OBSERVATION

Monozygotic Twins Discordant for Huntington Disease After 7 Years

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Background: Huntington disease (HD) has only rarely been identified in identical twins. All described twins have had disease onset within 1 year of each other, suggesting that disease onset is determined solely by genetic influences.

Objective: To describe a unique set of monozygotic twins in whom clinical HD onset is at least 7 years apart.

Design: A 71-year-old woman was diagnosed as having HD based on medical history, physical examination results consistent with HD, and a CAG trinucleotide repeat number of 39 in the HD gene on chromosome 4. Her onset was 6 years earlier. Her genetically confirmed identical twin, carrying the same number of CAG repeats, was neurologically healthy when examined the next year. Only the HD-manifest twin had chronic bronchitis, rheumatoid arthritis, type 2 diabetes mellitus, and chronic anemia. Both had hypertension.

Conclusions: To our knowledge, this is the first report of monozygotic twins discordant for HD by more than 2 years. The onset of HD symptoms in a patient with 39 triplet repeats at least 7 years earlier than her identical twin suggests the possibility that the disease may be initiated (or delayed) by environmental factors. We have identified increased cigarette use and longer exposure to various industrial toxins as potential explanations for the earlier onset in one twin.

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Huntington Disease (HD) is an autosomal dominant disorder characterized by the triad of chorea, dementia, and behavioral abnormalities. The abnormal gene is characterized by an excess number of CAG trinucleotide repeats that code for glutamine in the Huntington protein. People with 40 or more repeats are thought to always develop the disease if they live long enough. Repeats in the 36 to 39 range are in a gray zone in which penetrance is less than 100%. Factors that determine whether the disease appears in patients with an indeterminate number of repeats are unknown. In general, the more repeats, the earlier the disease onset, but violations of this rule are common.

REPORT OF A CASE

A 71-year-old woman was brought for evaluation of a progressive decline in gait and cognition. The problem began about 6 years earlier, around the time of a surgical repair of an abdominal aortic aneurysm. She had chronic obstructive pulmonary disease due to cigarette smoking, type 2 diabetes mellitus, rheumatoid arthritis, and chronic anemia, ascribed to the rheumatoid arthritis and hypertension. She had lost 9 kg in recent months and was thought to have depression. A feeding tube had been placed. Her brain magnetic resonance image, unchanged from a study 1 year prior, showed mild atrophy, small-vessel ischemic disease, and several punctate areas of mineralization in the cortex. No caudate atrophy was present. Her medications were prednisone, alendronate sodium, sertraline hydrochloride, amitriptyline hydrochloride, insulin, atenolol, omeprazole sodium, epoetin alfa, iron sulfate, and multivitamins. She had stopped smoking about 6 years earlier. She was fully oriented, but thought Richard Nixon was the president. Although she registered 3 objects, she could recall 0 at 2 minutes. Her clock drawing was markedly abnormal. She could spell the word “farm” but spelled it backward as “marf.” Her cranial nerve findings were normal, including eye movements. She had brisk reflexes, normal strength, generalized chorea, and a moderate degree of ataxia in her arms and legs. She was unable to stand without being pulled up. Her base was wide. Her stride was reduced, and her balance...
was poor. Gene testing revealed an HD gene with 39 CAG repeats in one allele and 12 in the other.

