Probable autosomal recessive Marfan syndrome

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SUMMARY A probable autosomal recessive mode of inheritance is described in a family with two affected sisters. The sisters showed the typical picture of Marfan syndrome and were of normal intelligence. Both parents and all four grandparents were personally examined and found to be normal. Homocystinuria was ruled out on repeated examinations. This family suggests genetic heterogeneity in Marfan syndrome and that in some rare families the mode of inheritance may be autosomal recessive.

Marfan syndrome is well established as a disease caused by an autosomal dominant gene (McKusick, 1972). The purpose of this report is to present a family with Marfan syndrome in two sisters but with normal parents and grandparents and completely negative family history, suggesting a probable autosomal recessive mode of inheritance.

Family report

The probosita, Case 1 (III.4, Fig. 1) was the oldest in her sibship. The family (Fig. 2) is Ashkenazi Jewish. The parents were not related, the mother being of German origin while the father's parents were born in Lithuania. Both parents, all four grandparents, and the two sisters of the probosita were personally and ophthalmologically examined with maximal dilatation of the pupils. The father (II.4) (height 178 cm) and mother (II.5) (height 160 cm) (Fig. 2a standing on both sides of the children) were found to be in good health and without eye or heart disease at last

examination, at the age of 36 and 35, respectively. The next born sister (III.5) (Fig. 2, a and b, centre) was a 10-year-old normal girl (height 126 cm) with normal ophthalmological examination. The youngest sister, Case 2 (III.6), was also affected (Fig. 2, a and b, smallest child). The grandparents (Fig. 1) I.1, I.2, I.3, and I.4, were, respectively, 159, 158, 162, and 156 cm in height and were in good health in their sixties without any sign of Marfan syndrome.

CASE 1

(III.4) The probosita (Fig. 2, a and b, tallest of the children, c centre) was born in August 1964 and at that time her mother was 23 years old and the father was 24. At the age of 12 the girl was very tall (height 174 cm, that is 10 cm above the 97th centile). She had joint laxity and arachnodactyly. Cardiological evaluation disclosed only a midsystolic click. She had superiorly dislocated lenses (Fig. 3). Her intelligence was above average. She had no malar flush and no osteoporosis. She had no history of thrombotic lesions of arteries and veins. She had a history of a febrile convulsion in infancy but at present her electroencephalogram is normal. Repeated urine examination did not reveal any increase in amino acids and in particular homocystine was not detected. Homocystinuria can, therefore, be excluded.

CASE 2

(III.6) The youngest sister of the probosita (Fig. 2, a and b, smallest child) was born in May 1974. At the age of 2 years the girl was tall (height 92 cm, that is 1 cm below the 97th centile). She had similar manifestations of Marfan syndrome to those of her affected sister but because of her much younger age

Fig. 1 Pedigree.

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Fig. 2 The family. (a) The normal parents on both sides and the children. (b) The proposita age 12 (left), normal sister age 10 (centre), affected sister age 2 (right). (c) The hands of the mother right (with ring), the father left, and the proposita centre.

they were less striking. She had long slender fingers (Fig. 4). She had slightly superiorly dislocated lenses that could be detected only on maximal dilatation of the pupils. She had normal intelligence. She had no malar flush and no history of thrombotic lesions of arteries and veins. Her electroencephalogram was normal. Cardiological examination was normal.

Repeated urine examination did not disclose any increase in amino acids, and as homocystine was not detected, homocystinuria can be excluded and the diagnosis of Marfan syndrome is established in the two sisters.

Discussion

Lutman and Neel (1949) have already stated, 'that in an occasional case the disease may be due to a recessive

Fig. 3 Case 1. Bilateral superior dislocation of the lenses. The iris and lens of one eye.

Fig. 4 The hand of Case 2.

factor cannot be ruled out, but the absence of a significant amount of consanguinity in the parents of affected persons suggests that this is not often true'. The proof that a sporadic case is the result of a fresh dominant mutation is usually in the next generation when an affected offspring is born (Fried and Mundel, 1974). The finding of two affected sisters with normal parents could be explained by non-penetrance of the

dominant gene in one of the parents but this must be very rare as there are no well-documented cases of skipping of generation in this disease (McKusick, 1972). One of the parents could be a carrier of a segmental or gonadal mutation but this is again very rare.

Finally, the most probable explanation of this pedigree is that of an autosomal recessive mode of inheritance even in the absence of consanguinity in the parents. Genetic heterogeneity in Marfan syndrome is a possibility that should be taken into consideration as it has practical consequences in genetic counselling. If the sisters have a recessive disease, the risk for their children in the future will be negligible in contrast to the risk of 50% if they have the usual dominant form of the disease. Follow-up of this family in a generation time will be of interest and all families with affected sibs and normal parents should be reported.

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