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Familial Aggregation of Schizophrenia-Like Symptoms in Huntington's Disease

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An increased incidence of schizophrenia-like symptoms in Huntington's disease (HD) has been well-documented in the past. The reasons for this association, however, have never been explained. At the University of Washington Medical Genetics Clinic, we had the opportunity to evaluate a unique juvenile-onset HD proband who had schizophrenia-like symptoms. This patient was referred to our clinic because of new onset of somatic delusions and command auditory hallucinations early in the course of her illness. Since we had already evaluated other affected individuals in her family, we selected another family with a nonpsychotic juvenile-onset proband for comparison. Using these two families in a small case-control study, we investigated the following hypotheses which could explain the association between schizophrenia-like symptoms and HD: first, schizophrenia-like symptoms may be related to the number of CAG repeats in the HD gene; second, schizophrenia-like symptoms may segregate in certain HD families, for unknown reasons; and third, there may coincidentally be an unrelated gene for schizophrenia in certain HD families. Comparisons of clinical characteristics and the HD genotype showed that family history of schizophrenia-like symptoms segregated with the HD gene; however, age of onset of HD, size of CAG repeat, and sex of the transmitting parent were not associated with psychotic symptoms. Further genetic and neurobiological studies are necessary to investigate the potential mechanism underlying this association. Am. J. Med. Genet. (Neuropsychiatr. Genet.) 81:323–327, 1998.

KEY WORDS: Huntington's disease; genetics; schizophrenia

INTRODUCTION

Huntington's disease (HD) is an autosomal-dominant neurodegenerative disorder with principal symptoms consisting of choreiform movements and dementia as well as a wide variety of psychiatric symptoms. There have been reports of increased frequency of schizophrenia, major affective disorder, and personality changes associated with HD [Folstein, 1989; Mendez, 1994; Shiwach and Norbury, 1994]. The temporal sequence of symptoms relative to motor disturbance and dementia varies considerably. As a whole, functional psychiatric illness has been reported in 5–17% of all patients with HD, but has never been well-explained [Dewhurst et al., 1969; Besson et al., 1991]. In this report, we are specifically interested in the increased incidence of schizophrenia-like symptoms in HD. Is this a manifestation of underlying neurodegeneration associated with HD, or a specific psychiatric symptom that may present in subtypes of HD? Here we report on 2 juvenile-onset HD probands who differ with respect to the presence of schizophrenia-like symptoms. We will compare their age at onset, number of CAG repeats within the HD gene, and family psychiatric history to investigate possible differences that may account for this observed phenotypic variability.

MATERIALS AND METHODS

We ascertained the 2 HD probands and their families from the Neurogenetics Clinic at the University of Washington (Seattle, WA). The 2 juvenile-onset probands presented to our clinic because of atypical symptoms (schizophrenia-like symptoms in one and unusu-

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ally early onset in the other). In both cases, the affected fathers (and in one case, the paternal grandfather) were evaluated by one of the authors (T.D.B. or D.T.). After obtaining informed consent, we obtained medical and psychiatric records on all available family members. Psychiatric assessments were made through the use of medical records and personal interviews using the Structured Interview for the DSM-IV (SCID-IV) [First et al., 1995]. Probands and affected family members also underwent genetic counseling for HD genotyping. The HD gene containing the CAG repeat was amplified and its size measured using standard techniques [Goldberg et al., 1993] at the University of Washington Medical Genetics Laboratory.

RESULTS

Family 1 (Fig. 1)

III-2. This proband presented with incoordination and memory problems at approximately age 13. On neurological examination, she had increased tone in all extremities as well as the presence of pathological reflexes. No choreiform movements were noted. Head MRI showed bilateral moderate caudate atrophy. HD genotype confirmed the clinical diagnosis: 68 [CAG repeats] (affected allele), 15 [CAG repeats] (unaffected allele); see Table I. Two years later, she was hospitalized in a psychiatric hospital for treatment of new-onset psychosis. On mental status examination, she had evidence of somatic delusions and auditory and visual hallucinations. She believed that the devil possessed her and that she was "becoming an old woman." She reported visual hallucinations of her hands becoming wrinkled like those of an old woman, as well as "horns coming out" of her head. In addition, she reported auditory command hallucinations, which instructed her to kill herself and her parents. These symptoms were extremely distressing and required psychiatric hospitalization. She had no significant depressive, manic, or dementing symptoms at time of evaluation; her neurological examination also remained essentially unchanged. The patient met DSM-IV criteria for schizophrenia (with the exception of the criterion "absence of preexisting brain disorder"). Aside from her increased muscle tone, symptoms were indistinguishable from those of patients with a diagnosis of DSM-IV schizophrenia.

