

“Clinical Profile of Genetically Proven Huntington’s Disease Patients from Eastern India”

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*Dr Shyamal Kumar Das was deeply involved with the study including manuscript preparation; however, he met an untimely demise. We wish to keep his name in authorship for his significant contribution.

Abstract

Background and Aims: To study the clinical profile of genetically proven Huntington’s disease (HD) patients from eastern India. **Methods:** This cross sectional study selected patients of HD after genetic confirmation of expanded CAG repeats in Huntingtin (*HTT*) gene. We performed detail clinical evaluation including cognitive and neuropsychological assessment, and imaging of brain. **Results:** This study included 75 patients (male: 57.3%; female: 42.7%). Mean age at onset was 37.12 (range 16-62) years; juvenile variety (onset below 20 years) was detected in 5.3%. Paternal transmission was commoner. Manifestations at onset were motor in 81.3% patients, behavioral in 10.7% and cognitive impairment in 8%. After chorea, next common movement disorder was dystonia. Frontal lobe dysfunction was found in 77.3% patients. Behavioral disturbances were observed in 77.3% patients and commonly manifested as depression, irritable behavior and anxiety. Among the three onset groups (motor/behavioral/cognitive), there was no significant difference regarding age at onset, gender distribution, pattern of inheritance (paternal/maternal), and at the time of evaluation, all groups had essentially similar pattern of clinical features. Mean CAG repeat of the patients was 48.25 (range 40-79). Our study showed some differing clinical characteristics compared to previous studies from the Indian subcontinent. **Conclusion:** Clinical features in our study showed differences from previous studies from the Indian subcontinent. We had more cognitive-onset patients. However, behavioral onset was lower in our study. Motor, behavioral and cognitive onset groups of HD were comparable regarding demographics, family history, CAG repeat lengths and major clinical features at the time of evaluation.

Keywords: Behavioral, Cognitive, Huntington’s disease, Motor, Onset symptom

INTRODUCTION

Huntington’s disease (HD) is a progressive neurodegenerative disorder of autosomal dominant inheritance associated with motor disturbance, cognitive decline and behavioral abnormalities.^[1] HD is caused by trinucleotide expansion of CAG (cytosine-adenine-guanine) in Huntingtin (*HTT*) gene on chromosome 4p 16.3. The Asian prevalence of HD of 0.4 per 100,000 (95% CI- 0.26-0.61) is much lower compared to the overall prevalence of 5.70 per 100,000 (95% CI- 4.42-7.35) in Europe, North America and Australia.^[2] Although there is no epidemiological study from India, a prevalence rate of 1.75 per 100,000 has been shown in Indian immigrant population of UK.^[3] Since studies from India are rare, we decided to study the clinical profile of genetically-proven HD patients from a tertiary care neurological center in Eastern India.

METHODS

This cross-sectional study was conducted over 4 years from 2011 to 2015. Patients were selected during their visit to the Bangur Institute of Neurosciences, Kolkata (BIN), a referral neurological institute, according to the clinical criteria for HD described by Folstein *et al.*,^[4] and were included in this study after genetic confirmation of expanded CAG repeats. Molecular genetic analysis for the expanded CAG repeat length

was done in all patients with typical clinical features of HD even in the absence of a family history of HD. They all gave written informed consent for genetic testing following pre test counseling and were offered post test counseling after test results were known. Genetic test was done in our institute’s genetic laboratory. Alleles with a CAG repeat length of 36-39 was defined as reduced penetrant (RP) and ≥ 40 as fully penetrant (FP). Allele length of less than 36 was considered nonpathogenic.^[5] Ethical approval for study was given by Ethics committee of our Institute. We collected the data according to Huntington Study Group^[6] in standardized format. Clinical data on patients’ demographics, age of onset of symptoms, age of presentation, pattern of presentation of symptom and

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signs were noted in a semi-structured proforma. CAG repeat length of corresponding patients were analyzed and recorded. We used Unified Huntington's Disease Rating Scale (UHDRS) for assessment of patients. The Kolkata Cognitive Screening Battery^[7] was administered with detail cognitive and neuropsychological assessment in every patient. We carried out imaging of brain-CT scan or MRI according to feasibility. For statistical analysis, data were analyzed by SPSS 20.0 and a P value ≤ 0.05 was considered statistically significant.

Methodology of genetic analysis

Patients were referred from Movement Disorders clinic of BIN, followed by recruitment from the Neurogenetic clinic of the institute. After signing informed consent, about 5 ml of venous blood samples were collected from patients and preserved in EDTA at -20°C . DNA was isolated from the blood samples by Phenol Chloroform method and stored at -20°C .

