Hereditary late-onset chorea without significant dementia: Genetic evidence for substantial phenotypic variation in Huntington's disease

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Article abstract—We examined five individuals and obtained information concerning six other members from two unrelated families, nearly all of whom developed chorea after age 50 (one patient developed chorea at age 40). The severity of chorea progressed in all patients and became disabling in some individuals approximately 15 years after onset. Cognitive impairment was absent or minimal. All five examined patients were cognitively normal, even 10 to 30 years following the onset of chorea. Formal neuropsychometric testing demonstrated mild cognitive impairment in two individuals. Nevertheless, all patients were able to maintain employment or carry on with their usual household tasks until chorea was severe. One individual first became demented 30 years after the onset of chorea. Neuroimaging (with CT or MRI) in four patients failed to demonstrate significant caudate or putaminal atrophy 8 to 15 years following the onset of chorea. Three other family members (who were not available for examination) were said to have suffered chorea (without any mental decline) beginning after age 50, with subsequent survival of 20 years (in one) and 30 years (in two). Given this constellation of history and findings, three experienced neurologists and two medical geneticists concluded that these patients had a familial chorea syndrome distinct from Huntington's disease (HD). However, genetic analysis of the trinucleotide (CAG) repeat length associated with HD (in 4p16.3) determined repeat lengths of 44 and 46 in four patients tested (within the HD range). We conclude that these patients have HD and that such families represent further convincing examples of significant phenotypic variation for HD.

The most commonly recognized form of familial chorea is Huntington's disease (HD). This condition is inexorably progressive and is associated with dementia, psychiatric abnormalities, and other neurologic signs in addition to chorea. Age of onset is usually between 30 and 50 years. Typically, deterioration results in death at an average age of 54 years, 15 to 20 years after disease onset. Clinical variants include a juvenile form, with rigidity as a prominent feature, and late-onset HD.

There are, however, other forms of familial chorea. For example, benign familial chorea, characterized by childhood onset and a relatively benign course, stands in contrast to HD, whereas dentato-rubro-pallidal-luysian atrophy (DRPLA), another autosomal dominant condition, may closely mimic HD. Other familial disorders with chorea as a prominent feature have also been described.

There are instances of late-onset, nonhereditary chorea without other neurologic manifestations designated as senile chorea. Some have argued that senile chorea may frequently represent late-onset HD. However, HD does not account for all reported cases of senile chorea, and there is genetic evidence for senile chorea being a distinct entity from HD.

We recently encountered two unrelated families with 11 members affected by adult-onset chorea. Each pedigree displayed a pattern compatible with an autosomal dominant mode of inheritance. Cognitive and psychiatric dysfunction were absent, mild, or only present many years after the onset of chorea. Coupled with a prolonged, relatively benign course and a lack of neuroimaging abnormalities, these features led three experienced neurologists and two medical geneticists expert in HD to conclude that these patients had a familial chorea syndrome that was distinct from HD.

The recent discovery of the HD gene and its associated trinucleotide (CAG) repeat expansion has led to a better understanding of the genetic basis of HD and its variants.
facilitated confirmation of diagnosis in symptomatic patients. We applied polymerase chain reaction (PCR) analysis of the HD trinucleotide repeat sequence to affected members of these two families with late-onset chorea to determine whether they indeed represented a unique disorder of familial late-onset chorea or HD with an atypical presentation.

Methods. Clinical information. Pedigrees of two unrelated families with late-onset chorea are illustrated in figures 1 and 2. Case reports concerning affected members are presented below.

PCR analyses. Trinucleotide repeat length analyses were performed on two members from each family (III.8 and III.10 from family 1 and III.12 and III.14 from family 2). Nuclear DNA was isolated by extraction from leukocytes using the method of Kunkel et al. The CAG repeat size was measured as previously described. Assessment of the trinucleotide repeat length included 76 base pairs on non-CAG sequences, which were then subtracted from the observed size. The resulting value was divided by three to obtain the CAG repeat length.

Case reports. Family 1 (figure 1). III.8. The proband had a 15-year history of mild, generalized, slowly progressive chorea when first seen at age 65 years. She was a homemaker and continued to perform all her normal household duties without difficulty 15 years after onset of chorea. Apart from chorea, she had no other complaints. On direct questioning, she thought that she might have had a mild decline in memory, but her husband disagreed with this impression. Medical history was significant only for a 15-year history of hypertension and mild hypercholesterolemia.

