The initial study of clinical and molecular genetic features of Huntington’s disease in Sri Lanka

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Abstract

Background Huntington’s disease was one of the first hereditary diseases for which genetic testing was offered starting way back in 1993. This study describes the clinical and genetic characteristics of patients with Huntington’s disease in Sri Lanka.

Methods Data of 37 consecutive patients tested from 2007 to 2012 at the Human Genetics Unit was maintained and analyzed retrospectively. Clinical data and genetic diagnostic results were reviewed. Statistical analysis was performed using descriptive statistics and the Student t-test.

Results Twenty three (62%) had a family history. The presenting symptoms noted were motor symptoms in 34 (91.9%) and psychiatric or behavioral disorders in 3 (8.1%). The age of presentation of symptoms ranged from 15 to 72 years with 2 patients with Juvenile onset (<20 years) Huntington’s disease and 3 with late onset (>60 years). The mean age of onset of symptoms was 43±13.5 years. The age of presentation of those with a family history was significantly lower than that of those without a family history (p<0.05). A significant inverse correlation was seen between the size of the CAG repeat in the HDD gene which caused Huntington’s disease and the age of onset (p<0.0005).

Conclusions The clinical and molecular features seen in this group of patients with Huntington’s disease was similar to that reported in scientific literature.

Keywords: Huntington’s disease, CAG repeats, autosomal dominant
Background

Huntington’s disease (HD) is a progressive neurodegenerative disease. The causative molecular mechanism is autosomal dominant inheritance of (CAG)n triplet repeat expansion mutations\(^1\). The disease manifests as impaired coordination, chorea, cognitive decline and neuropsychiatric symptoms\(^2\). The age of onset is inversely related to the CAG repeat length. This relationship accounts for 50 – 70% of the age variance but does not provide information on the initial symptoms, course or duration of the disease\(^3\).

Worldwide prevalence of HD is 5 – 10 per 100,000 but varies geographically. Population studies suggest that the mutation originated in Europe and the highest prevalence is seen in populations of Western European descent with an incidence of 70 per 100,000. In Africa and Asia the incidence is low as less than 1 per 100,000\(^4,5\).

In Sri Lanka, data regarding demographic, clinical and genetic characteristics of those receiving genetic testing for HD is not published. This study is an initial effort to analyze these aspects in a cohort of patients.

Methods

Records of a total of 37 consecutive patients seen from June 2007 to February 2012 were assessed. They were outpatients in our genetics clinic referred by either neurologists or psychiatrists. The patients were undergoing diagnostic testing in a genetic diagnostic laboratory as part of their routine care. They had all provided written informed consent for genetic testing after pre-test counseling, and we provided post-test counseling after the test result was available. Research carried out in accordance with the Declaration of Helsinki of the World Medical Association.
The sample had symptomatic patients with motor symptoms, cognitive decline or psychiatric symptoms with or without a family history. Data was collected on gender, age of onset of symptoms, signs and symptoms at onset, age at presentation for genetic testing and CAG repeat size.

A CAG repeat length of 36-39 was considered as reduced penetrant disease causing alleles, while >40 was considered as fully penetrant disease causing alleles. Allele length less than 36 was considered as non-disease causing alleles.

Statistical analysis was conducted using descriptive statistic $\chi^2$ analysis and Student’s t – test. A p value of <0.05 was considered as statistically significant.

**Results**

A total of 37 patients 16 (43.2%) were male. The presenting symptoms were neurological in 34 patients (91.9%) while psychiatric symptoms or behavioral disorders were seen in 3 (8.1%). The overall mean age was 43±13.5 years. (Range 15 - 72).

Distribution of patients with reduced penetrant alleles (RP): fully penetrant alleles (FP) were 5 (13.5%):30 (81.1%). Heterozygous allele mutation was seen in all positive patients. Two patients (5.4%) with HD phenotype revealed normal CAG repeat length of the $HDD$ gene. Mean age at onset of symptoms of the two patient populations (FP and RP) were 40.4 ± 10.8 years (range 15 – 57 and 64±6.8 years (range57 - 72) respectively. Juvenile onset HD (<20 years) was seen in 2 patients in the FP mutation group while late onset HD (> 60 years) was seen in 3 patients in the RP group. A significantly higher age of onset was observed in the RP patient population (Student’s t-test, p<0.0005).
Positive family history was present in 1(20%) of RP and 21 (70%) of FP patients. The mean age of onset in patients with a positive family history (RP and FP) was 39.4±12 years. Those with a negative family history had a mean age of onset of 52.1±11.9 years. The Student’s t-test showed a significant increase in the mean age of those with a negative family history (p<0.01).

**Discussion**

In this study we describe the clinical and genetic characteristics of individuals presenting for diagnostic testing of HD in Sri Lanka.

Symptoms at onset were predominantly motor as expected, however a few patients presented with behavioral/psychiatric symptoms. Studies have shown that psychiatric symptoms (e.g., depression, anxiety and obsessive–compulsiveness) are present in patients with HD disease and may be the earliest markers of the disease. This highlights the need of awareness amongst neurologist and psychiatrist for the early identification of patients.

Inverse correlation between age of onset of symptoms and CAG length and was present. This correlates with previous study results. Patients in the RP group had a lower prevalence of positive family history than the FP group. Ages of onset of symptoms were also significantly higher. It has been stated that those with reduced penetrant alleles >20% of individuals remain undiagnosed due to their mild clinical phenotype. These factors indicate that many patients may be missed in the absence of genetic testing.

Thirteen of the 35 patients (37.8%) did not have a family history of HD. Creighton et al and the data reported by a comprehensive British Columbia population study report an incidence of approximately one quarter of affected individuals with a negative family history. The causative factors for negative family history may be new mutation, non-paternity, a parent
dying prior to the onset of symptoms or failure to diagnose in a parent. The result signifies that even in the absence of a family history the diagnostic probability of HD should be entertained if clinical features are compatible.

The mean age of onset of disease in those with a negative family history was significantly higher than those with a positive family history. The initial expression of a mutation in a proband of a family occurs at a late age with each succeeding generation the age of onset reduces\textsuperscript{11}. This is in accordance with anticipation, a feature of triplet repeat mutation disease.

**Conclusion**

From this study we may conclude that molecular results for HD in Sri Lanka are similar to previously published data. Psychiatric symptoms as possible presenting features of HD are important in diagnosis. Increased age of presentation with absent family history is clinically and genetically plausible though they fall outside the conventional clinical definitions of Huntington’s disease.

Hence with a genetic diagnosis a greater number of new diagnoses are established with significant implications for both incidences of HD and for an increased number of at – risk individuals.

**Competing Interest**

No financial or non financial competing interests were received for the project.
Authors Contribution

DS analyzed the molecular genetic studies, statistical analysis and drafted the manuscript. RJ provided review and critique of the manuscript. VD conceived of the study, and participated in its design and coordination and helped to draft the manuscript. All authors read and approved the final manuscript.

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