II-2. The father of III-2 (the juvenile-onset proband) presented with motor symptoms at age 27. At that time, he demonstrated irrational behavior and angry outbursts, resulting in marital discord and divorce. He was diagnosed with HD at age 32. At that time, he also developed psychotic symptoms of grandiose and paranoid delusions and he was admitted to a psychiatric hospital. He believed that he would find a gold mine and would become wealthy. Although he was noted to have a "euphoric affect," there were no other manic or depressive symptoms. He also did not have significant chorea or cognitive deficits. Five years later, he was again hospitalized psychiatrically for attempting to respond to auditory hallucinations to assault others. At age 42, he had significant chorea and was bedridden. His HD genotype also confirmed the clinical diagnosis of HD: 52 [CAG repeats] (affected allele), 27 [CAG repeats] (unaffected allele).

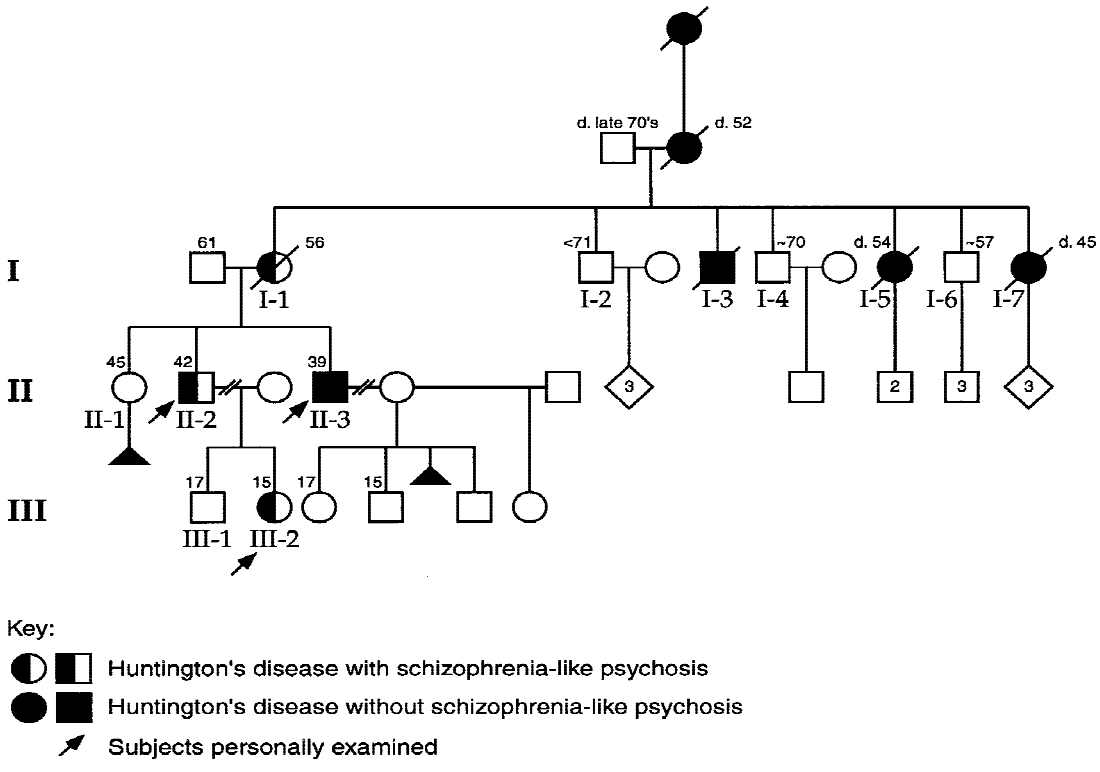

Fig. 1. Pedigree of juvenile onset proband with schizophrenia-like psychosis.

TABLE I. Age of Onset and HD Genotype

Subject	Age of onset of HD	Age of onset of psychosis	Current age or age at death	CAG repeat (affected/unaffected allele)
Family 1				
III-2	13	15	15	68/15
II-2	27	32	42	52/27
II-3	26	not applicable	39	60/27
I-1	25	33	56	53/21
Family 2				
III-1	5	not applicable	13	81/23
II-5	24	36 (with dementia)	37	60/12
I-2	44	not applicable	Unknown	Not done

II-1. The aunt of III-2 was examined at age 37. Her neurological and mental status examinations were completely within normal limits. She had no psychiatric history at the time.

