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Variable X-linked recessive hypopituitarism with evidence of gonadotropin deficiency in two pre-pubertal males

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Two half-brothers with short stature secondary to growth hormone deficiency and a family history implicating X-linked transmission were studied extensively for other endocrine abnormalities. The proband had a normal physical examination, except for small stature and small external genitalia. ACTH and TSH release were normal. LH and FSH responses during an i.v. GnRH test were severely blunted. His half-brother also had a normal physical examination, except for severe short stature and very small external genitalia. Deficiencies of ACTH, and TSH as well as GH were documented. An i.v. GnRH test showed no LH or FSH response. These studies support the existence of an X-linked recessive form of hypopituitarism and portend the clinical usefulness of the i.v. GnRH test in evaluating gonadotropin reserve.

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Inherited hypopituitarism is an uncommon but well-documented condition (Rimoin et al. 1966, McKusick 1971). Until recently, only an autosomal recessive pattern of inheritance could be demonstrated convincingly. In 1971, two separate reports suggested an X-linked recessive pattern of inheritance (Phelen et al. 1971, Schimke et al. 1971). This report of two cases of multiple, but variable, deficiencies of anterior pituitary hormones further suggests the X-linked mode of inheritance and illustrates the probable usefulness of the gonadotropin-releasing hormone (GnRH) test in the diagnosis of gonadotropin deficiency in pre-pubertal children.

Case Reports

Case 1, D.H. (UMMC 1-183-460), was born on January 26, 1965 to a 34-year-old white female after an uncomplicated full-term pregnancy (Fig. 1). His birth weight was 4.5 kg; his length was not available. He was seen initially at the University of Michigan Medical Center for evaluation of short stature at 5½ years. Physical examination revealed a short, pudgy, white male with small

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Table 1

Serum LH and FSH responses to i.v. synthetic GnRH

Subjects	Age (years)	Dose (μg/kg)	Maximum LH increment (mIU/ml)	LH response area 120 min (mIU-min)	Maximum FSH increment (mIU/ml)	FSH response area 120 min (mIU-min)
D.H.	9- 1/12	10 μg/m²	0	0†	2.2	149.0
	10- 2/12	10 μg/m²	3.3	56.9†	2.3	78.7
	10- 3/12	2.5 μg/kg	2.0	28.3	2.4	140.5
P.H.	6	2.5 μg/kg	2.1	36.5†	0	0†
R.H.	11-10/12	2.5 μg/kg	4.0	232.0	4.1	281.8
Controls*						
(n = 4)		10 μg/m²	8.0 ± 2 (4–14)	390 ± 105 (185–623)	5.0 ± 0.5 (3–6)	195 ± 54 (99–349)
(n = 10)		2.5 μg/kg	8.4 ± 1.3 (3.9–18.8)	567 ± 105 (330–1359)	9.3 ± 1.7 (1.9–18.8)	715 ± 125 (211–1410)

* Mean ± s.e. mean ( ) = range for short normal prepubertal males with bone ages less than 10 years.
† Non-significant response.

external genitalia; the length of the stretched phallus was 2.5 cm (−4 s.d.). His height was 87 cm (−5 s.d.), weight 11.4 kg (−3 s.d.) and head circumference 49.5 cm (−2 s.d.). Vital signs were normal. Significant laboratory studies included normal serum protein bound iodine (5.1 μg/dl), skull roentgenograms, and a skeletal age of 2 years. Fasting serum growth hormone (GH) was less than 2 ng/ml after a 3-day pretreatment with diethylstilbesterol (Bacon et al. 1969). An estrogen-primed arginine-insulin stimulation test (ATT/ITT) showed a maximum GH response of 3 ng/ml.

At $7\frac{10}{12}$ years of age, he was admitted to the C. S. Mott Children's Hospital for further evaluation. A repeat estrogen-primed ATT/ITT demonstrated a maximum GH response of 5.8 ng/ml. Serum thyroxine iodine was 5.4 μg/dl (nl 2.9–6.4). Urinary 17-hydroxycorticosteroids were 1.9 mg/m²/24 hours (nl $\bar{x} = 3.1$ mg/m²/24 hours). Eight-hour deoxycorticoid response to i.v. metyrapone test was 9 μg/dl (nl > 6 μg/dl) (Bacon et al. 1975). Subsequently, luteinizing hormone (LH) and follicle stimulating hormone (FSH) responsiveness to i.v. synthetic GnRH (Parke, Davis) was abnormally low on three occasions (Table 1). Treatment with human growth hormone, 2 IU i.m. three times per week was begun at $9\frac{1}{12}$ years.* Pretreatment growth velocity was 3.5 cm per year. During the first 12 months of GH therapy, D.H. grew 7.0 cm despite poor compliance.

