

'Pseudo-dominant' inheritance in Friedreich's ataxia

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SUMMARY A family is described in which Friedreich's ataxia occurred in two generations. It is proposed that this resulted from a homozygote-heterozygote mating. The heterozygote frequency for the Friedreich's ataxia gene is in the order of 1 in 110, so the likelihood of the disease developing in an individual child of a patient is 1 in 220. This risk is probably higher than that often assumed when counselling patients with this disorder.

Friedreich's ataxia is probably the most common of the hereditary ataxias. For this reason it has been reasonably well defined both clinically and genetically. Symptoms usually develop by the age of 20. Dysarthria, limb and gait ataxia, tendon areflexia, and signs of pyramidal and posterior column tract damage are characteristic findings. Skeletal deformity and cardiomyopathy are frequent.¹ Inheritance is now accepted to be autosomal recessive.² Most reports of autosomal dominant inheritance are almost certainly incorrect in that, on close examination, they describe patients with the Roussy-Lévy form of Charcot-Marie-Tooth disease or cerebellar degenerations with clinical features different from those of Friedreich's ataxia.^{3 4}

This paper describes a family in which Friedreich's ataxia occurred in two generations. The pedigree is illustrated in fig 1.

Case reports

Case III.8 was a female aged 52. She had no symptoms and full neurological examination and ECG were normal.

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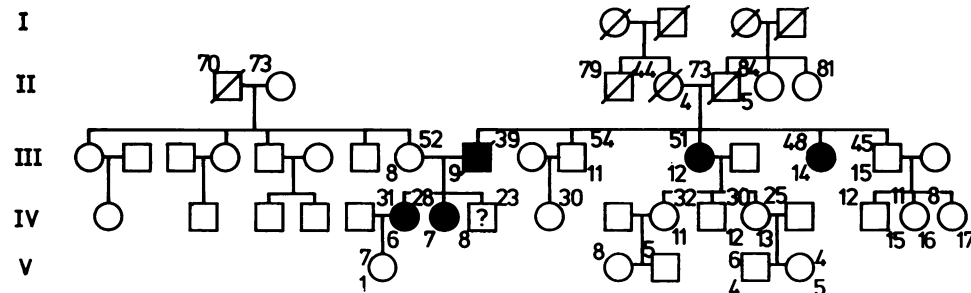


FIG 1 Pedigree of family. (Numbers above symbols indicate age in years at time of study or at death.)

Case III.9 was a male who died aged 39. He was said to have become unsteady aged about 27. Examination at the age of 35 revealed dysarthria, marked intention tremor in the upper limbs, severely ataxic gait, absent tendon reflexes, and extensor plantar responses. He died in 1966 following a subarachnoid haemorrhage from an aneurysm at the left internal carotid bifurcation.

Case III.11 was a male aged 54 who was neurologically normal.

Case III.12 was a female aged 51. She had difficulty in skating aged 17 because of poor balance and was unable to carry full cups as a teenager. She had a progressively unsteady gait and was only able to walk indoors with a frame; she was otherwise chair-bound. She had been hypertensive for 4 years. Examination revealed cerebellar dysarthria, moderate ataxia in the upper limbs, and mild pyramidal weakness and severe ataxia in the lower limbs. The left biceps jerk was just present, but all other tendon reflexes were absent and the plantar responses were extensor. Vibration sense was reduced in the feet and she had severe ataxia of gait.

On ECG there was mild left axis deviation (-30°), and T wave inversion in leads I, aVL, and

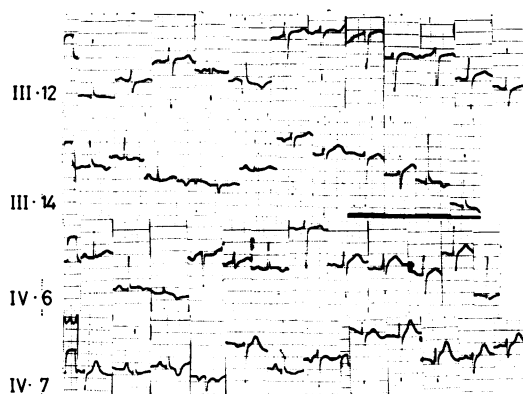


FIG 2 Electrocardiographs of patients III.12, III.14, IV.6, and IV.7. Single complexes are arranged in the following order (from left to right): I, II, III, aVR, aVL, aVF, and V1-6. Calibration: 1 mv = 2 large squares (one large square for leads V2-6 in IV.7).

V1 (fig 2). CT scan and blood sugar were normal. Motor nerve conduction velocities (MNCV) in the median and peroneal nerves were 51.5 and 47.0 msec⁻¹, respectively. Median and ulnar (finger/wrist) sensory action potentials (SAP) were reduced in amplitude (5 and 2.8 μ v) but had normal latencies to peak of 2.8 msec.

Case III.14 was a female aged 48. A tendency to stagger was noticed at the age of 22 and Friedreich's ataxia was diagnosed at the age of 27. She was just able to walk with a frame indoors. Examination revealed moderate dysarthria, mild pyramidal weakness and severe ataxia in the upper limbs, and moderate pyramidal weakness and severe ataxia in the lower limbs. All tendon reflexes were absent and the plantar responses were extensor. Joint position sense was reduced in the toes and she had a markedly ataxic gait. ECG showed left ventricular hypertrophy on voltage criteria and T wave inversion in leads I, II, V5, and V6 (fig 2).

Case III.15 was a male aged 45. The neurological examination was normal.

