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Clinical short communication

Clinical phenotype in carriers of intermediate alleles in the huntingtin gene

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ABSTRACT

Objective: To describe the phenotype of individuals with intermediate allele (IA) CAG repeat length in the *huntingtin* (*HTT*) gene evaluated at the Parkinson's Disease Center and Movement Disorders Clinic (PDCMDC) at Baylor College of Medicine (BCM).

Background: Huntington disease (HD) is caused by a mutation in the *HTT* gene of 36 or more CAG trinucleotide repeats. Since our original case report of pathologically proven HD with 29 CAG repeats, a growing body of evidence has accumulated supporting the observation that individuals with IA (27 to 35 CAG repeats) may exhibit clinical, imaging, and pathologic manifestations of HD. About 6% of the general population has CAG repeats in the IA range in at least one allele of the *HTT* gene. The presence of IA is a challenge for genetic counseling.

Methods: Medical records of patients with IAs seen at the PDCMDC at BCM from January 2008 to the present were reviewed to assess age at symptom onset, dominant clinical features and presence of psychiatric and cognitive symptoms.

Results: Four men and five women were found to have IAs (range: 27–35) in the course of their evaluation at the PDCMDC. The age at onset of clinically evident symptoms ranged from 27 to 78 years. Six individuals had chorea, three had gait disturbance, two had stereotypies, and one patient had multiple motor tics. All nine had psychiatric symptoms, with depression being the most common.

Conclusion: Our series of 9 individuals with IA in the *HTT* gene exhibit a variety of motor and non-motor features that overlap with the HD phenotype. These individuals and their offspring should be considered at risk for development of progressive HD.

1. Introduction

Huntington disease (HD) is an autosomal dominant, neurodegenerative disease caused by a mutation in the *huntingtin* (*HTT*) gene of 36 or more CAG trinucleotide repeats [1]. It is the most common monogenic neurodegenerative disorder in populations of European ancestry. [2] Although 40 CAG repeats are fully penetrant, the disease may occur with 36–39 CAG repeats, but this range has reduced penetrance, typically resulting in a later age at onset and slower disease progression [2]. Since our original case report of pathologically proven HD with 29 CAG repeats [3], a growing body of evidence has accumulated supporting the observation that individuals with IA may exhibit clinical, imaging, and pathologic manifestations of HD.

About 6% of the general population has intermediate allele (IA) length of CAG repeats (range: 27–35) in at least one allele of the *HTT* gene [2,4], but the frequency of IAs depends on the population studied. For example, the frequency of IAs in the Prospective Huntington at Risk Observational Study (PHAROS) was 5%, but it was only 2.5% in the Cooperative Huntington's Observational Research Trial (COHORT) [5,6]. Because the reported clinical manifestations and heritability of IAs are so variable, the presence of IA represents a challenge for genetic counseling.

2. Methods

Medical records of patients with IAs seen at the Parkinson's Disease Center and Movement Disorders Clinic (PDCMDC) at Baylor College of Medicine (BCM) from January 2008 to the present were reviewed to assess age at symptom onset, dominant clinical features and presence of psychiatric and cognitive symptoms. Patients were selected from review of a comprehensive video log of patients evaluated and then videotaped at the PDCMDC. All video-taped patients included in this manuscript signed a consent form at the time of their initial evaluations, giving permission to use their clinical data for purposes of

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Table 1
Clinical phenotype and CAG repeat length for the 9 individuals with IA in the HTT gene.

Case Number	Gender	Age at symptom onset, y	Dominant movement disorder(s)	Cognitive/behavioral symptoms	CAG repeats
1	Male	Late 40s	• Chorea of face and hands that progressed to generalized chorea (face, trunk, & limbs) with a dystonic component affecting the face • Wide-based dancing gait • Mild dysarthria • Motor tics comprised of sniffing, throat-clearing, and coughing • UHDRS motor score 39 • No family history of abnormal involuntary movements or psychiatric disease	• Paranoid delusions. • Visual hallucinations. • Irrational behavior and irritability. • MoCA score 17/30	30/17
2	Female	40	• Leg tapping stereotypies • "Pill-rolling" stereotypies • Essential tremor	• Anxiety	29/17
3	Female	34	• Psychogenic tremor and psychogenic dystonia • Mild chorea of face and hands	• Bipolar disorder. • Anxiety. • ADD.	29/17
4	Female	35	• Psychogenic paroxysmal dystonia and psychogenic Parkinsonism	• Depression	29/17
5[b]	Female	45	• Chorea of face then limbs • Gait disturbance with occasional falls • Stereotypies including finger rubbing and toe tapping	• Depression • Irritability • Difficulty with concentration. • MoCA score 23/30	29/17
6[b]	Male	78	• Progressive chorea of arms and legs • Dysarthria • UHDRS score 34	• Irritability • Behavioral change • MoCA 25/30	32/29
7[b]	Male	37	• Chorea in the legs that progressed to head, trunk, and arms	• Anxiety • Panic attacks • Short-term memory impairment	27/19
8[a,b]	Male	60	• Mild generalized chorea • Intermittent frontalis contraction • Shuffling gait	• Depression • Cognitive impairment • MMSE 27/30	29/20
9	Female	35	• Intermittent involuntary movements of the left worse than right arm and leg jerking for 4–5 years	• Depression • Anxiety	35/17