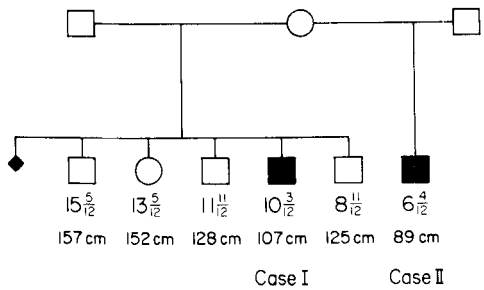

Fig. 1. Family pedigree, illustrating X-linked transmission. Case 1, D.H.; Case 2, P.H.

Case 2, P.H., the half brother of D.H., was born on December 19, 1968, after an uncomplicated full-term pregnancy (Fig. 1).

* Human growth hormone was supplied by the National Pituitary Agency of the University of Maryland and the NIAMDD.

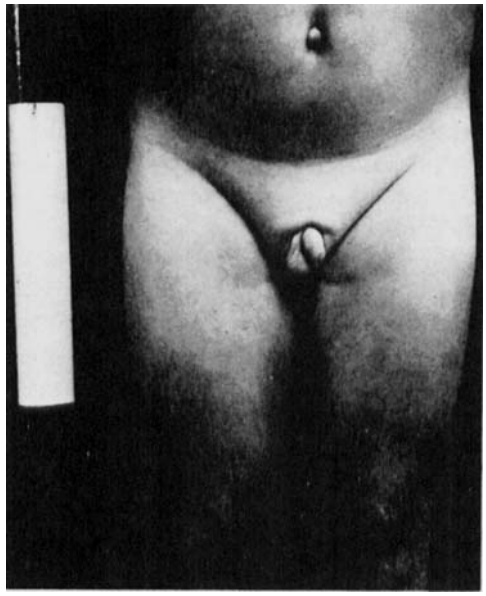

Fig. 2. Photograph of P.H. (Case 2) illustrating small external genitalia (segments of reference bar equal to 6 inches).

His birth weight was 3.8 kg; his length was not available. A circumcision was deferred because of his small penile size.

P.H. was first seen at the University of Michigan Medical Center at age $3\frac{11}{12}$ years. Physical examination revealed a short, pudgy, immature-appearing white male with a high pitched voice. His height was 79.5 cm (−7 s.d.), weight 11.0 kg (−2 s.d.) and head circumference 48.3 cm (−2 s.d.). Vital signs were normal. Examination of the external genitalia revealed a small penis, 1.5 cm in length (−6.5 s.d.) (Fig. 2). The left testicle was palpable in the inguinal canal. The right testicle was 1.0 cm in length.

Laboratory studies revealed a skeletal age of 18 months, serum thyroxine iodine of 2.1 μg/dl, low urinary 17-hydroxycorticosteroids (0.7 mg/m^2/24 hours) and serum thyroid stimulating hormone of 9 μU/ml. P.H. was begun on 1 grain desiccated thyroid U.S.P. daily (p.o.) and 2.5 mg hydrocortisone b.i.d. (p.o.). During the next 2 years he grew 6.8 cm and gained 500 g. At $5\frac{5}{12}$ years an estrogen-primed ATT/ITT was performed; maximum growth hormone response was 0.3 ng/ml. There was no increase in serum cortisol concentration during the insulin tolerance test. During an i.v. metyrapone test there was no detectable rise in serum deoxycorticoids. At 6 years of age, he failed to demonstrate a significant gonadotropin response during an i.v. GnRH (Table 1). P.H. was begun on GH therapy at 6 years, and after 8 months of intermittent therapy (2 IU i.m. 3 times per week, 2 out of every 3 months), he grew 5.1 cm.

The family history (Fig. 1) revealed that the biologic fathers of D.H. and P.H. were different; this paternal difference was confirmed by detailed blood typing. The maternal family history was traced for six generations with no evidence of consanguinity or short stature, and the family history of the father of P.H. was also negative for short stature. The father of D.H. could not be located.

An $11\frac{11}{12}$-year-old full brother of D.H. was also evaluated (Fig. 1). This child (R.H.) was 128 cm tall (−2.5 s.d.), and he had surgically corrected cryptorchidism on the right. He had a delayed bone age ($6\frac{1}{2}$ years), a normal serum growth hormone concentration of 5.6 ng/ml (nl $>$ 5.0 ng/ml) after estrogen priming and exercise (Keenan et al. 1972), and low normal FSH and LH responses to GnRH stimulation. A peak growth hormone level of 7.0 ng/ml was also obtained during the GnRH test.

Three other siblings were found to be normal in height and weight. The mother was 157.5 cm tall and in good health. After an estrogen-primed exercise stimulation test her serum growth hormone rose to 8.6 ng/ml. The mother was XgA negative and no other X-chromosome markers could be identified.

