Isolated growth hormone deficiency

Two families with autosomal dominant inheritance

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Poskitt, E. M. E., and Rayner, P. H. W. (1974). *Archives of Disease in Childhood*, 49, 55. **Isolated growth hormone deficiency: two families with autosomal dominant inheritance.** Two families, each with a father and a son affected by isolated growth hormone deficiency, are described. The inheritance in these cases seems to be due to an autosomal dominant gene. Isolated growth hormone deficiency appears to be a heterogeneous condition.

Isolated deficiency of growth hormone (GH) with sexual maturation has been described frequently (Nadler, Neumann, and Gershberg, 1963; Brasel *et al.*, 1965; Goodman, Grumbach, and Kaplan, 1968; Tanner *et al.*, 1971). Though of varied aetiology, the condition may be familial. Tanner (1972) has recently stated that 15% of children with isolated GH deficiency not due to a tumour have similarly affected sibs, though at this hospital there are no affected sibs among 30 cases of isolated GH deficiency. The reported familial cases usually show an autosomal recessive pattern of inheritance (Trystad and Seip, 1964; Pertzalan, Adam, and Laron, 1968). However, two GH-deficient parents described by Rimoin, Merimee, and McKusick (1966) have had both dwarfed and normal children. Such a family could be explained by autosomal dominant inheritance, and it does seem that dominantly transmitted GH deficiency occurs (Sheikholislam and Stempfel, 1972). Two families are described which may illustrate this condition.

Methods

Glucose 1.75 g/kg body weight was given orally for prolonged glucose tolerance testing, and glucose and growth hormone levels were estimated at 0, 30, 60, 120, 240, and 300 minutes. A dose of soluble insulin 0.1 unit/kg was given intravenously during insulin sensitivity testing and blood samples for glucose and growth hormone were obtained at 0, 10, 20, 30, 40, 60, 80, and 100 minutes. Glucose was estimated by a semi-automated method (Discombe, 1963). Growth hormone estimation was carried out by a modification of the double-antibody immunoassay (Hartog *et al.*, 1964).

Results are recorded in IU (MRC first International reference preparation for radioimmunoassay).

Case reports

Family B.

Case 1. A male was born at term of a normal delivery in 1943. His parents were unrelated and there was no family history of short stature. Birthweight was 3150 g. He developed normally except that by the age of 2 he was noticeably short. Thyroid extract was given for 2 years without effect on his growth. When aged 7½ his height was 92.5 cm, a height age of 3 years, and his weight was 13.6 kg, a weight age of 2½ years. He had small facial features with prominent forehead, but body proportions were otherwise normal. Bone age was 5½ years with no epiphyseal dysgenesis. Serum cholesterol was 281 mg/100 ml. Urinary ketosteroids were 3.9 mg/24 hours. A further 3-month course of thyroid had no effect on growth, skeletal maturation, or serum cholesterol and he was given methyl testosterone 20 mg daily to stimulate growth. This produced acceleration of growth and bony maturation so that at a chronological age of 9.3 years his height was 109 cm (height age 5 years) and bone age was 9 years. His clinical attendances were infrequent; but in 1959, when aged 16½, he was admitted to hospital with asthma and his pituitary status was reassessed. His height was 133 cm, equivalent to the 50th centile at 9 years and his weight was 28.6 kg. He showed signs of pubertal development with sparse facial hair, moderate pubic hair, and increased testicular size. 17 keto- and hydroxysteroid excretions were 5.4 mg and 8.2 mg/24 hours, increasing to 12 mg/24 hours and 55 mg/24 hours after 40 IU ACTH intramuscularly. Methyl testosterone was started again and he received in addition a course of prednisone for his asthma. Over the next 3 years he grew 7 cm, reaching a final adult height of 140 cm (Fig. 1). Pubertal development continued with further increase in testicular size. In 1963, when aged 20, he married. His wife was 150 cm

FIG. 1.—Linear growth curves of Cases 1 and 2.

tall. A year later a son, Case 2 below, was born. Then a girl was born in 1966, birthweight 3.7 kg, and a second son was born in 1971, birthweight 3.28 kg. Both the latter children showed normal growth and GH response during a prolonged glucose tolerance test. Subsequent to the recognition of GH deficiency in Case 2, a prolonged glucose tolerance test was performed on Case 1. There was complete failure of GH production, despite blood sugar levels of 34 mg/100 ml at 4 hours, suggesting GH deficiency in Case 1 as well (Table I).