II-3. The uncle of III-2 developed twitching and incoordination at approximately age 26. He was diagnosed with HD at age 28. His psychiatric history is remarkable only for a history of alcohol abuse in his mid-20s. He did not develop significant cognitive decline until age 37, at which time he was placed in a nursing home. At the time of last examination (age 39), he did not exhibit any psychotic symptoms. His CAG repeat size was larger than that of his psychotic brother: 60 [CAG repeats] (affected allele), 27 [CAG repeats] (unaffected allele).

I-1. The paternal grandmother of the juvenile-onset proband had behavioral disturbance in her mid-20s. According to her daughter, she had acted in a bizarre fashion, e.g., on one occasion, she was found yelling while walking nude on the road. She also reportedly had bouts of anger and moodiness. She had apparently had a diagnosis of "schizophrenia" at one time and was hospitalized in the state mental hospital, but detailed records are unavailable. By age 40, she had significant chorea, spasticity, and cognitive and functional decline, necessitating nursing home placement. She died at age 56. The number of CAG repeats showed 53 (affected allele) and 21 (unaffected allele).

I-5. The paternal great-aunt of III-2 had been affected since approximately age 34. There was no mention of psychotic symptoms or behavioral disturbance. She died in a nursing home at age 54 from advanced HD.

I-7. Another paternal great-aunt of III-2 had been affected since age 40. No other clinical information is available. She died at age 45. Neuropathological studies showed severe atrophy of the caudate consistent with HD.

Family 2 (Fig. 2)

III-1. This juvenile-onset proband was initially seen at the University of Washington Children's Hospital and Medical Center at age 5, because of deterioration in cognitive and motor skills. A diagnosis of HD was made on the basis of neurological examination and

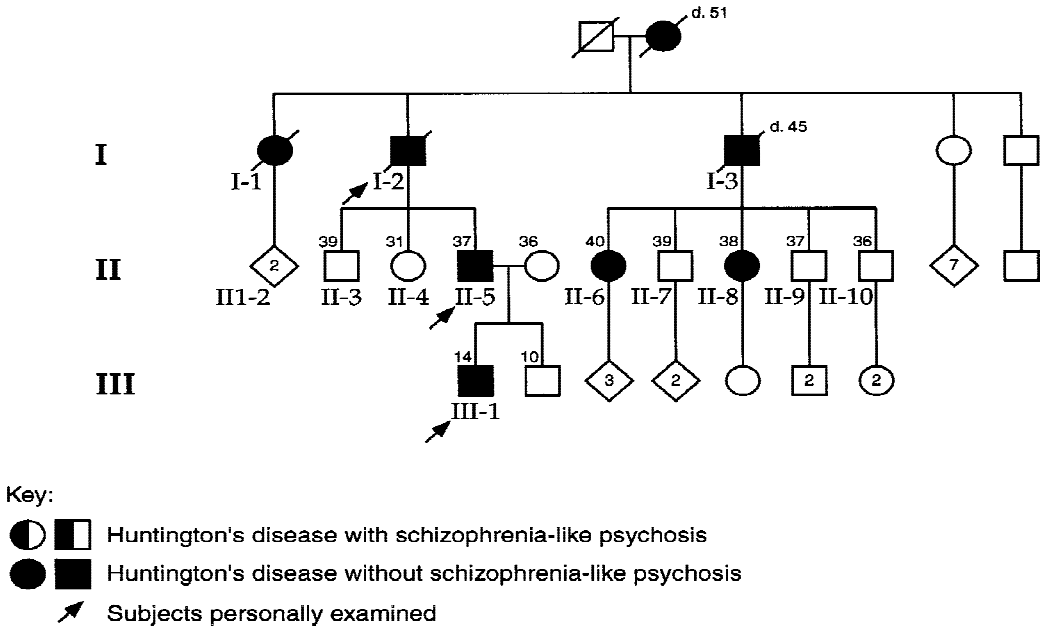

Fig. 2. Pedigree of juvenile onset proband without schizophrenia-like psychosis.

positive family history. At age 13, he had marked rigidity in his lower extremities and his cognitive skills were at the 6-year-old level. He had choreiform movements. His mental status examination revealed no hallucinations or delusions. His HD genotype consisted of an affected allele size of 81 CAG repeats and unaffected allele of 23.

II-5. The father of III-1 presented with motor, cognitive, and personality changes at approximately age 24. An HD diagnosis was made at age 28 on the basis of neurological examination and head CT findings. At age 36, the patient was hospitalized because of progressive dementia and new onset of delusions of infidelity. On mental status examination, the patient did not exhibit evidence of delusions, but he had significant cognitive impairment. His CAG repeats showed an affected allele of 60 and unaffected of 12.

