

NON-CHOREIC MOVEMENT DISORDERS AS INITIAL MANIFESTATIONS OF HUNTINGTON'S DISEASE

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ABSTRACT - We describe seven patients with genetically confirmed Huntington's disease (HD) who had non-choreic movement disorders as presenting symptoms or signs. Patients with movement disorders other than chorea in the early stages tended to have larger CAG trinucleotide repeat expansion in comparison with more "typical" HD patients.

KEY WORDS: Huntington's disease, movement disorders, chorea.

Distúrbios do movimento não-coreicos como manifestação inicial da doença de Huntington

RESUMO - Nós descrevemos sete pacientes com doença de Huntington, geneticamente confirmada, cuja apresentação motora inicial foi diferente de coreia. Pacientes com manifestação motora inicial diferente de coreia apresentaram maior número de expansões repetidas de CAG trinucleotídeo quando comparados com aqueles com sintomatologia motora "típica".

PALAVRAS-CHAVE: doença de Huntington, distúrbios do movimento, coreia.

Huntington's disease (HD) is an autosomal dominantly inherited, progressive, neurodegenerative disorder characterized by cognitive decline, psychiatric disturbances, and involuntary movements — classically choreic. Symptoms usually present with slow progression leading to dementia and death approximately 15-20 years after disease onset¹. HD results from an expanded and unstable trinucleotide repeat in the IT15 gene on chromosome 4 (4p16.3) that encodes a large protein called huntingtin (Htt) with more than 3000 amino acids². The function of normal Htt and the mechanism whereby mutant Htt mediates harmful effects remain unclear. Htt may act as a molecular scaffold, regulating several cellular processes including endocytosis, vesicle transport, excitatory synapses, transcriptional events and mitochondrial function²⁻⁵. Normal IT15 alleles carry up to 35 repetitions of the CAG trinucleotide. Persons with more than 39 repeats will develop HD, while those with intermediate repeats (36 to 39) may or may not develop the disease. These middle range expansions are unstable and individuals with such repeat lengths may have affected offspring. These offspring may represent de novo expansions, expansions of extremely late onset or "non-penetrant" muta-

tions. On the other hand, patients with juvenile onset HD have greater expansions [>100 (CAG)_n] typically inherited from an affected father since a marked expansion of the repeat length is more likely to occur in spermatogenesis^{1,3,4}.

Symptoms begin insidiously, most commonly between the ages of 35 and 50 years, with substantial variation that depends, in part, on the CAG repeat expansion length¹. Chorea, or choreoathetosis, is the movement disorder most frequently associated with HD, although some individuals may exhibit other forms of motor symptoms as their initial presentation^{1,6,7}.

We describe the clinical features of a cohort of Brazilian HD patients who initially presented with movement disorders other than chorea. We also investigate the correlation of the clinical profile of this subgroup with their respective CAG expansion length in comparison with "typical" choreic HD patients.

METHOD

We evaluated 44 individuals from a total of 30 families followed at the Movement Disorders Unit from 1996 to 2000 with final diagnosis of HD. All patients presented motor symptoms as their initial manifestation of the disorder and were assessed by the same author (NB) using

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a standardized protocol. In addition to clinical manifestations at the time of examination, assessment included particular focus on characteristics of initial motor symptoms as collected from the patients, caregivers and medical records, trying to fit the descriptions in to one of the following movement disorders⁸:

1. Chorea: irregular, random, involuntary, jerky movements that may vary from slow, distal and of low amplitude to more severe and proximal ballistic movements;

2. Dystonia: abnormal sustained muscle contractions, causing twisting and repetitive movements or abnormal postures;

3. Tremor: rhythmic oscillations of a body part produced by alternating or synchronous contractions of reciprocal muscles that may occur at rest or action (postural and/or intentional);

4. Myoclonus: sudden shock-like movements due to muscle contractions or inhibition of ongoing muscle activity;

5. Tics: brief, nonrhythmic, intermittent, repeated, stereotyped non-voluntary movements or sounds. May be "simple," (cough, grunt, facial twitch, or shoulder shrug), or "complex" (word, phrase, or a stereotyped sequence of movements). Usually a sense of a build-up of the need to tic is described, followed by temporary relief until the sense of the need for the movement begins again;

6. Parkinsonism: coexistence of at least two of the following cardinal signs: bradykinesia, tremor, rigidity and postural disturbances.

