Familial essential ('benign') chorea¹

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Summary. A family is described with essential non-progressive chorea occurring in an autosomal dominant inheritance pattern over four generations. A few families with an apparently similar disorder have been reported previously. This condition is characterized by early childhood onset of chorea which is not progressive and is compatible with a long life. It is not associated with dementia, seizures, rigidity, or ataxia. It is a socially embarrassing condition and may, sometimes, be associated with behavioural problems and learning difficulties. For genetic counselling, it is important to distinguish this disorder from Huntington's disease and other hereditary disorders associated with chorea.

Numerous diseases have been associated with chorea, but the most common hereditary disorder producing chorea is Huntington's disease. Because there is no definitive test for Huntington's disease apart from necropsy, it is sometimes difficult to differentiate it from other causes of chorea. A family history of chorea is considered extremely useful in arriving at the diagnosis of Huntington's disease. However, in the past 8 years there have been a few reports of a non-progressive hereditary movement disorder referred to as 'benign familial chorea' which is distinct from Huntington's disease. We have recently evaluated a family with such a condition and wish to describe the salient features of this seldom mentioned clinical entity and compare it with other familial disorders associated with chorea.

Description of family

The proband (V.5) was a 6-year-old white boy who was the product of a full-term, uncomplicated pregnancy and delivery. He passed the usual developmental motor, language, and social milestones of infancy and childhood at normal times. However, between the ages of 1 and 2 years his father noticed slight jerky movements of his son's hands which he recognized as the same

movements occurring in the other members of his family. The boy did average work in kindergarten and first grade but had some difficulty with handwriting and drawing. He had no rheumatic fever, seizures, meningitis, or serious head trauma.

Physical examination showed a co-operative boy of normal size and proportion for his age. He had mild choreiform movements of his fingers and hands at rest, which were increased with stress but were never severe. The movements were sudden, jerky, of small amplitude, and generally involved distal parts of the upper extremities. Similar movements were occasionally noted of the shoulders, feet, and head. Facial grimacing is only rarely seen. He had modest difficulty in maintaining tongue protrusion. There was an excessive amount of finger 'piano playing' when his arms were outstretched. He did not have myoclonus, intention tremor, ataxia, or dystonia. He was clumsy in performing co-ordinated motor tasks such as hopping on one foot and he was unable to skip. Handwriting and figure drawing were done unsteadily and irregularly. Deep tendon reflexes were brisk and symmetrical and plantar reflexes were down-going. Muscle tone was normal. Testing of cranial nerve function and appreciation of sensory modalities was normal. The remainder of the physical examination was unremarkable. He had no heart murmur.

The following laboratory tests were normal: skull x-rays, electroencephalogram, urine amino-acid and mucopolysaccharide screen, serum calcium and phosphorus, anti-streptolysin-0 titre, and caeruloplasmin. The Wechsler-Intelligence Scale for Children showed a verbal IQ of 106 and performance IQ of 90, with a full-scale score of 98. His poorest subtest score was on picture completion. Results of the Frostig Visual Perception test are normal for his age.

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Fig. Pedigree of family with familial essential chorea. Those members marked * have either been examined or their medical records have been reviewed.

The family and clinic physicians noted no change in the frequency or severity of his adventitious movements.

The proband's younger brother (V.6) was examined and had no adventitious movements.

The proband's father (IV.3) was 29 years-old and was first noted to have jerky movements before the age of 5. He referred to these movements as 'nervous fidgets'. He recalled being teased about the movements in school and was embarrassed by them. He left school after the 8th grade, completed two years of military service, and at present is an unemployed carpenter. He recalled that the jerks were worse as a child but improved during adolescence, such that they were barely noticeable. On examination he was quite anxious, with a tendency to stammer. He had frequent subtle choreiform movements of his fingers, hands, and feet which often appeared like 'fidgeting'. He had no facial grimacing, ataxia, tremor, or myoclonus. The clinical impression of his intelligence was 'low normal'. His handwriting and figure drawing were normal. His deep tendon reflexes were brisk and symmetrical. Except for old trauma to his left eye, the remainder of his neurological examination was normal. His skull x-rays and complete blood count were normal, including red blood cell morphology. Acanthocytes were specifically searched for and not found.