Case IV.6 was a female aged 31. Her mother noticed an abnormal gait at the age of 18 and she began to stagger at the age of 20 with progressive difficulty in walking. Examination revealed mild dysarthria and titubatory tremor of the head, mild pyramidal weakness of the lower limbs, and moderate ataxia in all four limbs. The right biceps jerk was just present and all other tendon reflexes were absent. The plantar responses were extensor and the gait was moderately ataxic. On ECG there was T wave inversion in leads II, III, aVF, and aVR (fig 2).

Case IV.7 was a female aged 28. Her feet were noted to 'turn in' when aged 11. She had great difficulty walking after surgery, and was wheelchair-bound at the age of 14. Her hands were very clumsy. Examination revealed pallor of both optic discs (acuity 6/18), severe dysarthria, mild distal wasting, moderate pyramidal weakness, and severe ataxia in the upper and lower limbs. The tendon reflexes were all absent, the plantar responses were extensor, and joint position and vibration sense were reduced in the feet. There was mild thoracic scoliosis and pes cavus. ECG revealed right axis deviation (+105°), T waves were inverted in leads III, aVF, and V1, and there was clockwise rotation (fig 2). Glucose tolerance test was within normal limits. Ulnar and median MNCV were 52.8 and 65.8 msec⁻¹, respectively. No ulnar, median, or sural SAP were detectable.

Case IV.8 was a male aged 23 who claimed to have a 'reeling' gait but refused examination. No obvious abnormality of gait could be seen on observation.

Cases IV.13, 15, 16, 17, V.1, 4, 5 were all examined and found to be neurologically normal.

Cases IV.11 and 12 were unavailable for study but both currently play tennis or football and have no symptoms.

Discussion

The clinical features of the affected subjects in this family fulfil the criteria described by Geoffroy *et al*¹ for a diagnosis of Friedreich's ataxia. All had progressive ataxia, dysarthria, pyramidal signs, and tendon areflexia. The presence of cardiomyopathy is of diagnostic importance. The ECG changes found (fig 2) are typical of those seen in association with this disease⁵ and do not occur in other inherited cerebellar ataxias (A E Harding, unpublished data). The neurophysiological findings of normal motor and abnormal sensory conduction are also characteristic of Friedreich's ataxia.⁶

There are two unusual features of Friedreich's ataxia in this family apart from the pattern of inheritance. Firstly, the ages of onset in III.9 and III.14 are somewhat later than usual. Most patients with this disease develop symptoms around puberty,¹ although occasionally as late as the third decade.⁷ It may be that the given ages of onset were inaccurate; both subjects were somewhat stoical and a considerable period of time had elapsed since the onset of the disorder.

Secondly, there is considerable variation in severity, between different family members, particularly IV.7 and her sister. The former certainly deteriorated after surgery, presumably as a result of prolonged bedrest, but even so the discrepancy in disability is

more than would be normally expected in Friedreich's ataxia.

It is tempting to assume that the patients reported here suffer from a dominantly inherited form of Friedreich's ataxia. If this were so, expression of the gene must have been very limited in either II.4 or II.5, presumably the former, who was asymptomatic before her death aged 44. It is also significant that members of earlier generations were unaffected and only one sibship in generation IV contained affected subjects.

There is only one family previously described in which a subject transmitted classical Friedreich's ataxia to his offspring. In 1885, Vizioli⁸ reported a sibship in which eight of 16 were affected; both parents were normal and died aged over 70. One of the patients had two affected and three normal children, but two of his affected sibs had a total of five unaffected children. There are no pedigrees in previously published reports which show transmission of the disease through three generations. It seems most likely that the explanation of the pedigree described here, and that of Vizioli,⁸ is that a heterozygote-homozygote mating resulted in affected offspring.

The incidence of Friedreich's ataxia is unknown. The Friedreich's Ataxia Group has approximately 600 members (personal communication, 1980), but this figure obviously falls short of the total number in Great Britain. If the incidence of cousin marriage among parents of affected subjects (C) is known, the gene frequency (q) can be calculated from the formula

$$q = \frac{a(1-C)}{16C - Ca - 15a},^9$$

where a is the frequency of first cousin marriage in the general population.

In a recent study of Friedreich's ataxia (A E Harding, unpublished data), five of 90 sibships had parents who were first cousins, all of whom were British. The mean age of affected subjects was 32.3 ± 13.8 . Most of their parents would therefore have married between the years 1925 and 1957 and there are no accurate figures available concerning the rate of cousin marriage during this period. Bell¹⁰ found the incidence of first cousin marriages around 1930 (among parents of children aged under 15 admitted to general hospitals in the late 1930s) to be 0.485%. The frequency of first cousin marriages in the general population over the period 1925 to 1957 was probably, on average, about 0.4%. This figure takes into account a fall in the incidence of consanguineous marriages after 1930, and also the probability that children admitted to hospital are

more likely to be the offspring of consanguineous matings than those in the general population.

Assuming that $a = 0.004$, and that the population of Great Britain is 54 390 000,¹¹ the homozygote frequency is estimated at 1 in 48 116. The heterozygote frequency is therefore approximately 1 in 110 (where $2q = 1/110$). The probability of each child of a homozygote being affected is thus in the region of 1 in 220, assuming no consanguinity. (This was denied in the family reported here.)

Although some patients with Friedreich's ataxia are too disabled to reproduce, a significant number request genetic counselling and have children. The genetic risk for transmission by these homozygous subjects is admittedly low. Yet the gene frequency of Friedreich's ataxia in Great Britain is perhaps greater than often assumed and, as demonstrated by the family described in this report, such a risk cannot be entirely dismissed.

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