Neurologic findings were limited to mild generalized chorea and hyperkinetic dystonia. Her Mini-Mental State Examination score was 38 of 38 (within the normal range).

She scored in the average range on the following neuropsychological tests: Wechsler Adult Intelligence Scale-Revised (WAIS-R) (Full Scale IQ = 94), Wechsler Memory Scale-Revised (WMS-R), Auditory-Verbal Learning Test (AVLT), Wide-Range Achievement Test-Revised, Stroop's Color Word Test, Trail Making Test, Bender-Gestalt, Boston Naming Test, and Russell's Category Test. Mildly subnormal scores were recorded on two tests—the Wisconsin Card Sorting Test and the Controlled Oral Word Association Test. These results were considered consistent with her education and occupational background.

An MRI of the brain performed 15 years after the onset of chorea showed mild generalized atrophy (figure 3a). A blood smear for acanthocytes, slit-lamp examination, urine screen for inborn errors of metabolism, general chemistry panel, ceruloplasmin level, antinuclear antibody (ANA) level, thyroid-stimulating hormone (TSH) level, vitamin B₁₂ and folic acid levels, and hematology group were all normal or negative.

III.10. The brother of the proband was initially seen at age 63, after a 10-year history of mild generalized chorea. He had no complaints apart from chorea. He continued to operate a successful farm independently, performing all his usual chores. He was not aware of any change in his cognitive capacity. On direct questioning, his wife thought that he may have had a subtle decline in memory and had become somewhat indecisive since age 61 years. He had no history of psychiatric illness.

Neurologic examination showed mild generalized chorea and mildly impaired rapid alternating movements bilaterally. The Mini-Mental State Examination revealed impaired delayed verbal recall (he recalled one of four words learned after a 5-minute delay) but was otherwise normal (total score: 35/38).

Neuropsychological testing revealed limited abnormalities. These were restricted to impaired verbal learning and retention on the AVLT (he learned eight of 15 words after five trials and recalled three after 30 minutes). The WAIS-R was performed in the average range (Full Scale IQ = 97), consistent with his education and occupational background. A brain MRI 10 years after the onset of chorea showed mild generalized cerebral atrophy (figure 3b). A blood smear for acanthocytes, slit-lamp examination, chemistry panel, vitamin B₁₂ and folic acid, FTA-ABS, and TSH were normal or negative. An ANA titer was 1:160.

II.4. The mother of the proband had been evaluated by neurologists at the University of Iowa in 1953 and at the Mayo Clinic in 1958. Neither senior neurologist sus-
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live injury until approximately 2 years before her death physically impaired (C.R.) indicated that she remained cognitively and family age 79 years. However, her husband's son, and family may have made her speech unintelligible by their mother's death, but her speech remained comprehensible and their hypopharyngeal swallow was noted. Her hyphagia was not noted. She was admitted to a nursing home facility. She

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at age 85, 33 years after the onset of chorea. She weighed 60 pounds at the time of death.

Her mother, father, and two sisters all died in the seventh and eighth decades of life. None had any neurologic or psychiatric disorder. Her two other siblings died immediately after birth and at age 16 from diphtheria. One paternal uncle was said to have had “St. Vitus’ dance” at one time and died in his thirties (of unknown cause). No other relatives were known to have had any neurologic diseases.

**DNA analyses.** The upper allele CAG trinucleotide repeat length was 46 units in both patients III.8 and III.10 from family 1 and 44 units in both patients III.12 and III.14 from family 2. An upper allele repeat sequence of >36 triplets is considered to be within the HD range.14

**Discussion.** The two families described here share certain features that are atypical of HD: (1) dementia was not a prominent feature; (2) survival following onset of chorea was prolonged, with deceased patients dying an average of 28 years after chorea began; and (3) neuroimaging, performed between 8 and 15 years after the onset of chorea in four individuals, showed no disproportionate caudate or putaminal atrophy.