Ten micro liters of whole blood were collected into EDTA from the 44 individuals after informed consent was provided. Genomic DNA was extracted from blood lymphocytes by standard methods⁹. The CAG repeat size was assessed by polymerase chain reaction (PCR) analysis using the HD1 and HD3 primers flanking the CAG repeat⁹. PCR products were separated on polyacrylamide gel and stained with silver nitrate. Sequencing standards were selected to allow exact determination of the size of the PCR product, including an M13 sequencing ladder and appropriate normal and abnormal controls whose CAG repeats had been sequenced independently⁹.

A parametric test (unpaired two-tailed Student's t-test) was used to compare the onset ages in the two subgroups. A non-parametric test (Mann-Whitney U-test) was used to compare the CAG triplets of the two groups. A non-parametric

test (Mann-Whitney U test) was also used to test the mean difference in CAG repeats among patients grouped according to onset symptoms and age at onset classes. The tests were considered significant at $p < 0.05$.

RESULTS

Out of the 44 patients, 54.5% were male. Age of onset ranged from 22 to 57 years, with an approximately normal distribution and a mean age of onset of 36.3 ± 8.3 years. Expanded CAG repeats alleles ranged from 41 to 55 (mean 46.5) and were responsible for 64 per cent of the variation in age at onset of motor symptoms.

Seven out of the 44 (15.9%) patients described their presenting motor symptom as a movement disorder different outside the chorea-ballismus spectrum. We were able to identify three different forms of movement disorders for this group: parkinsonism, dystonia and tics (Table 1).

a. Patients with parkinsonism (1, 2, 3, 4) – Four patients (three male, two with maternal inheritance) presented with parkinsonism, all in a symmetrical rigid-akinetic form with ages of onset ranging from 28 to 42 years (mean 33.2). One subject presented significant postural instability and no one showed resting tremor. Patient number 4 had a previous diagnosis of Parkinson's disease. No patient was receiving neuroleptic drugs at the time of symptoms onset. All patients carried heterozygous expanded alleles ranging from 49 to 55 (mean 51.2) (CAG)_n.

b. Patients with dystonia (5, 6) – Dystonia was detected in two patients with ages of onset 24 and 33 years, one female and both with paternal inheritance. Patient 5 presented with generalized dystonia affecting the trunk, cervical (retrocollis) and right upper extremity, progressing to proximal lower limbs after about 2 years. Patient 6 started with cervical dystonia combining mild retrocollis and mild to moderate left laterocollis and torticollis. After about 3

Table 1. Characteristics of the patients with non-choreic movement disorders.

Patient number	Sex	Age of onset	Motor symptom	CAG size	Inheritance
1	M	33	Parkinsonism	49	Maternal
2	M	28	Parkinsonism	55	Maternal
3	F	30	Parkinsonism	51	Paternal
4	M	42	Parkinsonism	50	Paternal
5	F	24	Dystonia	53	Paternal
6	M	33	Dystonia	48	Paternal
7	M	33	Tics	48	Paternal

Table 2. Age at onset of first motor symptoms and CAG expansion.

	N	Mean	SD	Range	P
Onset of symptoms					0.267
Non-choreic	7	33.1	±6.8	(24-42)	
Choreic	37	36.9	±8.5	(22-57)	
CAG Expansion					0.007
Non-choreic	7	50.1	±3.3	(45-55)	
Choreic	37	45.8	±3.5	(40-54)	

Mann-Whitney U-test.

years this patient had documented dyskinetic facial and tongue movements as well as mild axial trunk jerks that persisted until the next clinic visit after 6 months. Both patients carried heterozygous CAG expansions: 53 in the first and 48 in the second described above. None of the patients were taking neuroleptics at the time of symptoms onset.

c. Patient with tics – One patient with tics as the initial manifestation at the age of 33 years. This is a male patient with paternal inheritance. Movements were described as blinking and left lower face contractions accompanied by vocal tics (throat clearing and sniffing). No signs of obsessive-compulsive disorder or chorea were documented on follow up clinical assessments. This patient carried a heterozygous CAG expansion with 48 (CAG)_n.

All seven patients underwent brain imaging (magnetic resonance imaging or computerized tomography) and six patients had normal results. In one patient, brain CT showed signs of typical caudate atrophy with compensatory lateral ventricle enlargement and a variable degree of generalized brain atrophy.

Considering the whole group of seven patients together, mean age of onset was 33.1±6.8 years, 3.8 years younger than the remaining 37 patients with HD and “typical” choreic motor onset (mean 36.9±8.5). This difference was not statistically significant (p=0.267). Considering molecular differences, the study group presented significantly larger expansions [50.1±3.3 (CAG)_n] in comparison with the remaining patients [45.8±3.5 (CAG)_n] (p=0.007) as shown in Table 2. Figure shows the relationship between age of onset of choreic and non-choreic motor symptoms and CAG repeat size.