The proband's paternal grandmother (III.4) was 47 years old and had been affected with the family movement disorder since early childhood. She, too, was teased as a child, had trouble with writing in school and only completed the 9th grade. She had two separate year-long admissions to a 'sanitarium' at ages 9 and 12 for diagnosis and treatment of her condition (primarily rest and various diets). She was told she probably had Sydenham's chorea, though she had no history of rheumatic fever. She believed that her jerky movements were less severe as an adult than they were as a child. However, they continued to annoy and embarrass her. She reported that a doctor once told her that she had Huntington's disease. In adulthood, she noted

sudden extension spasms of her neck lasting a few seconds (not observed by us). (Her affected mother also had these spasms.) She had taken numerous medicines for her movements without any beneficial effects (including benzodiazepines and phenobarbitone). Examination showed frequent mild choreiform movements of her hands, feet, and head. She had no tremor, myoclonus, or ataxia. Cranial nerve testing and deep tendon reflexes were normal. She had no pathological reflexes. She was of average intelligence with a good memory.

This paternal grandmother (III.4) had two daughters by a second husband. One of the daughters was unaffected. The other (IV.5) was 18 years old and had had adventitious movements since age 5. She had no history of rheumatic fever. Her examination was remarkable only for frequent mild choreiform movements of her hands, feet, arms, and face. The movements were moderately increased by stress and anxiety. She was of normal intelligence, had no tremor, no ataxia, no dystonia, and no heart murmur. Forty-five milligrams of phenobarbitone per day has not changed her movements.

The paternal great-grandmother of the proband (II.2) was the earliest known affected family member. Her parents were unrelated, of English ancestry, and neither was known to have had a movement disorder. Her mother died of diphtheria at age 44 and her father died of heart disease at age 96. Examination of her father at age 72 showed no abnormal movements. Her father was 31 when she was born. Her birth was uncomplicated and she began walking and talking at normal ages. She was said to have had a severe febrile illness at 1 year of age and difficulty in walking, and 'nervous fidgets' were always noted after that time. She attended school and was in the 'middle of her class' academically. She recalled often having to leave class because of 'fidgeting, squirming' and facial grimacing. At age 12 she was told she had rheumatic fever with St Vitus's dance. Apparently her movements became worse at this age for

several months and then showed some improvement. However, for her entire life she had almost constant mild to moderate choreiform movements, made worse with stress. She had 4 unaffected sibs, all of whom have had unaffected children. However, 3 of this woman's 6 children are affected.

Records of an examination at age 41 reported choreiform movements of her arms and face, mild 'intention tremor', and a divergent squint. These abnormalities did not interfere with fine motor tasks. She had no ataxia, spasticity, or sensory deficits. Optic discs were normal. The frequency and severity of her movements did not change during her adult life, but they were a continual social embarrassment to her. At one time she is said to have received electroshock therapy for her 'nervousness'.

At age 65 she developed carcinoma of the colon. It was then known that her children also had chorea and her physicians raised the possibility of Huntington's disease. Examination at another hospital showed a thin, apprehensive woman with 'severe nervousness'. At rest she was 'nearly free' of adventitious movements and drank easily from a cup of tea. However, with stress or anxiety she had almost constant jerking movements of her arms and legs and sucking in and out of her lower lip. Descriptions of her movements included 'jerking, twisting, turning, grimacing' and one observer noted 'tremor' on finger-to-nose testing. A neurologist described her movements as 'more choreiform than athetoid'. Her memory and intellect were normal, deep tendon reflexes were all present, and symmetrical and her plantar reflexes were down.

The following laboratory studies were normal: chest x-ray, skull x-rays, complete blood count (including red blood cell morphology), routine serum VDRL, electroencephalogram, and brain scan. Lumbar puncture had a normal opening pressure with CSF protein of 52 mg/100 ml, no cells, and normal protein electrophoresis. A pneumoencephalogram showed the entire ventricular system and was normal for her age. The caudate nuclei were well outlined and were normal in size and shape. (This study has been reviewed and the findings confirmed.)

The patient's neurological diagnosis at discharge was 'probably old residual Sydenham's chorea'. She died at age 66 from complications of colonic cancer. There was no necropsy.

