Article abstract

A set of male monozygotic twins concordant for Huntington's disease is described. The monozygosity of the twins and the diagnosis of Huntington's disease are well established. The twins are now age 30, and although the severity of their chorea differs, they have a similar degree of mental deficit. This family is of additional interest because the daughter of one of the twins has childhood Huntington's disease, and the mother of the twins had the adult-onset rigid variant of the disease. Such unusual families afford some insight into the variability of the clinical manifestations of this hereditary disease.

Monozygotic twins with Huntington's disease in a family expressing the rigid variant

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The family described here is of German ancestry. The earliest known family member who probably was affected with Huntington's disease (I-1) died at age 53 in a mental hospital with a diagnosis of chronic Saint Vitus's dance and psychosis. She had eight children (figure). One of her sons (II-7) had the onset of weakness, apathy, and multiple minor complaints at age 36. Records of psychiatric hospitalization in 1937, when he was 45, show that he had "definite choreiform movements" of face, mouth, and all extremities and signs of moderate mental deterioration. Deep tendon reflexes and muscle tone were recorded as normal, and no Babinski reflex was present. His diagnosis was "psychosis with Huntington's chorea." He died a few years later under unknown circumstances. He had an older sister (II-5) with a history of chronic Saint Vitus' dance, but no neurologic information is available on his other siblings. He had two daughters, one of whom (III-2) is living and apparently well at age 63. She has not been examined.

According to hospital records, the other daughter (III-1) had a "stormy marriage" and, beginning at age 17, frequent emotional upsets. At age 28, she was noted to be "moody, easily excitable" and had periods of serious depression. Because of progressive depression and social withdrawal, she was first admitted to a state psychiatric hospital at age 36 with a diagnosis of schizophrenia. Records relate that at age 37, she had a right facial paresis, awkward gait, and clumsiness, but did not have chorea. At age 40, she was "depressed and distressed," appeared undernourished, and had facial grimacing and unsteady gait. She also had rigidity of all four extremities, torticollis with her head tonically deviated to the right, a central right facial paresis, hyperactive deep tendon reflexes with sustained ankle clonus, and bilateral Babinski and Hoffman reflexes. A pneumoencephalogram was described as normal. The clinical diagnosis was Huntington's chorea. Her condition slowly deteriorated. At age 44, she was withdrawn and uncooperative, with trismus, marked torticollis, choreic posture and movements of her hands, and the above-mentioned abnormal reflexes. She was unable to walk. She died of aspiration pneumonia in 1962 at age 44. Autopsy showed mild generalized cerebral cortical atrophy and gross atrophy of the caudate nuclei. Microscopic examination revealed nerve cell loss and gliosis in the corpus striatum, gliosis in the frontal white matter and the thalamus, and normal cerebellum. The final neuropathologic diagnosis was Huntington's disease.

This woman (III-1) had three children who lived beyond infancy, a daughter and twin sons. Her daughter (IV-1) had behavioral problems as an adolescent and had

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Supported by NIH grants 1 F22 NS01561-01, GM15253 and Research Career Development Award GM43122 (G.S.O.).

Received for publication October 9, 1974.

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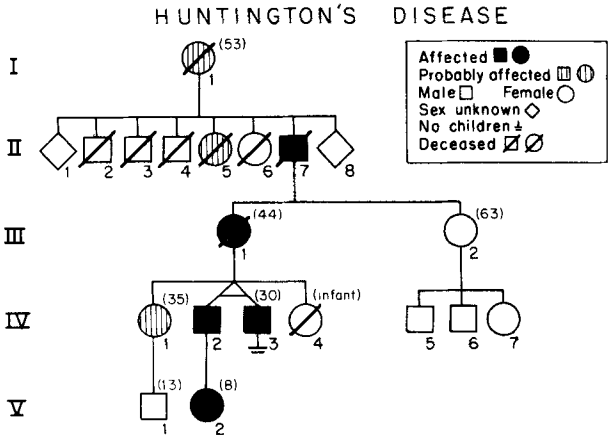

Figure. Family pedigree. Numbers in parentheses represent age at time of study or age of death.

numerous abnormal subscale scores on a Minnesota Multiphasic Personality Inventory administered at age 28. Since graduation from high school, she has been unable to maintain employment and has complained of chronic neck stiffness. Examinations by neurologists when she was 28 and 29 years old showed subtle facial and hand movements suggestive of chorea. Emotional lability and brisk deep tendon reflexes were noted. Muscle tone was not described. Her behavior has deteriorated. She has been physically violent and required transient psychiatric hospitalizations. Although she has not been examined recently, it seems likely that she is affected. No information is available on her 13-year-old son (V-1).