Polymerase chain reaction (PCR): The PCR amplification was carried out in a final reaction volume of 25 μl containing ~ 100 ng of genomic DNA, 1x PCR buffer, 2 mM MgCl_2 , 0.2 mM dNTPs, 10 picomoles forward primer, 10 pico moles reverse primer, 1.25 U taq polymerase and total volume was made up with distilled water. The PCR conditions are as follows: 95°C for 5 min., followed by 30 cycles of amplification (95°C for 30 sec., 62.5°C for 30 sec. and 72°C for 1 min). The final extension was carried out at 72°C for 7 minutes.

RESULTS

Among the 75 patients included in this study, 43 (57.3%) were male and 32 (42.7%) female. Mean (SD) age at onset of patients was 37.12 (± 8.89 ; range 16-62) years, while mean (SD) age of presentation was 43.21 (± 10.14 ; range 23-65) years. Mean duration of symptoms (between onset of disease and diagnosis) was 5.18 (± 3.18 ; range 1-15 years). Juvenile variety (age at onset below 20 years) of Huntington's disease (JHD) was detected in 4 (5.3%) patients; among them 3 patients presented with chorea and one with akinetic rigid syndrome, and was transmitted from father in all 4.

Family history

Disease was transmitted from father in 44 (58.7%) patients and from mother in 17 (22.7%). Both parents were apparently unaffected in 14 (18.7%).

Symptoms at onset

Most of our patients (81.3%) had initial motor manifestations-majority with chorea except one patient (JHD) who presented with akinetic rigid syndrome. 8 (10.7%) patients showed behavioral symptoms at onset, while 6 (8%) had cognitive impairment initially.

Neurological manifestations

Ocular movement

Most common ocular abnormality was slow saccade in both horizontal and vertical gazes (vertical > horizontal) in 72 subjects (96%). It is one of the earliest finding as well. Smooth

pursuit was affected in only 14 (18.7%) patients, mainly towards the later part of the disease. Upward restriction of gaze was present in 10 (13.33%). Only 3 (4%) patients had normal ocular movement.

Speech

Dysarthria was observed in almost half of the patients (n: 34, 45.3%), among them about 17 patients (22.6%) had unclear speech, but could be understood. 10 patients (13.3%) had to repeat the sentence for understanding, and in 7 patients (9.3%) speech was totally incomprehensible.

Motor manifestations

Chorea was present in 74 (98.7%) patients and was the most common presenting feature, distributed equally in all age groups and gender. Only one patient in juvenile age group presented with akinetic rigid syndrome. Chorea was usually generalized involving bucco-oro-lingual, extremities and trunk. After chorea, next most common motor feature was dystonia [Figure 1]. Dystonia was observed in more than half of patients (n: 43, 57.3%). Most common site of dystonia was in cervical region followed by extremities; generalized dystonia was present in 11 patients (14.66%). Dystonia is more common either below 20 years or above 50 years, equally distributed in both sexes. Most of our patients were treated with Tetrabenazine. Some patients received haloperidol. However, there was no significant difference regarding usage of haloperidol between patients with and without dystonia. We found 7 (9.3%) patients to have tics. Tics are difficult to differentiate from chorea in HD patients and these were accepted only after confirmation by movement disorders specialist.

Bradykinesia and rigidity were each present in 34 (45.3%) patients. Rigidity was appendicular in most of our patients, except 6 patients who showed both appendicular and axial rigidity. Gait was abnormal in most of our patients (n: 68, 90.7%). Walking difficulty due to severe chorea was documented in 44 (58.66%). Gait was slow in 23 (30.66%) patients due to dystonia and/or bradykinesia. Tandem walking was impaired in 21 (28%) patients. Pyramidal system involvement was present in 24 (32%), and it was usually noticed in advanced disease. It is challenging to assess cerebellar function in the presence of chorea. However, distinct signs of cerebellar dysfunction were evident in 6 (8%) patients.

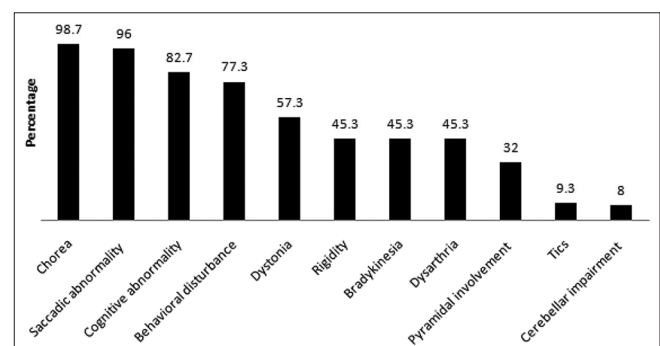


Figure 1: Clinical Manifestations

Cognitive impairment

Cognitive assessment showed abnormality in 62 subjects (82.67%). Detail cognitive evaluation including attention, memory, object naming test, verbal fluency, language, executive function and visuo-construction were performed, which suggested frontal lobe dysfunction in 58 (77.33%) patients in the form of poor attention, impaired abstract thinking and executive dysfunction. The next most common manifestation was episodic memory impairment (n=16; 21.33%), which usually occurred in advanced disease.