A paternal great uncle (III.8) of the proband had also been affected with 'bad jerking' movements since childhood and he left school after the 7th grade. The family considered him to be of normal intelligence. He had been unable to maintain employment and had serious behavioural problems leading to imprisonment. He was not examined.

Another paternal great uncle (III.3) was 49 years old and had been affected with uncontrolled movements since early childhood. According to school records, he did not attend school beyond age 8 because he was 'too restless and undisciplined'. From ages 8 to 17 he was confined to a state school for the mentally retarded, though his family regarded his intelligence as average.

His Stanford-Binet IQ score at 12½ years was 71. On examination at 17 years he had purposeless jerks of all extremities, distal and proximal, and facial grimacing. He had no heart murmur and no history of rheumatic fever. During adult life he had had considerable difficulty obtaining and maintaining employment. He had two children, one of whom the family considered to be also affected with a movement disorder. This man and his children lived out of state and had not been recently examined.

Discussion

This family had a hereditary movement disorder, best described as chorea, with the following clinical characteristics: (1) autosomal dominant pattern of inheritance; (2) early childhood onset of rapid, jerky movements that were usually distal and often appeared as 'nervous fidgeting'; (3) non-progressive course compatible with a full adult life span; (4) high penetrance but variable severity and expressivity; (5) not associated with dementia, seizures, rigidity, or ataxia; (6) often associated with anxiety, social embarrassment, school problems, or behavioural difficulties; and (7) no evidence of caudate atrophy on pneumoencephalography performed on one adult, affected with chorea for more than 60 years.

Several hereditary neurological disorders are associated with chorea. The inheritance, prognosis, and treatment of these diseases are variable, so it is important to differentiate them. The Table compares the characteristics of familial essential chorea (as described in the present family and other reported families) with those of five other genetic diseases associated with chorea.

The disorder occurring in this family may have been included in the so called 'biotypes' of Huntington's disease described many years ago by Davenport and Muncey (1917). The present disorder is quite unlike childhood-onset Huntington's disease which is always progressive and usually associated with rigidity, seizures, and mental deterioration (Byers and Dodge, 1967). The present family does not have acanthocytes, hyporeflexia, or prominent orofacial dyskinesia as described in the familial chorea-acanthocytosis-normolipoproteinemia syndrome, which is clinically similar to Huntington's disease (Critchley, Clark, and Wikler, 1968; Levine, Estes, and Looney, 1968; Cederbaum *et al.*, 1971; Aminoff, 1972). The familial paroxysmal choreoathetosis syndrome is a heterogenous clinical entity, but the paroxysmal nature of the chorea, its precipitation by sudden movement, and the electroencephalogram abnormalities noted in some patients are not present in this family (Kertesz, 1967; Perez-Borja, Tassinari,

TABLE
HEREDITARY DISORDERS

	Familial Essential Chorea	Huntington's Disease	Familial Chorea with Acanthocytosis
Inheritance	AD, ? AR in some families	AD	Probably AR with ? manifestation in carriers (? AD)
Age of onset	Childhood	Adult (less than 10% before age 20)	Young adult (occasional childhood)
Course	Non-progressive (? occasionally slowly progressive)	Progressive	Progressive
Usual movement disorder	Mild to moderate chorea	Increasingly severe chorea in adults	Chorea and prominent oro-facial dyskinesia
Intellect	Usually normal, behavioural problems (? occasional mild mental retardation)	Progressive dementia	Variable, mild to moderate dementia or normal
Seizures	No	Seizures common in childhood onset, occasional in adults	Occasional
Associated findings	Intention tremor in some patients, electroencephalogram usually normal	Rigidity and ataxia in children, chorea less common in children, abnormal electroencephalogram	Red cell acanthocytosis, hyporeflexia, muscle atrophy, normal beta lipoprotein, abnormal electroencephalogram
Pathology	Unknown, normal pneumoencephalogram	Cerebral cortical/striatal atrophy	Unknown, cortical and caudate atrophy on pneumoencephalogram in some cases
Biochemical defect	Unknown	Unknown (? basal ganglia neurotransmitter defect)	Unknown
Treatment	Not well defined	Haloperidol, diazepam, reserpine, phenothiazines—palliative	Not well defined