The patient informed us that she had an identical twin. The identical twin was examined by the same group of movement disorders specialists (J.H.F., M.E.T., and H.H.F.) who had seen the affected twin, about 9 months later, and the identical twin was healthy. Eighteen months after the initial contact, she reported over the telephone that she was still healthy. She was also genetically tested, and found monozygotic (MZ) with the same CAG repeat numbers in the HD gene. The asymptomatic twin had hypertension but none of the other disorders of her sister. She had stopped smoking cigarettes at the age of 35, whereas the twin with manifest HD had stopped at the age of 65, after her chronic obstructive pulmonary disease had developed. There were no differences in childhood illnesses, alcohol use, prescribed drug use as children, or caffeine intake. The birth home was across the street from a factory that produced large machines used to manufacture precision cutting tools from the late 1800s to 1987. “Numerous chemical spills and leaks occurred over the years.”1 The air was described as polluted, and in 1993, 2 years after the factory closed for the second time, the site was designated a federal toxic site requiring cleanup. It was considered primarily a “brownfield” site, containing mainly oil products, and the principal chemicals of concern identified were dichloroethene, trichloroethylene, and vinyl chloride. Both twins had been equally exposed to the factory’s toxins until the age of 23, when the asymptomatic twin moved away. The twin with manifest HD remained in her original house. The asymptomatic twin moved about 3.2 km away, within the same neighborhood, in New Bedford, Mass. Although the factory closed first in 1985, it was reopened from 1988 to 1991, and samples of air and soil are still analyzed by health department authorities, with reports provided to neighbors. The asymptomatic twin lives sufficiently far away that the air and soil in her neighborhood are not tested. A dietary/nutritional, lifestyle, and medication intake interview was performed, showing no significant differences.

The twins had 5 siblings, of whom 2 were still alive. None were known to have neurological or psychiatric problems, but have not been examined. None of the children of the twins are thought to be affected.

Tests to identify subclinical disease in the unaffected twin, such as positron emission tomography, were not attempted, because publication of the result would potentially identify the twin’s disease status against her wish.

**COMMENT**

Unlike Parkinson disease, in which environmental factors have been associated with disease risk, HD has been known as a genetic disorder with little, if any, environmental influence. At least 12 presumed or confirmed MZ twins with HD have been described, and the data are mixed. Sudarsky et al described MZ twins who had a similar age of symptom onset and motor and behavioral abnormalities despite having been raised in separate households from birth. In contrast, Georgiou et al described a pair of twins who, although sharing identical CAG repeat lengths, had marked differences in clinical and behavioral symptoms. Oepen and Bird and Omenn described MZ HD twins who presented with variable movement disorders but a similar degree of cognitive dysfunction. Nevertheless, the age of symptom onset in these previously described twins had not been more than a couple of years apart.

Only on rare occasions have other dominantly inherited nervous system disorders shown discordance for disease onset. A pair of MZ twins with familial amyloid neuropathy developed the illness 13 years apart. In another report of MZ twins, one had cerebral adrenoleukodystrophy by clinical examination and magnetic resonance imaging starting at the age of 10 years, whereas the other remained healthy 1 year later. Both had the same genetic mutation.

The occurrence of discordance for HD 7 years after onset in one twin suggests the possibility that environmental agents may have an influence on disease initiation. We were able to identify significant differences in exposures to cigarettes and to various industrial toxins, both of which were greater in the twin with manifest HD. We found no reports linking cigarette smoking and HD. At least one study in a rodent model of HD suggests the possibility that environmental factors may retard the progression of the disease.

Although strokes can mimic or aggravate HD, it was unlikely that the asymptomatic twin’s small-vessel ischemic disease was contributory. This was an incidental finding, was minimal, and did not involve the basal ganglia or thalamus. Similarly, although there have been reports of increased incidence of diabetes mellitus in HD patients and HD animal models, there has been no suggestion that diabetes mellitus is a major contributor to the HD phenotype.

Concordance rates in MZ twins for diabetes mellitus are 57% at 10 years and 76% at 15 years. In one study of concordance in patients with rheumatoid arthritis, there was a zero concordance rate in MZ twins in a point prevalence study, implying a lack of significant genetic correlation. The differences between the twins in these medical aspects are, therefore, not surprising, and may or may not be linked to their different susceptibilities to the HD gene abnormality.

Dietary influences on age of symptom onset in those with HD have been reported, with higher milk intake associated with an earlier age of onset in a study of 51 families of patients affected with HD. Another study showed high vitamin A and low vitamin C and niacin intakes in HD patients compared with control subjects. We found no differences in milk or vitamin consumption. However, the symptomatic twin used 7 prescription drugs and 3 over-the-counter medications that her asymptomatic twin never took.

Other potential factors that could have influenced the disparity in expression of the HD mutation in this pair of twins include the late age of onset and the borderline number of CAG repeats (39 repeats). It is possible that sensitivity to environmental factors might play a greater influence in marginal HD cases such as this one.
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