Materials and Methods

Growth hormone, FSH and LH concentrations were determined by established double antibody radioimmunoassay techniques (Kelch et al. 1975). GnRH stimulation tests were carried out in the Upjohn Center for Clinical Pharmacology, and were interpreted as previously described (Kelch et al. 1975). An LH response was considered significant when five of the six samples between +8 and +45 min were greater than 3 standard deviations above the mean of the five pre-infusion samples. An FSH response was considered significant when four of the five samples between +20 and +90 minutes were greater than 2 standard deviations above the mean of the control samples. XgA and detailed blood typing for confirmation of parentage were performed through the courtesy of Dr. Henry Gershowitz of the Department of Human Genetics at the University of Michigan.

Discussion

The family pedigree is consistent with an X-linked recessive trait, but there is some variability in its expression. Case 1 (D.H.) presented with many of the typical features of a growth hormone deficient child, with the additional physical findings of small external genitalia. Anterior pituitary testing demonstrated probable gonadotropin deficiency as well as GH deficiency.

Case 2 (P.H.) presented with many of the classical findings of growth hormone deficiency, and extremely small external genitalia. He was deficient in TSH, ACTH, GH and most likely LH and FSH. Maintenance doses of thyroid hormone and cortisol did not increase his growth velocity.

One other sibling in this family (R.H.) also had significant short stature (Fig. 1). His bone age was delayed but he had a normal physical examination except for unilateral cryptorchidism, normal growth velocity, and normal serum thyroxine. Complete GH deficiency was ruled out by low normal GH responses to stimulation tests. LH and FSH responses to GnRH (Table 1) were significant, and the $\triangle$ max values and response areas were at the lower limits of the normal range.

The occurrence of inherited forms of growth hormone deficiency has been well documented. Rimoin et al. (1968) reported an extensive review of the world's literature from which they were able to gather reports of 51 kindreds in which more than one individual had apparent growth hormone deficiency. Analysis of these families implicated an autosomal recessive form of inheritance as the most likely mode of genetic transmission in most instances. However, included in these and other reviews (Brasel et al. 1965) there are occasional family histories in which only male siblings are affected, suggesting an X-linked mode of inheritance. This possibility was given further support in 1971 when Schimke et al. (1971) and Phelen et al. (1971) reported unrelated kindreds that demonstrated family pedigrees strongly implicating an X-linked pattern of inheritance with variability in the expression of other hormonal deficiencies. McKusick (1971) has subsequently classified this X-linked transmitted form of hypopituitarism as type IV.

The evaluation and subsequent classification of a child with evidence of one or more anterior pituitary hormone deficiencies is complicated by the fact that the complete manifestation of the condition may take years to develop (Goodman et al. 1968). The diagnosis of gonadotropin deficiency in the prepubertal individual must be made with caution in view of the known marked delay in onset of sexual maturation associated with GH deficiency (Rimoin & Schimke 1971). A possible physical clue is the presence of small external genitalia

which is known to occur in hypopituitary infants (Goodman et al. 1968, Rimoin & Schimke 1971, Feldman & Smith 1975). Men with isolated gonadotropin deficiency also have small external genitalia and, sometimes, a history of micropenis during infancy and childhood (Laron & Karishanski 1975). These observations would be consistent with the concept that fetal male genital growth after 12 weeks of gestation is dependent on the presence of fetal gonadotropins (Feldman & Smith 1975). The possibility that the absence of fetal growth hormone during gestation may produce a similar result has also been suggested (Laron & Sarel 1970).

The early diagnosis of gonadotropin deficiency would be beneficial for optimal management of these children. The possibility that a synthetic GnRH test might be useful in predicting gonadotropin deficiency in the prepubertal individual has been suggested previously (Grumbach et al. 1974, Kelch et al. 1976). We have recently studied LH and FSH responses to i.v. synthetic GnRH in prepubertal males with isolated GH deficiency and multiple pituitary deficiencies (including known or probable gonadotropin deficiency) and compared them to the responses of short normal prepubertal males. Our data revealed significantly lower responses in most of the patients with suspected isolated GH deficiency, and severely blunted or absent responses in the patients with multiple pituitary deficiencies. In this group of patients, replacement therapy with GH did not significantly increase the responsiveness to GnRH (Kelch et al. 1976).

In D.H., the presence of small external genitalia, the two nonsignificant LH responses, and the single significant but very blunted LH response suggest either complete or partial gonadotropin deficiency. The very blunted FSH responses would support this latter possibility. P. H. did not respond to GnRH, has multiple pituitary hormone deficiencies and very small external genitalia. The likelihood of his being gonadotropin deficient is great. R.H. demonstrated low normal responses for both GH and gonadotropins and, even though our impression is that he is normal, the possibility of a partial expression of X-linked recessive hypopituitarism cannot be excluded.

In the two previous reports of X-linked recessive hypopituitarism, the mothers of the affected individuals were of normal height. The mother of the two affected children in this report showed no signs of an endocrine abnormality. This would suggest that the heterozygous state in the female does not result in any detectable abnormality. An easily identifiable X-chromosome genetic marker that would allow us to follow the carrier state, such as XgA heterozygosity or color blindness, was not present in this instance. However, attempts at identifying such markers would be of interest and beneficial for genetic counseling.

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