Other hereditary disorders occasionally associated with chorea: (1) pseudohypoparathyroidism (X-linked dominant); (2) familial calcification of basal ganglia (AD and AR); (3) Hallervorden-Spatz Syndrome (AR); and (4) familial myoclonus syndromes (AD and AR). AD = Autosomal dominant; AR = Autosomal recessive.

and Swanson, 1967; Richards and Barnett, 1968; Horner and Jackson, 1969). The autosomal dominant inheritance in this family and the normal caeruloplasmin in the proband eliminate Wilson's disease from consideration. It is important to investigate the possibility of Wilson's disease in unexplained movement disorders because the progression of the disease is prevented by proper treatment. Lesch-Nyhan HGPRT deficiency is not the disorder in this family because of the presence of male-to-male transmission and the lack of self-mutilation and mental retardation (Kelley and Wyngaarden, 1972).

A number of other hereditary disorders are occasionally, though not typically, associated with chorea, or may include movements that are difficult to distinguish from chorea. Bruyn (1973) has given a relatively complete listing of these diseases. It should be noted that pseudohypoparathyroidism is thought to be an X-linked dominant disorder associated with resistance to parathyroid hormone, hypocalcaemia, skeletal anomalies, and mental retardation that is occasionally associated with chorea. Familial calcification of the basal ganglia represents several rare syndromes in which rigidity and Parkinsonian features are more common than chorea, and skull x-rays may show the mineral deposits in the basal ganglia and dentate nuclei. The age of onset of extrapyramidal or cerebellar signs is highly variable. Some persons with typical x-ray findings are asymptomatic. A few patients have had microcephaly, mental retardation, and

seizures. Both autosomal dominant and recessive inheritance have been described (Lowenthal and Bruyn, 1968; Moskowitz, Winickoff, and Heinz, 1971). Hallervorden-Spatz syndrome is a rare disease of childhood onset associated with mineral deposition in the basal ganglia. It is probably autosomal recessive and produces rigidity and progressive dementia in addition to choreoathetosis. There is no definitive diagnostic test during life (Meyer, 1963). There are numerous hereditary disorders producing myoclonus which in some instances may be difficult to distinguish from chorea, as noted by Refsum and Sjaastad (1973).

Other diseases with a genetic component that have sporadically produced choreiform movements include: Bassen-Kornsweig's ataxia—abetalipoproteinaemia (AR), various neuronal lipid storage disorders (AR), Friedreich's ataxia (usually AR), dystonia musculorum deformans (AD and AR), phenylketonuria (AR), ataxia telangiectasia (AR), Pick's disease (often AD), Alzheimer's disease (AD in some families), and Gilles de la Tourette (increased familial incidence) (Bruyn, 1973).

Finally, it should be noted that the disease in the present family does not represent benign essential tremor (the movement is not a tremor) or Sydenham's chorea (it is not related to rheumatic fever and is clearly hereditary).

One is left with referring to the disorder in the present family as familial essential chorea. 'Benign' familial chorea is an understandable designation for this condition if the term 'benign' is used relative to

ASSOCIATED WITH CHOREA

Familial Paroxysmal Choreoathetosis	Wilson's Disease	Lesch-Nyhan Syndrome
AD (? AR in some families)	AR	X-linked recessive
Childhood	Variable, usually childhood	Infancy and early childhood
Non progressive	Progressive	Progressive
Paroxysms of choreoathetosis sometimes induced by movement	Variable, including severe flapping tremor, chorea, or dystonia	Choreoathetosis
Normal	Progressive dementia	Mental retardation
Clinical heterogeneity, may be reflex epilepsy in some families	Occasional	50% of patients
Abnormal electroencephalogram in some families	Spasticity, rigidity, Kayser-Fleischer ring, liver disease, aminoaciduria, ↓ serum caeruloplasmin and copper, ↑ urine copper excretion	Self mutilation, ↑ uric acid, renal disease with calculi, gout, megaloblastic anaemia
Unknown	Hepato-lenticular degeneration with copper deposition	Non-specific cerebral degeneration
Unknown	Defect in copper metabolism	Deficiency of hypoxanthine guanine phosphoribosyl transferase
Anticonvulsants in some cases	Penicillamine	Allopurinol to prevent renal failure

