Clinical Report

Different Phenotypic Expression in Monozygotic Twins With Huntington Disease

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Monozygotic (MZ), 46-year-old, male twins, carrying the same Huntington disease (HD) mutation, presented with a different clinical course. In one of the twins, the disease process started at the age of 32 years with chorea, dysarthria, and a depressed mood. Over 14 years, the disease progressed to total functional dependence. The second twin presented at age 35 with gait disturbances. His behavior became aggressive with an obsessive pattern, whereas the motor features included hypokinesia, rigidity, gait unsteadiness, and dysarthria. This is the first report of genetic identity associated with different age of disease onset as well as a different motor and behavioral phenotype. Postzygotic events are a likely explanation for the observed differences of phenotype in these genetically identical twins.

KEY WORDS: Huntington disease; chorea; behavior; zygosity

INTRODUCTION

Huntington disease (HD) is an autosomal dominant disorder that involves hyperactive involuntary movements, voluntary movements that involve bradikinesia, and akinesia and cognitive impairments. The clinical expression of HD is primarily determined by an unstable expansion of exonic CAG repeats in the gene encoding the huntingtin protein which is located on the short arm of chromosome 4 [The Huntington’s Disease Collaborative Research Group, 1993]. However, the mechanisms by which this mutant protein, which harbors a polyglutamine repeat sequence, causes neurodegeneration remain unknown. Mitochondrial depolarization at lower calcium loads than controls occur early in HD pathogenesis and may be a direct effect of mutant huntingtin on the organelle [Panov et al., 2002]. The variability in age at onset of the disease is mainly attributed to genetic factors. A direct correlation has been shown between the likelihood of onset at a given age for each CAG repeat length [Duyao et al., 1993; MacMillan et al., 1993; Snell et al., 1993; Ashizawa et al., 1994; Brinkman et al., 1997; Nance, 1997]. The pathological changes associated with the disease, which include neuronal cell loss, are correlated with increased CAG repeat length when age is taken into account [Furtado et al., 1996; Antonini et al., 1998]. Although the major factor that contributes to age of onset and phenotypic expression is probably CAG repeat length, the gender of the affected person has been implicated as well as other genes. Examples include the GluR6 kainate receptor polymorphism, apolipoprotein E genotypes, and mitochondrial energy variants [Rubinsztein et al., 1997; Kehoe et al., 1999; MacDonald et al., 1999; Panas et al., 1999]. In a recent study it has been claimed, however, that the CAG expanded repeat affects the disease progression only at a very upper pathological range and in rare cases initiating very early in the life, while it does not seem to affect in any way the severity of the phenotype in most HD patients [Squitieri et al., 2002].

Previous reports of monozygotic (MZ) HD twins are rare. In most reports, zygosity and the number of CAG repeats and/or zygosity are often not documented accurately [Schiott-Christensen, 1969; Oopen, 1973; Bird and Omenn, 1975; Sudarsky et al., 1983; Levy et al., 1999]. Twin data in general support the hypothesis that age at onset and several other clinical features of the illness are substantially determined by genetic mechanisms [Sudarsky et al., 1983]. However, it has
also been reported that the clinical expression of HD in MZ twins can be significantly different even if the number of CAG repeats is the same [Georgiou et al., 1999].

Herein, we describe MZ male twins who presented with disease symptoms three years apart and developed a different clinical course.

**MATERIALS AND METHODS**

**Determination of Zygosity**

Zygosity was determined by allelic determination of polymorphic short tandem repeat (STR) markers, located on six different chromosomes, using commercial kits [DC6000 and DC6031] supplied by Promega Corporation (Madison, WI). The following markers were used: THO1; TPOX; CSFIPO; VWA; FESPS; F13AO1. These markers are located on chromosomes 11, 2, 5, 12, 15, and 6, respectively.

Determination of the number of CAG repeats was as described by [Warner et al., 1993].

**STR Markers**

Both twins shared the same STR alleles: THO1: 6/7, TPOX: 8/11, CSFIPO: 10/12, VWA: 16/18, FESPS: 9/12, F13AO1: 4/4. The number of CAG repeats was 21 and 49 in both twins.

**CLINICAL REPORT**

**Family History**

The family is of the Karaite sect of Jews from Egypt. The father died at age 55 years of a clinically diagnosed HD. Several other family members were also affected.

