presentation and rate of progression. Past studies revealed a significant negative correlation between the repeat lengths and the age of disease onset (4,5). However the significance of the expanded triplet repeat for the rate of clinical progression is not clear (6). A detailed analysis of the correlation of disease progression rate with CAG repeat expansion may bring new insights into the mechanisms of the pathophysiology of HD.

Here we report the results of our investigation on the HD patients in the Turkish population. We reported the correlation between the ages of disease onset, disease progression rate and CAG repeat expansion of HD patients followed by our movement disorder clinic.

PATIENTS AND METHODS

Five patients with positive family history for HD and abnormal CAG repeat size were studied. For each patient, the age of HD onset was determined by asking the patient and multiple unaffected family members to recollect the first occurrance of chorea, rigidity, irritability, sleep disturbance, frequent falls, altered

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sexual behaviour, altered social behaviour or failing memory. Patients were assessed by "Quantified Staging of Functional Capacity for HD Patients" (7). We calculated the progression rate by dividing disease duration (year) with the functional capacity score of the patient.

Statistics: Age of disease onset and trinucleotide repeat length; progression rate and trinucleotide repeat length were studied statistically by Pearson correlation and regression analysis.

RESULTS

Three of the patients were women, two were men. Mean age of disease onset was 38.8±11.25 (25-54). The mean progression rate was 1.658±1.992 (0.3-5) and the mean CAG repeat length was 46.6±6.656 (40-55). We found a statistically significant negative correlation between the age of disease onset and trinucleotide repeat length (pearson r= -0.9514 $p<0.05$). There was a statistically significant positive correlation between CAG repeat length and progression rate (pearson r=0.8809, $p<0.05$). Between the age of disease onset and progression rate, we found a tendency for negative correlation not showing statistical difference (pearson r= -0.8298 p=0.0821). Detailed information about the cases is shown in table I.

Table I. Data of the patients included in the study Progression rate was calculated by dividin disease duration (year) to functions capacity score of the patient.

	case 1	case 2	case 3	case 4	case 5
Age of disease onset	54	25	45	38	32
Disease duration (yr)	4	5	2	2	8
Family history	Paternal	Metarnal	Maternal	Maternal	Paternal
Progression rate	0.3	5	0.63	0.36	2
CAG repeat length	40	55	41	45	52

DISCUSSION

Previous studies of CAG repeat expansion in HD patients revealed a strong association between the repeat lengths and the ages of disease onset (4,5). These data provided the moleculer basis for the phenomenon of anticipation (6). However these studies shed little light on the significance of CAG repeat lengths for the course of the disease. Illarioshkin et al (6) recently reported significant correlations between CAG repeat length and rate of progression of both neurologic and psychiatric features in 20 HD patients from Russia. In 1996, Brandt et al (8) studied the largest series to date of genetically tested 46 patients prospectively at regular intervals. In this report, patients in the long repeat length group were significantly younger at disease onset and there was a significant inverse correlation between repeat lengths and onset age. In the aspect of disease progression, they showed that patients with long repeat lengths showed more rapid decline in both the neurologic and cognitive measures of disease severity over a two-year follow-up period.

In our study, there was a significant negative correlation between CAG repeat length and age of disease onset. The progression rate correlated positively with trinucleotide repeat length, like in Illarioshkin (6) and Brandt's (8) studies. Therefore one may conclude that the degree of repeat elongation not only affects the beginning of the disease, but also, more interestingly it is relevant to the tempo of loss of normal function in HD patients.

Illarioshkin et al (6) recognized the significance of the repeat expansion which was more evident for larger expansions associated with more rapid progression of the disease. They suggested a "treshold" for accelerated progression with repeats longer then 52. In the light of this knowledge, our case 2 (table I) with 55 CAG repeat length had the severest progression rate supporting the Illarioshkin's study results.

Our study, including very limited number of patients, revealed the correlation between trinucleotide repeat length and disease progression. A large sample containing studies with a more comprehensive neuropsychological battery is needed to evaluate the Turkish population. In 1998 Apaydın et al (9) reported 3 genetically diagnosed Hungtington's disease patients with clinical and radiological findings. For the Turkish population, follow-up results will be more valuable to ascertain the disease progression and trinucleotide repeat length interrelationship, as in Brandt's (8) study. In conclusion, our study gave an impression of the important pathophysiological role of expanded CAG repeat during the entire course of the disease.

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