Behavioral assessment

Behavioral disturbances were observed in 58 (77.3%) patients and most commonly manifested as depression (n= 48; 64%), followed by irritable behavior (n= 46, 61.3%) and anxiety (n= 39, 52%). Obsession-compulsions were observed in 19 (25.3%) patients. Apathy was present in 12 (16%) patients.

Symptom at onset: Motor versus Behavioral versus Cognitive

61 (81.3%) patients had onset with motor symptoms, whereas 8 (10.7%) patients showed behavioral symptoms at onset, and 6 (8%) had onset with cognitive impairment. There was no significant difference regarding age at onset, gender distribution, and parental pattern of inheritance (paternal v/s maternal) in the three groups [Table 1]. However, all juvenile HD patients had motor onset. The expanded CAG repeat lengths were similar in the three groups.

At the time of presentation, depression was the most common behavioral manifestation in the motor-onset group, whereas irritable behavior was the commonest feature in behavioral-onset group, and cognitive-onset patients had equal proportions of depression, anxiety and irritable behavior. Irritable behavior was present in all except one behavioral onset patient. All cognitive-onset patients showed features of frontal lobe dysfunction compared to 73.8% in motor-onset group. There were some differences among the three groups such as anxiety being less common in motor-onset group. However,

these observations did not reach statistical significance. Hence at the time of evaluation, all the groups had essentially similar pattern of motor, cognitive and behavioral manifestations.

Radiology

Evidence of caudate atrophy was present in 33 (44%) and diffuse cerebral atrophy in 31 (41.3%) patients. Imaging was normal in 11 (14.7%) patients (out of which 7 were CT scans). Caudate and diffuse atrophy correlated with duration of disease.

Trinucleotide repeats

Expansion of CAG repeats was examined in all patients. Mean CAG repeat was 48.25 (SD \pm 7.2; Median 46; range 40-79). Mean (\pm SD) CAG repeat of patients with affected father was 49.95 (\pm 8.34) and that of patients with affected mother was 47.12 (\pm 4.69) (difference not significant; *P* value = 0.535). We found significant correlation between age at onset and numbers of CAG repeats with younger age at onset having larger CAG repeats ($r = -0.2926$, *P* Value = 0.011). There was no significant relationship between numbers of CAG repeat and the various clinical manifestations (motor, cognitive, behavioral) or severity of disability (motor, cognitive, behavior, functional or occupational).

DISCUSSION

We studied 75 cases over a period of four years. Age of onset in this study is similar to previous studies from India^[8] and the neighboring country of Sri Lanka.^[9] Only 5.3% of patients were of juvenile onset. Frequency of juvenile variety varies in different studies, and we found fewer JHD as compared to some other studies.^[8,10] A study from Argentina documented much higher frequency (16.9%) of JHD.^[10] The clinical features of JHD were similar to other studies.^[11,12] Overall, paternal inheritance was nearly 3 times commoner than maternal inheritance, and compared to the Indian study, paternal inheritance was commoner in our study though we found fewer JHD.^[8] Parental inheritance pattern varies in different studies

Table 1: Features at presentation: comparison according to symptom at onset

	Symptom at Onset			P
	Motor (n=61, 81.3%)	Behavioral (n=8, 10.7%)	Cognitive (n=6, 8%)	
Age at onset (Years) (Mean \pm SD)	37.11 \pm 9.25	36.75 \pm 8.05	37.67 \pm 7.03	0.98
Gender Distribution (Male: Female)	35:26	5:3	3:3	0.99
Family History (Father: Mother: Negative)	36:13:12	5:2:1	3:2:1	0.948
Dystonia	35 (57.4%)	5 (62.5%)	3 (50%)	0.99
Bradykinesia	27 (44.3%)	4 (50%)	3 (50%)	0.99
Rigidity	27 (44.3%)	4 (50%)	3 (50%)	0.99
Frontal dysfunction	45 (73.8%)	7 (87.5%)	6 (100%)	0.434
Depression	38 (62.3%)	6 (75%)	4 (66.7%)	0.899
Obsessive/Compulsive Symptoms	15 (20%)	2 (25%)	2 (33.3%)	0.881
Anxiety	29 (47.5%)	6 (75%)	4 (66.7%)	0.313
Irritable Behavior	35 (57.4%)	7 (87.5%)	4 (66.7%)	0.293
Radiology (Caudate atrophy: Diffuse atrophy: Normal)	28:25:8	3:3:2	2:3:1	0.855
CAG repeats (Mean \pm SD)	48.57 \pm 7.81	46.75 \pm 3.73	47 \pm 2.9	0.948