Abbreviations: MoCA, Montreal Cognitive Assessment. ADHD, Attention-Deficit Hyperactivity, MMSE, Mini Mental Status Exam.
[a] Pathologically proven HD [3,4].
[b] Cases previously described by Ha and Jankovic [4].

publication. All patients who possessed at least 36 CAG repeats were excluded. The clinical, neuropsychological, genetic, and other laboratory findings of these individuals were reviewed.

3. Results

Four men and five women were found to have IAs (range: 27–35) in one allele of the *HTT* gene with one allele in the normal range of CAG repeats. The age at onset of clinically evident symptoms ranged from 27 to 78 years. Six patients had chorea, three had gait disturbances, two had stereotypies, and one patient had multiple motor tics. Some of these individual exhibited multiple movement phenomenologies (Table 1). All nine individuals had psychiatric symptoms, with depression being the most common and three patients had functional (psychogenic) movement disorders. Ha and Jankovic previously published four of these cases in 2011 [4]. Three of the other five cases that have not been previously reported are described here, along with clinical information on the other two cases and an updated review of the literature.

4. Case 1

A 72 year old man, a retired welder, presented with a slowly progressive problems with his balance and involuntary movements of the face and hands in his late 40s. He was evaluated by a neurologist and diagnosed with "metal poisoning," but did not receive any treatment at that time because his symptoms were mild. Around age 62, he developed paranoid delusions that included believing that he was being influenced by magnetic fields due to still having poisonous metals in his body. Around age 66, he developed visual hallucinations and irrational behavior, leading to two psychiatric hospitalizations. He was prescribed haloperidol and took this for 1–2 years with resolution of hallucinations but persistent abnormal involuntary movements. At age 71, his balance and abnormal involuntary movements worsened, leading to a more extensive workup that included a 3-day EEG and other laboratory testing but no abnormalities were found. The patient does not have any family history of abnormal involuntary movements or psychiatric disorders, including his parents, 14 siblings, and 3 children ages 46, 43, and 36. His MRI brain revealed generalized brain atrophy. Genetic testing for dentatorubral-pallidoluysian atrophy (DRPLA) was negative, but he had 30 CAG repeats in one allele in the *HTT* gene and 17 repeats on the other allele. He was then referred to the PDCMDC for a second opinion. Further testing for lupus anticoagulant, antiphospholipid antibodies, ANA, DNAse B, TSH, ceruloplasmin, a paraneoplastic panel, peripheral blood smear, anti-streptolysin O, genetic testing for SCA-17, and genetic testing for Huntington Disease-Like 2 (HDL2) were unremarkable. More recently, the patient developed cognitive decline and mild dysarthria. His examination was significant for a United Huntington's Disease Rating Scale (UHDRS) motor score of 39, a Montreal Cognitive Assessment (MoCA) score of 17/30, saccadic pursuit, slowed saccadic initiation, moderate, generalized chorea worse in the face and jaw, a wide-based "dancing" gait and frequent motor tics comprised of sniffing, throat-clearing, and coughing (Video 1). He was treated with risperidone 0.5 mg daily with improvement in his chorea and paranoid delusions.

5. Case 2

A 69 year old woman with onset of a "no-no" head tremor at age 40 that occurred only under stress. She was diagnosed with essential tremor at about age 52 and was prescribed clonazepam, which was helpful. Since that time, her head tremor has not worsened. Over the past 1–2 years, she developed tapping of her feet that is associated with