TABLE I
Growth hormone response to prolonged glucose tolerance testing (1.75 g/kg body weight)

Time (min)	Case 1		Case 2	
	Glucose (mg/100 ml)	Growth hormone (μ U/ml)	Glucose (mg/100 ml)	Growth hormone (μ U/ml)
0	55	1	15	1
30	117	1	22	1
60	106	1	74	1
120	87	0	56	1
180	43	0	18	1
240	34	0	19	1
300	51	0	18	1

Case 2. A male, born in September 1964, was the first-born son of Case 1. He was a term forceps delivery, birthweight 3200 g. There were no resuscitative difficulties, and initially he appeared to thrive. His developmental milestones were normal, but by the age of 6 months small size was apparent. In addition, he was frequently very drowsy before breakfast, probably due to early morning hypoglycaemia. By 2 years of age he was only 6.60 kg (weight age 4 months) and 67 cm tall (height age 5 months). His hands and feet were small and his face was infantile with noticeable wrinkling of the forehead. Skull circumference was 45 cm, equivalent to the 50th centile for 11 months. Neither testis could be felt in the hypoplastic scrotum, but there were no other abnormalities. Skeletal maturation was equivalent to 15 months. Skull x-ray showed a normal pituitary fossa. Protein-bound iodide was 5.7 μ g/100 ml and serum cholesterol 189 mg/100 ml. There was normal increase in blood cortisol after 40 IU ACTH intramuscularly, but a prolonged glucose tolerance test showed a fasting blood glucose of 15 mg/100 ml and no measurable GH production despite hypoglycaemia of 18 mg/100 ml at 3 and 5 hours after glucose (Table I). He appeared to be a definite case of GH deficiency. Growth continued slowly (Fig. 1), and from May 1968 he received a one-year course of twice-weekly injections of 10 mg human growth hormone (Raben). In January 1971 he began a further course of GH and has continued this apart from a break of 4 months in 1972. While on GH he has had marked increase in growth velocity (Fig. 2), though

FIG. 2.—Case 2. Annual height increment in cm/year.

between the courses growth virtually ceases. Such a pattern is typical of the GH-deficient child during treatment.

Family G.

Case 3. A male of normal birthweight was born in 1925, the second son of tall, unrelated parents. His only sib is over 180 cm tall and there is no family history of short stature. He was breast fed and initially thrived, though he was described as very round and chubby. Short stature was marked by 3 years of age. By 12½ he was 120 cm tall, 15 cm below the 3rd centile for his age and a mean height for 7 years of age. He was obese with an infantile face and small hands and feet. However, his mental development was better than average as he won a scholarship to grammar school. X-rays at this time showed no bone disorder to account for short stature and bone maturation was not recorded. He was diagnosed a pituitary dwarf and treated with thyroid 15 mg twice daily and twice-weekly injections of Antuitrin G (a crude pituitary extract). Antuitrin G was continued more or less without a break for the next 8 years. This treatment had no apparent effect on his growth, which continued well below the 3rd centile for age (Fig. 3). At 16½ his voice was breaking and his growth showed a slight pubertal spurt. At 20, x-rays of long bones suggested epiphyseal fusion and he had reached his final height of 147 cm. Some years later he married a woman of 163 cm in height from a tall family. When he was aged 32

his first child, Case 4, was born. Since then he has had 2 daughters, both of normal stature.

In 1961 urinary hydroxycorticosteroid excretion was 11 mg/24 hours. In 1970, an insulin sensitivity test produced no GH response (Table II), thus supporting

TABLE II
Growth hormone response to insulin-induced hypoglycaemia

Time (min)	Case 3		Case 4	
	Glucose (mg/100 ml)	Growth hormone (μU/ml)	Glucose (mg/100 ml)	Growth hormone (μU/ml)
0	65	1	60	4
20	19	0	31	3
30	12	1	24	2
40	22	1	49	4
60	29	0	59	3
80	45	0		
100	52	0		

the clinical diagnosis of isolated growth hormone deficiency.

Case 4. The son of Case 3 was born in 1957 by lower segment caesarean section because pregnancy was complicated by an ovarian cyst. Birthweight was 3640 g and length 53 cm. At the age of 1 year he was short, with a length of 63 cm. By 3 years of age his height was 77.5 cm, a height age for 15 months, and bone age was equivalent to 30 months. He had the small features and prominent forehead of GH deficiency. He was treated with 10 mg methandienone daily between March and July 1960. Courses of 5 mg/day and 2.5 mg/day were given for 3 months from January and May 1961. This treatment produced growth of 9.5 cm between 3 and 4 years of age but also bony maturation, so that at a chronological age of 5 years his bone age had advanced to 6 years. In 1963 a further dose of methandienone produced an annual growth rate of 7 cm. After this he grew slowly, falling further from the 3rd centile for age (Fig. 3). At age 12 years 2 months his height was 127 cm (height age 8 years), and his weight of 36.6 kg was at about the 50th centile for age. He had marked truncal obesity with small hands and feet and immature body proportions. Serum cholesterol was 222 mg/100 ml, protein-bound iodide 5.1 μg/100 ml. There was no significant growth hormone response to prolonged glucose tolerance test or insulin sensitivity test (Table II). Plasma cortisol levels were normal. Now, at the age of 15½ years, he shows no signs of puberty, bone age is equivalent to 12½ years and he has started treatment with human growth hormone.