with some showing paternal predominance and others showing the reverse.^[8,10,13] Usually, in older age, maternal transmissions were commoner. Earlier age at onset cases are predominantly transmitted from fathers probably due to higher CAG repeat lengths as a result of greater CAG instability at meiosis during spermatogenesis.

The prominent clinical features were movement disorders (chorea, dystonia), saccadic abnormalities, cognitive impairment and behavioral manifestations (depression, irritable behavior, anxiety). Initial presentation of motor symptoms is comparable to similar studies from the Indian subcontinent [Table 2]. Commonly motor symptoms are more evident in early stages of HD.^[14] Chorea is the most frequent motor manifestation. In our study, dystonia was quite common and second to chorea in frequency. We found more frequent dystonia but lesser bradykinesia than the other Indian study.^[8] Our study found tics in 9.3% patients, whereas, no case of tics was reported from the other Indian study.^[8] Chorea and tics are both hyperkinetic disorders with often jerky component and sometimes difficult to differentiate clinically. However, all patients in our study were evaluated by expert movement disorders specialist. The report on frequency of tic disorder is scarce and one report from a Movement Disorders clinic in USA has shown that only one out of 68 cases of secondary tic disorders was due to HD.^[15] Another clinical variant of HD presenting as adult onset spasticity and cerebellar ataxia similar

to spinocerebellar ataxia^[16] had not been documented in this study though involvement of pyramidal tract and cerebellar system were present.

Slow saccades (96%) were one of earliest and most common examination finding. This is similar to other studies showing saccadic abnormalities to be the most common oculomotor dysfunction in HD.^[17] In fact, normal eye movement was less likely in HD as reported by other studies.^[18,19]

Initial presentation with behavioral abnormalities (10.7%) was lower than another Indian study with 26.1% of its patients having initial behavioral symptoms.^[20] This discrepancy may be due to prevalent social customs of hiding psychiatric problems to doctor or failure to recognize early psychiatric manifestations preceding motor symptoms in our population. In the course of the disease, 58 (77.3%) showed behavioral symptoms. Depression was the most common behavioral symptom (64%) corroborating with other studies, but suicidal tendency was rare (13.3%) and none of our patients committed suicide. We did not find any correlation of severity of behavioral manifestations and duration of disease. The frequency of behavioral disturbances has varied between 33% and 76%, depending on the methodology of the study.^[21]

Cognitive dysfunction was common in our study. Although, family members may be ignorant about the cognitive symptoms due to inadequate awareness, yet objective

Table 2: Comparison among studies from the Indian subcontinent

	Study from Southern India ^[8]	Study from Eastern India (present study)	Study from Sri Lanka ^{[9]*}	P
No of patients	26	75	35 (Fully penetrant- 30)	-
Gender Distribution	M:F- 17:9 (1.9:1)	M:F- 43: 32 (1.34:1)	M:F- 14:16 (1:1.14)	0.361
Mean Age of onset (SD) (in years)	36.9 (± 15.3)	37.12 (± 8.89)	37.5±10.2	0.977
Frequency of juvenile onset	4 (15.4%)	4 (5.3%)	2 (6.7%)	0.283
Positive family history	23/26 (88.5%)	61/75 (81.3%)	21/30 (70%)	0.208
Inheritance				
Paternal	11 (47.8%)	44 (72.1%)	13 (61.9%)	0.11
Maternal	12 (52.2%)	17 (27.9%)	8 (38.1%)	
Symptom at Onset				
Motor	23 (88.5%) (Chorea)	61 (81.3%) [Chorea- 60 (80%); Akinetic rigid syndrome- 1 (1.3%)]	28 (93.3%) [Chorea 26 (86.7%); Dystonia/parkinsonism -2 (6.7%)]	0.257
Behavioral	3 (11.5%)	8 (10.7%)	2 (6.7%)	0.851
Cognitive	-	6 (8%)	-	-
Signs				
Ocular	21 (80.8%)	72 (96%)	-	0.025
Dysarthria	21 (80.8%)	34 (45.3%)	-	0.002
Chorea	25 (96.2%)	74 (98.7%)	-	0.451
Tics	-	7 (9.3%)	-	-
Rigidity	8 (30.8%)	34 (45.3%)	-	0.194
Bradykinesia	25 (96.2%)	34 (45.3%)	-	<0.001
Dystonia	4 (15.4%)	43 (57.3%)	-	<0.001
Gait disturbance	19 (73.1%)	68 (90.7%)	-	0.025
Cognitive abnormality	12 (46.2%)	62 (82.7%)	-	<0.001
Behavioral disturbance	19 (73.1%)	58 (77.3%)	-	0.66
CAG repeats of patients [Mean (SD)]	48.4 (±8.7)	48.25 (± 7.2)	44.6 (±5)	0.047