an uncomfortable sensation on the lateral aspects of her feet, which is relieved when she moves her feet. She can suppress these movements and they do not preclude her from sleeping. She has repetitive circular movements of her forefinger and thumb, also associated with an uncomfortable sensation that is not as severe as the sensation in her feet. These movements cause social embarrassment. At age 68, she saw a neurologist who ordered HD genetic test that revealed 29 CAG repeats on one allele and 17 repeats on the other allele. The patient's 81 year old sister was diagnosed with dementia, but which type is unknown. Her sister was tested for HD and was told the results were normal, although the CAG repeat number is not known. Her father developed a tremor in his early 50s and was diagnosed with Parkinson's disease, although he never developed other manifestations of parkinsonism. There was no family history of other abnormal involuntary movements or psychiatric disease, including her 77 year old brother, her 38 year old daughter, and her son who died in a car accident at age 22. Other testing that was unremarkable included parathyroid hormone (PTH), thyroid studies, vitamin B12, HTLV 1 and 2, angiotensin converting enzyme (ACE), Lyme disease IgG and IgM, ceruloplasmin, and autoimmune testing that included an ANA, rheumatoid factor, anti-TPO, SCL-70 antibody, SSA and SSB, anti-smith antibody and anti-RNP antibody. An MRI brain report commented on mild, scattered chronic ischemic changes without volume loss in the caudate. Her examination was significant for a lateral head oscillation tremor, mild kinetic tremor in each hand, and stereotypies in the hands and feet (Video 2). The patient was diagnosed with essential tremor and leg stereotypy syndrome [7].

6. Case 3

A 40 year old woman with a family history of HD presented for evaluation of abnormal involuntary movements. The onset of symptoms began about 4 to 5 years prior to our evaluation when she noted intermittent involuntary foot movements occurring about once monthly. These involuntary movements suddenly worsened 4 months prior to her evaluation at the PDCMDC when they increased in frequency and intensity. This period of exacerbation coincided with the assumption of responsibility for her father's interest in her grandfather's estate. She described arm twisting movements and intermittent ballistic type arm movements worse on the left but fluctuating in frequency and intensity. If these movements occur while talking, then her speech becomes dysarthric. The patient has had symptoms of depression and anxiety since her teenage years. She was previously treated with alprazolam for panic attacks.

Her paternal uncle has genetically documented HD. Interestingly, this paternal uncle married an unrelated woman who also has HD. Their daughter and granddaughter both have HD, each with 45 CAG repeats, confirmed with genetic testing. At the patient's request, her father, who was asymptomatic, obtained testing for HD. His results are not available for review, however, the patient recalls that he was told he did not have HD, but that his children were at risk for developing HD, suggesting that he may have had an IA. His medical history was significant for myelodysplastic syndrome and hemochromatosis.

Prior to evaluation at the PDCMDC, the patient had an MRI brain that that was reviewed in our clinic and interpreted as “normal”, without evidence of cortical or striatal atrophy. Laboratory investigation was unrevealing and included normal rheumatoid factor, thyroid panel, ANA, Sjogren's antibodies, ceruloplasmin, and vitamin E levels. She also had a normal 72-h EEG that captured many of her typical events. Her examination was significant for intermittent left arm jerky pronation movements that worsened during the physical exam. Otherwise, there was no chorea, abnormal eye movements, rigidity, or other features of HD. During a follow-up visit, occasional jerk-like movement in her right more than left toes and left more than right fingers were noted. HD genetic testing revealed 35 CAG repeats on one allele and 17 repeats on the other allele.

7. Discussion

HD is an autosomal dominant, progressive neurodegenerative disorder [1]. The *HTT* gene, discovered in 1993, contains a triplet repeat CAG expansion, the length of which is inversely correlated with age at onset, but directly correlated with severity of the disease. [8] This stretch of CAG repeats in the *HTT* gene translates into an abnormally large polyglutamine (polyQ) domain near the N-terminus of the huntingtin (Htt) protein. [9] A recent cross-sectional, observational study of 5 large European population-based cohorts found that 10.7% of people had an intermediate range CAG repeat number in at least 1 polyQ disease-associated gene (including *HTT*), suggesting that a larger than previously suspected number of people in the generally healthy population may be at risk for developing a polyQ disease or giving birth to offspring with a de novo mutation [10,11]. Although the function of the Htt protein is not well understood, it appears to be involved with transport of vesicles inside the cells [12]. Proteolytic cleavage of mutant Htt protein with an expanded polyQ domain results in Htt fragments that aggregate and cause impaired mitochondrial function and transcriptional dysregulation. Htt is expressed in all cell types, but medium-sized spiny neurons in the striatum are particularly susceptible to the damaging effects of aggregated Htt fragments very early in HD. One study evaluating the phenotypic characterization of 21 patients with IA compared to 280 normal controls from the PREDICT-HD cohort did not find evidence to support differences in motor, cognitive, behavioral functional, or imaging outcomes between the two groups, however, this analysis was limited by the small sample size of IA patients [13]. On the other hand, two other HD consortium studies did find clinical abnormalities in individuals with IA compared to normal controls. For example in the Prospective Huntington Disease At-Risk Observational Study (PHAROS) IA carriers had more suicidal ideation, apathy, and worse behavioral scores compared to those with normal CAG repeat lengths [5]. Similarly, individuals with IAs in the Cooperative Huntington's Observational Research Trial (COHORT) study had more suicidality and behavioral abnormalities, as well as more motor impairment compared to controls [6]. It is not known why some individuals with IA exhibit clinical symptoms while others do not, but somatic mosaicism has been suggested as a possible explanation. Accordingly, it has been postulated that clinically affected individuals with IA express longer CAG repeats in their medium-striatal neurons than in other tissues in the same individual [14,15].