The male twins (IV-2 and IV-3) were born in 1945, products of a full-term uncomplicated pregnancy and delivery. Each weighed close to 8 lb at birth. They always appeared identical, and friends and teachers had trouble telling them apart. Each obtained better than average grades in high school and graduated from the same university. Both were active in sports, particularly gymnastics; however, twin IV-2 majored in architecture and twin IV-3 majored in physical education. Twin IV-2 has worked as a design architect and has not been in military service; twin IV-3 spent 2 ½ years as an officer in the army and has subsequently worked in physical education-recreation jobs. Both men married at age 21. Twin IV-2 was married for 8 years and then divorced; twin IV-3 obtained a divorce after 7 years. Twin IV-2 had a single unplanned child (V-1) and then underwent vasectomy. Twin IV-3 has had no children, but does not wish a vasectomy because he contemplates possibly having children. Both men developed frontal balding at age 19. At age 21, twin IV-3 was examined by a neurologist who found no abnormalities. In recent years, both twins have had difficulty performing adequately in their jobs, and twin IV-2 has had definite swings in mood and temper.

On examination in 1975, at age 30, twin IV-2 had slight but definite choreiform movements, primarily small distal jerkings of his hands. Alternating movements were done slowly and were not well coordinated. Deep tendon reflexes were symmetrical and hyperactive at the knees and ankles with unsustained ankle clonus. He had no pathologic reflexes. Eye movements were full; rapid and slow pursuit eye movements were normal. He had no rigidity, dystonia, or ataxia. The remainder of the physical examination was unremarkable. The patient was alert, cooperative, well oriented, and quite garrulous and carried on appropriate and coherent conversation. However, he had deficits in both recent and remote memory, and his fund of factual knowledge was poor for a college graduate. Although he was able to form abstract concepts, he had difficulty interpreting common proverbs.

Twin IV-3, in marked contrast to his brother, had obvious, frequent, moderately severe choreiform movements both distal and proximal. His gait and attempts at integrated movements were poorly coordinated. The chorea was present at rest but was exacerbated by movement and anxiety. He had occasional facial grimacing. Like his twin, he had hyperactive knee and ankle deep tendon reflexes, with unsustained ankle clonus but no pathologic reflexes. He had normal eye movements and no ataxia, dystonia, or rigidity. The remainder of his physical examination was unremarkable. He was alert, oriented, and cooperative. His memory and general fund of knowledge were somewhat better than his brother's, but he also demonstrated deficiencies. He had difficulty with calculations and interpretation of common proverbs. The moderate degree of mental deficit was similar in both twins. The unstable social and emotional aspects of this family have prohibited further detailed psychometric testing.

In addition to striking similarity in height, weight, facial features, hair color and pattern, and general physical appearance, these twins were identical for five blood groups and 22 red blood cell enzyme loci. The probability of monozygosity exceeds 99 percent.[1]

The daughter (V-2) of twin IV-2 was the product of an uncomplicated pregnancy that terminated spontaneously at 32 weeks' gestation; her birth weight was 1,400 gm. She had an uncomplicated 5-week postnatal hospital course without respiratory distress, icterus, or seizures. Her developmental milestones were passed at normal times. She walked at 13 months and was speaking fluently with a large vocabulary at 4 years of age. Her parents considered her normal. When she was 5 years of age, her teacher noted that she was awkward and tended to stumble. She was slow at academic tasks and required placement in special classes. Over the next 2 years her gait, coordination, and speech slowly deteriorated. She developed twitching hand movements and began sucking her lips.

Physical examination by a pediatric neurologist when she was 7½ years old showed gross motor incoordination and short attention span. Fidgety movements of her hands were thought to represent mild chorea. Muscle tone was mildly increased in her legs, with hyperactive knee and ankle deep tendon reflexes and unsustained ankle clonus bilaterally. A Babinski response was present on the left. Her gait was slow, awkward, and jerky. Cranial nerve examination and eye movements were normal.