Dementia was absent or minimal in four of the five examined patients, as it was for all four deceased patients from family 1 who died after a 20- to 30-year history of chorea. In contrast, significant cognitive and psychiatric decline is a hallmark of HD, usually leading to disability within a few years after diagnosis.21 Patient III.14 from family 2 did show a decline on serial neuropsychological test scores; however, his chorea and dystarthisia significantly interfered with psychological testing, confounding the results. Despite his scores, he was still able to provide a logical history 17 years after symptom onset. Likewise, III.10 from family 1 demonstrated abnormalities on memory testing but continued to function as a capable farmer. Patients with late-onset HD often exhibit a milder degree of dementia than those with earlier onset; however, the largest series of late-onset HD patients noted that all 25 examined patients were definitely demented within 7 years of the onset of chorea.5 The individuals in our series did not demonstrate dementia, not even of a mild degree, until between 8 and 30 years after chorea onset.

The patients in these two families remained free from disability for at least 10 years following the onset of chorea. Survival of affected members in our two families was longer than the 15 to 20 years typically seen in HD (28 years on average in the five deceased patients).5 The 33-year survival after onset of chorea seen in patient II.10 (family 2) is one of the longest ever reported in an HD patient. In one large series,1 no patient survived more than 27 years. However, MacMillan et al22 recently reported several individuals originally thought to have benign hereditary chorea who had HD proven by identification of trinucleotide expansion.

Consistent absence of disproportionate caudate and putaminal atrophy is also atypical for HD. In-individual patients with advanced HD and normal neuroimaging are unusual.21 In a prior series of patients with late-onset HD,5 all nine patients who underwent CT had caudate atrophy. Others have shown that loss of putamen volume may be a more sensitive finding than caudate atrophy in “mild HD” (in which cognitive processing is minimally affected).23

Despite their atypical clinical features, the DNA analysis in these patients indicates that they have inherited the mutation associated with HD. Their CAG trinucleotide repeat lengths fall within the range identified in late-onset HD.24 In a study of 133 patients with late-onset HD from 107 separate families, there was a significant negative correlation between the length of repeat and age of onset for the total cohort. However, for persons with onset age greater than 60, there was no significant correlation.24 With increasing age of onset, the effect of the repeat length on onset age appears to diminish.

The reason for the atypical phenotypic expression in our patients is unclear. Some of the phenotypic variability in HD can be attributed to the CAG repeat sequence length. For example, repeat length is inversely correlated with age of onset.5,6,25-27 Repeat length can also be correlated with disease severity. Patients with juvenile-onset HD tend to have a more severe and rapidly progressive course* and generally exhibit long repeat sequence lengths.15,25-27 However, there are notable examples of marginally prolonged repeat lengths occurring in childhood-onset HD.22 Repeat length alone explains about 50% of the total variance in onset age.26 Furthermore, in a large genetic analysis series restricted to late-onset HD, repeat length accounted for only 7% of the variation in age of onset for persons beyond the age of 50 years.24 Likewise, there was no significant correlation between age of onset and size of the lower allele repeat length or the sex of the affected parent or grandparent in this series.24 Finally, a small number of patients clinically diagnosed as having HD have not shown an expanded CAG repeat with a novel gene on 4p16.3. In at least four such cases, studies have excluded 4p16.3 as the region responsible for the HD phenotype.28

That all cases in our two families aggregated as late-onset HD suggests that other genetic factors may be involved. When it is determined how the CAG repeat expansion relates to HD, it may become apparent how certain clinical features are produced. Accumulating evidence suggests that the protein product of IT15 may be a DNA-binding protein involved in transcriptional regulation.29 If an expanded polyglutamine (glutamine being the amino acid encoded by CAG) stretch leads to altered expression of other genes, a wide range of phenotypic variation might be explained. In this regard, aspects of another autosomal dominant condition, DRPLA, which may closely mimic HD clinically, are of great interest. Until recently, in some
instances DRPLA and HD could only be differentiated by neuropathologic examination (in which major involvement of the globus pallidus, subthalamic nucleus, and dentate nuclei distinguished DRPLA from HD). DRPLA is associated with another CAG repeat expansion, this one occurring on chromosome 12. Such expansions may allow for the development of specific neurologic features including chorea, dementia, and psychiatric disturbances. Further genetic evaluations of families with unusual HD phenotypes, such as the patients described, may contribute to an understanding of the biology of phenotypic expression in HD.

References