Recessively inherited growth hormone deficiency in a family from Iraq

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SUMMARY A family from Iraq with five growth hormone deficient children in two closely related sibships is reported. The clinical forms and modes of inheritance of familial growth hormone deficiency are discussed briefly.

The inherited forms of growth hormone deficiency appear to be relatively uncommon,¹ but it is well known that in a proportion of cases the condition is inherited as a recessive disorder, either as an isolated deficiency,²⁻⁶ or as a multiple deficiency of anterior pituitary hormones.⁷⁻⁹ Most of the families reported have been from the United States,^{2 3 10 11} but examples from Europe,^{1 4} Israel,⁵ and Japan⁶ have been described. Some of the most striking examples have been found in closed communities with high consanguinity rates. We report a further family from Iraq with five growth hormone deficient children in two closely related sibships.

Case reports

The five children, three boys and twin girls aged from 2.9 to 7.7 years, were referred for investi-

gation of severe growth failure. As shown in fig 1, the two fathers are brothers who are married to first cousins. In each sibship there is one child of normal size. All four parents are of normal height and there are no other cases of abnormal short stature known in the family.

All five children appeared normal at birth but delayed growth became evident in early infancy. In other respects their health was normal and their parents considered them to be of normal intelligence.

The patients' clinical details are summarised in table 1 and their appearance is shown in fig 2. They were all extremely small (height -6.6 to -9.0 SD) and showed mid-face hypoplasia with apparently prominent eyes and prominent foreheads with normal cranial vaults. Ample subcutaneous fat was

FIG 1 Pedigree of the five children with growth hormone deficiency.

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TABLE 1 Clinical and laboratory data in the patients

	IV.1	IV.2	IV.3	IV.4	IV.5
<i>Clinical data</i>					
Sex	M	M	M	F	F
Age (yr)	7.7	6.4	5.2	2.9	2.9
Height (cm)	74	74	79	66	63.5
(SD)	(-9)	(-8.2)	(-6.6)	(-7.4)	(-7.8)
Weight (kg)	11	10	10	8	7
(SD)	(-4.2)	(-4.6)	(-4.3)	(-4.3)	(-4.9)
Head circumference (cm)	46	48	48.5	45.0	44.5
(SD)	(-4.6)	(-3.0)	(-2.4)	(-3.2)	(-3.6)
<i>Laboratory data (after overnight fast)</i>					
Blood glucose (mmol/l)	2.5	2.3	1.2	0.6	1.8
Growth hormone (mU/l)	<1.0	<1.0	<1.0	1.2	1.1
Prolactin (mU/l)	308	804	863	996	242
Thyroxine (nmol/l)	71	72	87	109	71
Plasma cortisol (nmol/l)	399	292	285	600	120
Bone age (yr)	2.7	2.0-2.7	2.0	1.5	1.25-1.5

FIG 2 Appearance of the children with inherited growth hormone deficiency, together with one parent from each family.

present (weight -4.2 to -4.9 SD), and in the three boys the penises appeared relatively small although the testes were normally descended.

INVESTIGATIONS

The results of the laboratory investigations are summarised in table 2. Bone age was markedly retarded in all the patients. Their pituitary fossae appeared rather small on lateral skull radiographs.

TABLE 2 Growth hormone and cortisol values after glucagon stimulation in IV.1 and IV.3

	Glucose (mmol/l)	Growth hormone (mU/l)	Cortisol (nmol/l)
IV.1			
0'	2.5	<1.0	399
60'	7.3	<1.0	—
90'	7.0	<1.0	—
120'	3.6	<1.0	816
150'	2.1	<1.0	480
IV.3			
0'	1.2	<1.0	285
60'	2.5	<1.0	—
90'	1.3	<1.0	700
120*	0.7	2.1	895

*Test terminated owing to severe symptomatic hypoglycaemia.

All five children showed asymptomatic hypoglycaemia after an overnight fast (blood glucose 0.6 to 2.5 mmol/l), and basal growth hormone levels estimated by radioimmunoassay¹² were below 1.5 mU/l. Plasma thyroxine was in the low-normal range (71 to 109 nmol/l), as was basal plasma cortisol (128 to 600 nmol/l). Serum prolactin was raised to between 804 and 996 mU/l in three of the children.

Glucagon stimulation tests were carried out in the oldest child from each family (IV.1 IV.3), as shown in table 2. After injection of 100 µg/kg glucagon there was no appreciable rise in plasma growth hormone in either child, but the plasma cortisol levels rose from 400 to 816 nmol/l in IV.1 and from 285 to 895 nmol/l in IV.3. In IV.1 blood glucose rose from 2.5 to 7.3 mmol/l at 60 minutes and then fell to 2.1 mmol/l at 105 minutes. There was a small rise in blood glucose from 1.2 to 2.5 mmol/l in IV.3, and severe symptomatic hypoglycaemia developed after 120 minutes (blood glucose 0.7 mmol/l).

Discussion

Like most of the reported families with inherited growth hormone deficiency, the present inbred family shows the typical pattern of a recessive disorder, and it is interesting that the facial appearance of our cases, with mid-face hypoplasia, is similar to that described in other families.^{6 11}

It is evident that growth hormone deficiency is a heterogeneous condition, both from the various modes of inheritance and from the different clinical forms observed in reported cases. While recessive inheritance is the most common pattern in affected families, X linked inheritance has been described,^{13 14} as has autosomal dominant inheritance.^{15 16}

In some families growth hormone deficiency seems to be an isolated defect and secondary sexual development is normal, although often delayed. In others there is a more widespread loss of anterior pituitary function, with varying combinations of hormone deficiency which, according to Rimoin,¹⁷ will always include the gonadotrophins. Rarely, growth hormone deficiency is inherited in association with another syndrome.^{18 19}

The size of the pituitary fossa also varies in different families. In some it is normal, while in others it may be small or enlarged.⁹ The two sisters described by Ferrier and Stone¹⁰ were each found to have a very small sella turcica in an abnormal sphenoid bone. In our cases the pituitary fossae appeared rather small on lateral skull radiographs but, as Di Chiro and Nelson²⁰ have pointed out,

this view alone is unreliable in estimating the volume of the fossa.

As only two of our cases were challenged with glucagon we do not have detailed results of pituitary function in all our patients. However, the normal basal values for cortisol and the increments obtained after glucagon in two patients indicate that there was no disturbance of pituitary-adrenal function. Similarly, the low-normal plasma thyroxine values suggest that TSH secretion was also normal. The raised basal plasma prolactin levels found in three patients are difficult to interpret but could possibly be related to stress.

Perhaps the most striking feature of our cases was their fasting hypoglycaemia which was not the result of secondary adrenal insufficiency. Although symptomatic hypoglycaemia in isolated growth hormone deficiency (as opposed to hypopituitary states) has been described,^{16,21} it is not a constant feature of this condition, being absent in all 24 cases described by Rimoin *et al.*¹¹ This inconsistency, together with the discovery of two different types of insulin response to arginine infusion in the latter series of patients, illustrates further the considerable heterogeneity that exists among cases of familial growth hormone deficiency.

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