*Comparison done with fully penetrant cases

evidence of cognitive dysfunction could be documented in majority (82.7%) of patients in the present study. This was almost twice compared to a previous study from India.^[8] Moreover, our study had 8% cognitive onset patients compared to none in that study.^[8] Cognitive dysfunction was more disabling in advanced disease. Features of frontal lobe involvement were common. Few patients had episodic memory impairment (21.33%), but semantic memory and language were normal even in advance disease. Previous studies show subcortical cognitive dysfunction with relative sparing of cortical function.^[22,23] It is considered to be due to involvement of cortico-striatal connection and basal ganglia. Psycho-motor slowness, poor attention and executive dysfunction were early features. Thus, we suggest detailed cognitive testing especially frontal lobe function assessment in every HD patient.

We found no difference among motor, behavioral and cognitive onset groups regarding demographics, family history and CAG repeat lengths. With progression of the disease, the cognitive and behavioral onset cases showed various motor abnormalities, and also patients of motor onset developed behavioral abnormalities and cognitive impairment (especially on detail cognitive assessment). Hence at the time of evaluation, the various clinical features were comparable among the three groups. Although anxiety and frontal lobe dysfunction appeared to be less common in motor onset cases, this did not reach statistical significance. Increased frequency of motor and cognitive dysfunction compared to behavioral disturbances has been observed in a Peruvian study on late onset Huntington disease.^[24] However, differential involvement of increased psychiatric abnormalities and preserved cognitive function has been documented in Israeli Karaite community.^[25]

CAG repeat length in our study was similar to the other Indian study,^[8] but higher than the Sri Lankan study.^[9] A previous Indian study had mean CAG repeat of 16.8 ± 2.08 in normal chromosomes and their range of CAG repeats in HD patients varied from 41-56.^[26] Higher CAG repeat lengths in our patients correlated with earlier age of onset. 3 out of 4 of our JHD had CAG > 60. Other patients with CAG > 60 did not have JHD. In fact, the largest CAG repeat (79) had an onset beyond the third decade. This variation of genotypic-phenotypic correlation might be explained by the distribution of *HTT* haplotypes and CCG repeats, or other possible modifier genes present in our population. We found no correlation between the number of CAG repeats and the various clinical manifestations or severity of disability. Similar result was obtained in another previous study.^[27]

This study had some limitations. Our institute is a tertiary neurological institute in our state and most of the suspected cases are referred to us for genetic study. However, this is not absolute and cases might have been missed. Socioeconomic and financial factors may also affect the referral rates, although we regularly see patients from all socioeconomic strata. It is difficult to comment on affected individuals not presenting to our clinic as population based study is needed to estimate

undiagnosed cases in the population. Chorea and tics are difficult to differentiate clinically. Also, the presence of chorea makes it difficult to evaluate cerebellar signs. Hence we accepted tics and cerebellar dysfunction only when definite clinical features were evident, after careful assessment by movement disorder specialist.

To conclude, clinical features of patients in our study showed some differences from previous studies from the Indian subcontinent. Compared to another Indian study, paternal inheritance was commoner in our study though we found fewer JHD. Initial presentation with behavioral abnormalities was lower in our study. However, we had more cognitive onset patients.

Although initially presenting with chorea, many of our patients also had dystonia. Saccadic abnormalities were an early feature and present in the vast majority. On detailed evaluation, cognitive impairment was documented in most of the patients including motor onset patients, and assessment of frontal dysfunction is essential. We found no significant difference among motor, behavioral and cognitive onset groups of HD regarding demographics, family history, or CAG repeat lengths, and in spite of varying onset, at the time of evaluation, the clinical features were comparable among the three groups. Overall, greater CAG repeat length led to earlier age of onset, but it did not affect the severity of disability.

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Conflicts of interest

There are no conflicts of interest.

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