The new mutation rate for HD is estimated to be 10% and arises from CAG repeat expansion of IAs [16]. New mutations for HD vary substantially between populations as a function of IA frequency and haplotype composition [17]. IAs are usually transmitted to offspring without expansion, however a proportion of transmissions expand into the affected range [18]. Several studies have found that males with IA are at a particularly high risk of transmitting the abnormal HD allele to their offspring, with an estimated risk ranging from 1 in 6241 to 1 in 951 [19]. It is possible, however, to have a maternal IA expand into the pathologic range [20]. Consequently, children of parents with IA are at risk for developing the disease due to a new mutation. As such, the international predictive testing guidelines were updated in 2013 to recommend that pre-test genetic counseling should mention IA as a potential outcome, and that IA may expand into higher repeat ranges upon transmission to future generations [21]. Discrepancies in pre-test genetic counseling of IA vary based on the patient's family history. Individuals from families with a long-standing family history of HD often receive minimal information about IA compared to individuals from new mutation families, despite IAs being more commonly identified on the non-HD side of families with a long standing history of HD [22].

From our case series of patients with IA, of the various movement disorder phenomenologies identified, the most common was chorea, but other movement disorders included gait disorders, stereotypies and tics. Any of these disorders, including tics, have been previously

reported to be possible initial clinical manifestations of HD. [23] Furthermore, all nine patients had psychiatric symptoms, with depression being the most common and three patients had functional (psychogenic) movement disorders. Two of the patients with functional (psychogenic) movement disorders were sisters who, interestingly, had minimal communication with each other prior the onset of their respective symptoms. They also had the same IA repeats - 29.

Our study provides further support to the growing body of evidence that individuals with IA may exhibit clinical, imaging, and pathologic manifestations of HD [2–4,8,24,25]. IAs are prone to paternal germline CAG repeat instability (perhaps because of somatic mosaicism in the testes) resulting in CAG expansion into the HD range upon transmission to the next generation [26,27]. IAs present a challenge for genetic counseling, as these individuals are often wrongly reassured that they are “disease free”, based on incorrect interpretation of results of genetic testing [28]. Laboratories testing for HD often report IA as being “mutable normal alleles,” without explanation that a proportion of individuals with IA may become symptomatic. Additionally, some of these laboratories report their interpretation of the results based from the American College of Medical Genetics and Genomics Standards and Guidelines for Clinical Genetics Laboratories, 2014 edition: technical standards and guidelines for Huntington disease, which does not recognize that IAs can be associated with the HD phenotype [29]. The retrospective nature of our analysis added some limitation to the desirable uniformity in the evaluation of these patients, such that some of these patients did not have a documented UHDRS or cognitive testing such as MoCA, so a more systematic analysis was not feasible. Some patients did not continue follow up at the PDCMDC, limiting observations about long-term outcome and possible more expanded CAG transmission in their offspring. A major limitation of our report is lack of autopsy data in the 8 of the 9 subjects. Thus, it is plausible that the phenomenology of these patients may be unrelated to their IA status, although we tried to the best of our ability to exclude other causes. Case series of symptomatic IA carriers, such as the one reported here, may contribute to better understanding of IA phenotype, its possible relationship to HD pathogenesis, and its role in genetic counseling. In this regard, a recent report of increased frequency of IA in patients with Alzheimer's disease compared to Parkinson's disease, frontotemporal lobar degeneration, and healthy controls suggest that IAs might have a role in the pathogenesis of neurodegenerative disorders other than HD [30].

8. Conclusion

Our series of patients with IA in the *HTT* gene exhibit a variety of motor and non-motor features that overlap with the HD phenotype. These individuals and their offspring should be considered at risk for development of HD as well as at risk for transmitting the HD allele to their offspring. Genetic counseling in these individuals is challenging because of lack of standards and guidelines for how to interpret IA and because the penetrance of the disease is difficult to predict.[31]

Disclosures

Dr. Joseph Jankovic:

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