Results of the following laboratory tests were normal: complete blood count, urine amino acid screen, spinal fluid total protein, sugar and cell count, skull x-rays, and electroencephalogram. A pneumoencephalogram showed moderate caudate atrophy. Psychologic testing done at age 5 revealed a verbal IQ of 93, performance IQ of 103, and full-scale score of 101. When she was 7½ years old, her verbal score on the Wechsler Intelligence Scale for Children was 86, performance score was 85, and full-scale IQ was 84.

This patient's clinical features, pneumoencephalographic findings, and family history establish the diagnosis of Huntington's disease with childhood onset.

Discussion. Two interesting features of this family warrant discussion: (1) the occurrence of Huntington's disease in monozygotic twins, and (2) the occurrence of childhood and adult rigid variants of Huntington's disease in the same family.

In the English medical literature, Russell[2] first reported a set of twins concordant for hereditary chorea in 1894. Their probable monozygosity was based on only a brief description of remarkable likeness in physical appearance. Myrianthopoulos and Rowley[3] reviewed the world's literature on Huntington's disease in twins up to 1960 and found reports of eight sets of twins affected with the disease, but there was not adequate documentation of monozygosity for any of these twins. Seven of the eight pairs were concordant for Huntington's disease. Only the twins reported by Rosenthal[4] were discordant for the disease at age 40, but he examined only one of the twins and gave no evidence for monozygosity.

Twin studies generally are biased toward reporting concordant pairs, but no well-documented monozygotic twins have been described as discordant for Huntington's disease. (Both concordant and discordant dizygotic twins have been reported.[5,6]) Myrianthopoulos and Rowley[3] described a new set of female twins concordant for Huntington's disease and documented their identity with nine blood group determinations in addition to physical similarities. Despite disagreement regarding the neuropathologic diagnosis of Huntington's disease in the single autopsied member of that family, the clinical diagnoses seemed certain. In 1969, Schiottz-Christensen[7] reported concordant monozygotic twins affected with familial dementia, seizures, and jerky movements of relatively long duration. Oepen[8] and Husquinet, Franck, and Vranckx[9] have subsequently described monozygotic twins concordant for Huntington's disease. In none of these three most recent reports was there neuropathologic confirmation of Huntington's disease.

There can be no doubt concerning the diagnosis of Huntington's disease in the family described here. The clinical manifestations are typical, and the disease was neuropathologically confirmed in the mother (III-1) of the affected twins. The monozygosity of the twins is also well established through comparison of five blood groups, 22 enzyme loci, and general physical characteristics.

The twins are clearly concordant for Huntington's disease, with a similar age of onset in the third decade. However, at this time, they demonstrate a marked difference in clinical expression of the disease. Twin IV-3 has obvious chorea, whereas twin IV-2 has almost unnoticeable, subtle movements. More extensive chorea eventually may develop in twin IV-2, but it is of interest that this disparity presently exists. The twins described by Myrianthopoulos and Rowley[3] and by Oepen[8] also had clear differences in the severity of chorea. Each of the present twins has shown a moderate and approximately equal degree of mental deterioration. Deterioration of mental status appears to have been fairly closely correlated also in the monozygotic twins reported by Myrianthopoulos and Rowley,[3] Oepen,[8] and Husquinet, Franck, and Vranckx.[9] Most of the twins with chorea reported in the older literature are not described in sufficient detail to compare relative degrees of movement disorder and mental deterioration.

We conclude from the few well-documented monozygotic twins with Huntington's disease reported to date that the mental deterioration is more similar and consistent and the movement disorder is more variable in each set of twins. It is possible that the gene effect on the cerebral cortex is a more consistent expression of the disease than the effect on the basal ganglia, as has been suggested from clinical observations of large numbers of patients. In an extensive review of the literature, Bruyn[10] noted that "there may occur cases without motor symptoms, but never cases without mental symptoms, although such cases have been reported sporadically...and subtle mental and personality changes precede the motor manifestations by quite a period of time in the majority of cases." It is difficult to substantiate this clinical impression with neuropathologic data, primarily because the degenerative changes in the cerebral cortex may be relatively difficult to identify and quantitate.[10] Atrophy of the caudate nucleus is more easily documented and is essential for the pathologic diagnosis. Nevertheless, involvement of the basal ganglia varies considerably. Dunlap,[11] for example, found that the putamen may sometimes be more severely affected than the caudate, and involvement of the globus pallidus is even more variable.