I-2. The paternal grandfather of the juvenile-onset proband developed progressive difficulty walking at age 44. A diagnosis of HD was made at that time. He was hospitalized in a psychiatric hospital at age 45. He was hospitalized three times because of behavioral disturbance. At time of admission, he had "increasing depression and hostile ruminations" and had made threats against his former employers. On mental status examination, he was felt to have significant depressive symptoms, with suicidal ideation (contemplated jumping off a bridge). He also displayed poor memory and judgment; however, there was no evidence of delusions or hallucinations. He was lost to follow-up at age 45.

DISCUSSION

These family data provide some preliminary support for the hypothesis that schizophrenia-like symptoms run in certain HD families. In family 1, schizophrenia-like symptoms were present in two, and possibly three, generations of affected individuals. In contrast, none of the affected individuals in family 2 developed psychosis early in the course of their illness. Although the father of the juvenile-onset proband in this family became delusional, this was in the presence of significant dementia. One previous case series found delusions of persecution in 23% of HD patients, most often in the context of dementia [Besson et al., 1991]. It appears that complex schizophrenia-like symptoms such as well-organized delusions are much more uncommon in HD than isolated hallucinations or delusions [Shiwach and Norbury, 1994]. Using a structured psychiatric interview (SCID-IV) and follow-up assessments by a board-certified psychiatrist (D.T.), the juvenile HD proband in family 1 showed no significant concurrent depressive or manic symptoms consistent with affective psychosis. Her delusional beliefs were systematized and did not have any affective theme. Schizophrenia-like symptoms in this family differ from those most commonly described in HD families, which follow depressive or manic symptoms or occur only in the context of dementia [Folstein, 1989]. However, no clear conclusions can be made from this case study, since the sample size was small and the juvenile-onset proband from family 2 is young and has not yet passed through the age at highest risk for schizophrenia.

Those with schizophrenia-like symptoms in family 1 did not have larger CAG expansions in the HD gene. The psychotic juvenile HD proband in family 1 had a CAG repeat of 68, while her nonpsychotic counterpart in family 2 had a CAG repeat of 81. In addition, there was not a larger expansion in repeat size in the father-to-child transmission in the psychotic family (increase of 16 repeats); in fact, the nonpsychotic family had a larger father-to-child expansion (increase of 21 repeats). One other observed difference between the two juvenile-onset probands is gender. Although we cannot dismiss this possible difference, the more important factor in HD is gender of the transmitting parent [Harper, 1991]. In each of these 2 cases, the transmitting parent was male. Comparison of the age of onset of HD shows that the nonpsychotic HD proband in family 2 had much earlier onset of Huntington's disease than the psychotic proband in family 1. Therefore, age of onset alone cannot explain the development of schizophrenia-like symptoms.

The data from these two families provide preliminary support for a predisposition to development of schizophrenia-like symptoms in certain HD families. Others have also reported the familial association of psychotic syndromes in certain HD families [Lovestone et al., 1996]. This predisposition does not appear to be closely related to CAG expansion. The mechanisms underlying a potential familial predisposition to schizophrenia-like syndromes in HD remain unclear. Possible familial influences include genetic and environmental factors. It might be hypothesized that childhood experiences associated with a parent who is severely ill might increase psychiatric illness in offspring of those affected by HD. Some have reported an increased incidence of conduct disorder in at-risk offspring of HD patients [Folstein et al., 1983]. However, Jensen et al. [1993] found that HD patients are at much higher risk for developing psychotic disorders than their unaffected relatives. This suggests that the chaotic environment associated with growing up with an affected parent may predispose at-risk individuals to develop some (conduct disorders) but not other (major affective and schizophrenia-like disorders) psychiatric disturbances. Another plausible explanation is that the HD gene causes both schizophrenia and HD. However, HD genotypes of the family members tested were all within the range reported for HD (>35 repeats), and a larger number of CAG repeats was not associated with the schizophrenia-like syndrome. While there is no evidence of genetic heterogeneity in HD [Kremer et al., 1994], it is possible that an as-yet undetected genomic difference exists, either in the HD gene itself or in a gene in linkage disequilibrium with the HD gene. Finally, although less likely, an entirely separate gene could explain the development of the schizophrenia-like syndrome in HD. Clearly, a study involving a larger number of HD families with psychotic symptoms is necessary to adequately address these hypotheses. In addition, research at the molecular genetics level is also necessary to clarify these possibilities. Clarification of the etiology of secondary symptoms (such as the schizophrenia-like syndrome) in HD will certainly contribute to our understanding of the pathogenesis of HD, as well as

offer insight into the neurobiology of psychotic phenomena.

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