Twin 1 was born and developed normally. He was an irritable boy with frequent rage attacks who later became an anxious adult, especially worried about his personal and his loved ones health. He also developed an obsessive behavior, with ritual activities of common daily life activities for example when preparing meals as well as seeking for symmetry and clean environment at home. He graduated from a technical academy and worked later as an engineer. His physical phenotype as a successful student and graduated from a technical academy as a mechanical technologist. His physical phenotype as a child was practically indistinguishable from his twin brother. From a behavioral aspect, he was irritable and remarkably organized with obsessive behavior, similar to his brother. He is married and has two children. His wife observed the first symptom in 1989, at the age of 35, when his gait became strange and dysrhythmic with facial tic-like movements. Although a mild dysarthria and enhanced irritability were noticed later, he continued to work for five more years. The leading motor features over this period were slowness and rigidity with prominent gait unsteadiness and mild memory difficulties. Later on, general chorea developed and was associated with gait instability. The addition of tetrabenazine and tiapride improved the gait and balance but also enhanced his rigid tone. Behaviorally, he developed a significant obsessive–compulsive disorder associated with impulsive aggressive behavior. At age 40, he was institutionalized in an in-home-care. At present he is severely rigid, without chorea but with significant unsteadiness, severe dysarthria, and mild dysphagia. His actual condition at age 46 and after 14 years with clinical symptoms, his clinical scoring includes: Functional capacity of 3 [home care level, gross task only in activity of daily living (ADL)], Independence scale of 20% (no speech, must be feed), and motor Unified Huntington Disease Rating Scale (UHDRS) score of 86.

Twin 2 was born and developed without remarkable health problems or traumatic events. He did not smoke, drink alcohol, or use any illicit drugs. He was a successful student and graduated from a technical academy as a mechanical technologist. His physical phenotype as a child was practically indistinguishable from his twin brother. From a behavioral aspect, he was irritable and remarkably organized with obsessive behavior, similar to his brother. He is married and has two children. His wife observed the first symptom in 1989, at the age of 35, when his gait became strange and dysrhythmic with facial tic-like movements. Although a mild dysarthria and enhanced irritability were noticed later, he continued to work for five more years. The leading motor features over this period were slowness and rigidity with prominent gait unsteadiness and mild memory difficulties. Later on, general chorea developed and was associated with gait instability. The addition of tetrabenazine and tiapride improved the gait and balance but also enhanced his rigid tone. Behaviorally, he developed a significant obsessive–compulsive disorder associated with impulsive aggressive behavior. At age 40, he was institutionalized in an in-home-care. At present he is severely rigid, without chorea but with significant unsteadiness, severe dysarthria, and mild dysphagia. His actual condition at age 46 and after 11 years of symptomatic disease includes a Functional capacity score of 3 (home care level, gross tasks only in ADL), Independence scale score of 40% (chronic care facility needed, limited self feeding, liquefied diet), and motor UHDRS score of 70.

**DISCUSSION**

Despite the presumed genetic identity of these twins, they are clinically different: a 3-year difference was observed in the age of onset of symptoms and their predominant motor symptoms were different. In addition, bulbar involvement (swallowing) appeared earlier in one compared to the other. The behavioral disturbances were also different. One twin was more...
depressed and negativistic while his co-twin was more aggressive and irritable.
From the disability perspective, the progression of the disease is quite similar in the two brothers. One can predict that after 14 years of illness, the second twin will be as disabled as his brother.

A pair of female MZ twins described by Oepen [1973] showed similar differences in the clinical presentation. One of the twins developed a hypertonic/hypokinetic movement disorder whereas the other developed hypotonic/hyperkinetic movements. Bird and Omenn [1975] suggested that MZ HD twins present similarly with respect to degree of cognitive deterioration but the movement disorder can vary. However, these early studies were not documented accurately neither for zygosity nor for the CAG repeat number. A later twin study [Sudarsky et al., 1983] supported the hypothesis that age at onset and several other clinical features of the illness are substantially determined by genetic mechanisms. However, more recently [Georgiou et al., 1999] a pair of MZ HD twins were described who, although sharing identical CAG repeat lengths, not only presented with marked differences in clinical symptoms but also behavioral abnormalities. One of the twins had hyperkinetic/hypotonic symptoms with chorea, less impaired attention level while his co-twin had hypokinetic/hypertonic presentation with more advanced dysfunction, requiring an earlier placement in a nursing home. They were assessed without medication at the age of 37 and 39 years by motor drawing tasks, cognitive and depression screens. Although the motor difference was evident, their cognitive deterioration was reported as being similar. Stochastic epigenic and pre- and post-natal environmental factors can explain different phenotypic differences in MZ twins [Reynolds et al., 2002].

The degree of DNA trinucleotide amplification may vary across different tissues in the same affected individuals [Petronis and Kennedy, 1995]. Furthermore, within the same tissue (striatal tissue in a mouse model), the mutation has been shown to be very unstable [Kennedy and Shelbourne, 2000].

REFERENCES