The childhood and adult-onset rigid forms of Huntington's disease in the family reported here are also of interest. Onset of Huntington's disease before the age of 10 occurs in only about 1 to 3 percent of all cases, and in another 3 to 5 percent of cases, onset is between 10 and 20 years of age.[12-14] There is less agreement on the prevalence of the adult-onset rigid form of the disease, but it probably accounts for about 10 percent of all adult cases, with a range of 6 to 14 percent reported in various series.[15] The mean age of onset for all rigid patients with Huntington's disease is 22 years, but this includes juvenile-onset cases.[16] Excluding juvenile-onset patients, the mean age at onset of the adult-onset rigid variant is 34 years, probably still earlier than the mean in patients with nonrigid adult-onset disease.[12]

The affected child (V-2) in the family described here has the mental deterioration, progressive incoordination,

early signs of rigidity, and relatively mild chorea typical of childhood-onset Huntington's disease.[13,17] Her affected parent is her father, which is the case in approximately 75 percent of all juvenile patients with Huntington's disease, a phenomenon that remains unexplained.[18]

Furthermore, the affected grandmother (III-1) of this girl had the adult-onset rigid variant of Huntington's disease characterized by increased muscle tone, signs of spasticity and long motor tract involvement, dystonia of jaw and neck, and central facial paresis.[10,15] She also had chorea and progressive dementia. Although her affected twin sons do not presently demonstrate rigidity, their hyperactive deep tendon reflexes and unsustained ankle clonus (for which they are concordant) may be harbingers of the development of the rigid variant. This is, however, not predictable. Bittenbender and Quadfasel[19] noted that the development of rigidity is not inevitable in chronic Huntington's disease, although the actual proportion of patients that eventually become rigid is unknown.

Since juvenile-onset patients are often rigid and adult rigid patients generally have an earlier age of onset, there is obvious clinical overlap between these two forms of the disease. Whether these two variants are genetically related to each other and distinct from more typical Huntington's disease (as suggested by Bittenbender and Quadfasel[19]) or whether they simply represent uncommon expressions of a single disease continuum (as suggested by Myrianthopoulos[16]) remains undetermined.[20] Published reports do not provide sufficient information to ascertain whether a preponderance of fathers of adult-onset rigid patients is affected (as is the case with fathers of patients with juvenile-onset disease). Several published pedigrees describe more than one person in a single family affected with the adult rigid variant of Huntington's disease.[6,19,21–23] As in the present family, the typical nonrigid form of Huntington's disease also may occur in these families. In several families, more than one member has been affected with childhood or juvenile-onset Huntington's disease.[13,24–26] Byers and Dodge[17] described a man with Huntington's disease who fathered two sons with childhood Huntington's disease, each by a different woman.

We know of no systematic study correlating intrafamilial occurrence of childhood Huntington's disease with the adult rigid variant. Published pedigrees lack sufficient clinical information on affected family members to attempt such a study retrospectively. However, Jervis,[24] in describing childhood Huntington's disease in two pairs of siblings, states that the father of two of these children was once diagnosed as having dystonia musculorum deformans. The present family provides additional evidence that the childhood-onset and adult-onset rigid variants of Huntington's disease are genetically related. Whether these variants represent a separate genetic entity or part of a continuum of expression of Huntington's disease as a single genetic defect remains to be elucidated.

Addendum: Since the acceptance of this paper a monozygotic twin pair concordant for juvenile Huntington's Disease has been reported in abstract form (Bachman D, Butler I, McKhann G: The use of depakine in the treatment of identical twins with juvenile Huntington's chorea. Proceedings of the Fourth Annual Child Neurology Society Meeting, Hamilton, Ontario, Canada, October 3 and 4, 1975, Abstract 8).

Acknowledgment

The patient with childhood Huntington's disease was referred for evaluation by Dr. John B. Moon. Medical records and the neuropathologic report on patients II-7 and III-1 were provided by Colorado State Hospital, Pueblo, Colorado. Blood group and enzyme loci testing were kindly performed by Dr. Eloise Giblett of the King County Blood Bank, Seattle.

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