Discussion

The 4 cases described have characteristic clinical and biochemical features of GH deficiency. Such children are usually of normal birthweight but short

FIG. 3.—Linear growth curves of Cases 3 and 4.

stature is noticed in infancy. Failure to gain weight is less marked than failure to grow in height, though anorexia in early life may produce low weight, as in Cases 1 and 2. Episodes of spontaneous or postprandial hypoglycaemia may complicate early childhood. In later childhood, obesity is a problem. Certain clinical features also suggest GH deficiency, notably normal body proportions with small hands and feet but immature facies, prominent forehead with markedly soft wrinkled skin, and normal skull size. In boys there may be hypodevelopment of genitalia and cryptorchidism.

The biochemical diagnosis of GH deficiency lies in showing the absence of GH secretion in response to a challenge, such as hypoglycaemia produced by intravenous insulin or as a result of a prolonged glucose tolerance test. All 4 cases described show negligible GH response to profound hypoglycaemia, strongly suggesting GH deficiency.

GH deficiency may be associated with deficiency of other anterior pituitary hormones. The cases we described have no evidence of adrenocorticotrophic or thyrotrophic deficiency. More frequently gonadotrophin deficiency accompanies GH deficiency. However, Cases 1 and 3 have shown adequate gonadotrophin secretion by their fertility. Case 2 is still too young for gonadotrophin secretion to be significant. Case 4, at 15½, might be expected to show signs of puberty with high gonadotrophin excretion, but puberty is delayed in untreated GH-deficient patients who ultimately become sexually mature (Goodman *et al.*, 1968). Bone maturity is a more reliable indication of the appropriate time of onset of puberty than chronological age (Tanner, 1972). Thus, Case 4 can still be expected to develop spontaneous puberty as his present bone age at 12½ is only just within the pubertal range.

The pattern of inheritance in these two families does not readily fit into an autosomal recessive pattern. There is no family history of short stature other than in the family of the wife of Case 1 in which shortness involves all members and constitutional short stature seems more likely a diagnosis than any pathological dwarfing. She herself has normal GH secretion.

All 4 cases described are males, so the possibility of a recessive but sex-linked condition should be considered. However, the pattern of both father and son affected is not that of an X-chromosome linked condition. Moreover, there are no other short males in the families and Case 1 has a second son of normal stature and growth hormone secretion. This excludes the possibility of a sex-linked condition. Isolated growth hormone deficiency is,

however, more common in males than females (Tanner, 1972), and it may be that there is some sex-limiting factor operating.

The most likely pattern of inheritance in the 2 families described remains that of autosomal dominant isolated GH deficiency. Rimoin and Schimke (1971) classify this condition as type II isolated GH deficiency. They suggested that these cases are distinguishable from autosomal recessive (type I) isolated GH deficiency by the absence of the soft wrinkled skin usually a feature of GH-deficient adults. They also characterize type II deficiency by lack of both hypoglycaemic attacks and insulin hypersensitivity. These patients have abnormally high insulin secretion to a glucose load in contrast to the decreased secretion of type I and nonfamilial GH deficiency (Merimee *et al.*, 1968).

However, Sheikholeslam and Stempfel (1972) did not confirm these findings in their cases of dominantly inherited GH deficiency. Our adult patients, and to a lesser extent their children, have typical wrinkled facial skin. Unfortunately, insulin secretion has not been studied, but Case 2 had fasting hypoglycaemia and early morning hypoglycaemic episodes. Cases 3 and 4 had profound hypoglycaemia in response to exogenous insulin. Thus it seems our cases do not have the specific features of type II deficiency either. Deficiency of pituitary GH may result from failure of production of GH-releasing factor in the hypothalamus and this could be the genetic abnormality in our cases. However, the functional defect and clinical effect would be identical with primary GH deficiency. Merimee *et al.* (1968) suggested that the unusual features of their type II patients may be due to production of an altered GH molecule, undetectable by immunoassay yet with selective biological activity. If this is so, a group of patients with dominantly inherited growth hormone deficiency may include examples of several inherited disorders of the neuro-hypophyseal-pituitary axis. This could explain clinical and biochemical variation within the group. Further investigations of the GH-releasing pathway and other methods of GH assay may be required before the apparent heterogeneity in this condition can be resolved.

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