Huntington's disease. The dementia and relentlessly progressive course of Huntington's disease, which make it a clinically 'malignant' condition, are absent from the present disorder. However, the disease in this family has caused the affected members considerable distress in the form of social embarrassment, difficulty in obtaining employment, and many admissions to hospital for diagnosis and treatment. The behavioural problems and difficulty with co-ordinated motor tasks shown by several affected members could represent a mild degree of diffuse cerebral involvement by this disease. Conversely, the behavioural problems could primarily represent the affected person's emotional reaction to a physical embarrassment. The maladroitness and 16-point differential between verbal and performance IQ scores in the proband support a mild neurological deficit beyond simple chorea. For these reasons familial essential chorea or familial non-progressive chorea are more appropriate terms for this disorder than 'benign'.

A few families have been previously reported with a syndrome similar to the one we are describing. Haerer, Currier, and Jackson (1967) described a family with hereditary non-progressive chorea of early onset in several members in three generations. A subsequent report (Refsum and Sjaastad, 1973) has suggested that the family reported by Haerer actually suffers from a form of myoclonus, emphasizing the ambiguous nature of clinical terms describing various movement disorders. The present family's movements are best described as chorea, though

that term is imprecise, and it may sometimes be difficult to distinguish chorea from other forms of movement disorder. In any event, chorea is simply a clinical description of certain variable adventitious movements, not a disease entity. It is not surprising that a genetic autosomal dominant disease is variable in its expression.

Pincus and Chutorian (1967) described a familial benign chorea associated with intention tremor in two families. They noted childhood onset, autosomal dominant inheritance, normal intellect, and lack of progression. An intention tremor of mild to moderate degree was seen in the upper extremities. The gait was not ataxic. Sadjapour and Amato (1973) reported a family with nonprogressive chorea, childhood onset, and no tremor. The children were maladroit, had dull normal IQ's, and were not doing well in school. Some family members had been institutionalized for psychosis or mental retardation, but their precise mental status was unknown. Chun and co-authors (1973) presented two families with childhood onset, non-progressive chorea. Neither intellectual deficit nor intention tremor were described. Inheritance appeared to be autosomal dominant.

Chun and co-authors (1973) and Nutting, Cole, and Schimke (1969) have each reported a family with childhood onset, nonprogressive chorea compatible with recessive inheritance. The family members reported by Chun had learning difficulties and possible mild mental retardation. No mention was made of examination of the parents, who

had four affected and three unaffected children. Nutting described normal parents who had one affected boy, two affected girls, and two unaffected girls. The patients had only mild to moderate choreoathetosis without tremor or intellectual deficit.

The characteristics of the reported families with essential chorea are summarized in the first column of the Table. The prevalence of familial essential chorea is undetermined, but is undoubtedly greater than the few reported cases suggest. This clinical syndrome may well have more than one aetiology with both dominant and recessive inheritance possible. In the present family either the paternal great grandmother (II.2) represents a new mutation or one of her parents (presumably her mother, I.2) was an unrecognized carrier of the gene.

The underlying pathophysiological and biochemical mechanisms of familial essential chorea remain undetermined. Chorea is usually thought to represent impairment of the corpus striatum, with the severe involvement of the caudate and putamen in Huntington's disease being the classic example. Caudate atrophy in advanced Huntington's disease is often, but not always, demonstrable by pneumoencephalography (Blinderman, Weidner, and Markham, 1964). It is of interest that the caudate was of normal size in the 65 year-old affected adult in this family studied by pneumoencephalography. The clinical overlap with intention tremor and possibly myoclonus noted in previous reports of this condition suggests extension of the disease process to the cerebellum-dentate nucleus system in some cases. No effective drug therapy has been found in our limited experience with this family, and further modes of drug therapy are planned.

The differentiation of this relatively mild and nonprogressive disorder from Huntington's disease and other hereditary disorders associated with chorea is of obvious importance for advising affected families about prognosis and giving genetic counselling. The early childhood onset, lack of progression over many years, and absence of dementia clearly distinguish this disorder from Huntington's disease.

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