DISCUSSION

In this study we evaluated the clinical and molecular characteristics of patients with genetically confirmed HD in whom the initial motor manifestation

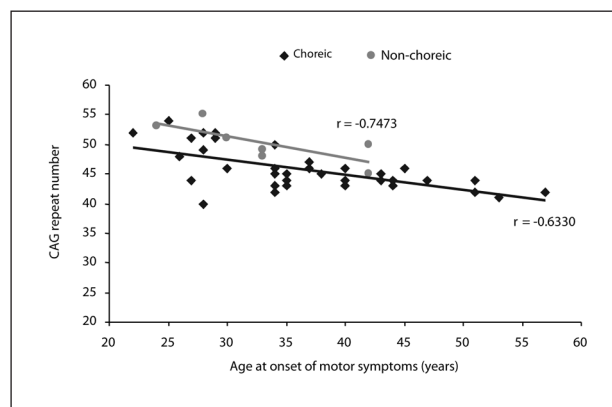


Figure. Relationship between age of onset of motor symptoms and the CAG repeat number.

was a movement disorder other than the classically described chorea. We found three different forms of movement disorders and were able to show that in this particular subset of patients, age of onset may be earlier than in “typical” HD, although the difference for our sample did not reach statistical significance. We also demonstrated that these variable manifestations at onset reflect larger CAG expansions, which may be originated by meiotic instability as most of our patients (71%) had paternal inheritance.

HD is a devastating neuropsychiatric disorder for which therapeutic interventions, other than providing mild symptomatic relief, have been rather fruitless to date^{10,11}. One of the main focuses of current basic and clinical research in HD relies on neuroprotective approaches, which invariably require early or even pre-symptomatic intervention¹¹. While definitive diagnosis requires genetic testing, it is widely accepted by clinicians that the clinical diagnosis of HD is usually made in the presence of a specific motor disorder¹. It should be realized, however, that the onset of motor abnormalities is not a sensitive measure of disease onset. Prior to these manifestations, mood disorders, subtle cognitive problems and oculomotor abnormalities have often already appeared, ac-

accompanied or followed by mild motor abnormalities that only gradually evolve into a full-blown recognizable extrapyramidal syndrome¹². In addition to these subtle clinical manifestations, movement disorders that are not as typical for HD as chorea may delay diagnosis or make clinical suspicion even harder to ascertain the onset.

Recent studies have already reported atypical clinical features in HD affected individuals, these studies, however, have reported these features during the disease course and not, necessarily, at the onset^{1,12,13}.

Although chorea is the most common involuntary movement in HD (90%), virtually any expression of basal ganglia dysfunction can occur^{1,12}. One study of 205 HD patients found 15 with atypical motor symptoms at onset. These included parkinsonism, ataxia and dystonia, in patients with a higher mean CAG repeat expansion than others with chorea⁷. Parkinsonism is associated with the rare Westphal variant form of HD¹. In our study, patients 1, 3 and 4 had an onset with age ≥ 30 years, illustrating a highly atypical and misleading presentation. Signs of parkinsonism commonly develop during the course of HD, however, the cases presented here show that this syndrome may be present also at onset, in the absence of chorea or a Westphal variant. Cases of adult-onset HD with prominent dystonia and a paucity of chorea may represent 1 in 8 cases found by researchers in specialty clinics¹³. As for patient 6, showing at onset segmental dystonia, a recent report described a HD patient with early-onset blepharospasm followed by torti-retrocollis¹⁴. The presence of tics at onset of HD has already been described¹⁵, while Kerbeshian et al.¹⁶ and Alonso H et al.¹⁷ described patients with childhood-onset Tourette's disease and later adult onset typical HD. Angelini L et al.¹⁸ also reported the case of childhood onset HD with tourettism in the absence of family history.

The effect of CAG expansion length on phenotype has been reported in other polyglutamine degenerative disorders such as dentato-rubral-pallido-luysian atrophy (DRPLA) and spinocerebellar ataxia 3^{6,19-21}. In DRPLA, for instance, a higher frequency of chorea has been reported in patients who carry shorter expansions than in those who manifest with myoclonus epilepsy⁶. Another aspect that should be highlighted is that longer CAG repeat length may have a small effect on rate of disease progression²², so one should expect a slightly less favorable outcome among our patients with non-choreic movement disorders as

their motor presentation of HD. Unfortunately, our study had the limitation of not having a longitudinal design and this hypothesis cannot be inferred at this time.

Our study illustrates the broad range of clinical manifestations of HD and the usefulness of testing for the HD mutation in select cases with familial movement disorders.

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