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Hypopituitarism and Idiopathic Delayed Puberty: A Longitudinal Study in an Attempt to Diagnose Gonadotropin Deficiency before Puberty*

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ABSTRACT. Fifty-five hypopituitary patients (43 boys and 12 girls) treated with human GH were studied longitudinally before and during puberty, occuring either spontaneously or induced with testosterone enanthate (100 mg/month, im) in boys and ethinylestradiol (10 μg/day, orally) in girls. In addition, 53 boys with idiopathic delayed puberty (IDP) were studied. Gonadotropin integrated responses (IRs) during 90 min after the iv injection of 25 μg/m² LRH, bone ages (BA), and plasma levels of dehydroepiandrosterone sulfate and testosterone were determined at least yearly.

Prepubertal hypopituitary patients with gonadotropin deficiency were characterized by: 1) a lowered FSH IR to LRH in most boys and in all girls; 2) a low LH IR for BA; 3) adrenarche either absent or delayed for BA; 4) height age close to BA; and 5) the presence of several pituitary deficiencies.

In contrast, most prepubertal hypopituitary patients without gonadotropin deficiency showed: 1) a normal FSH IR to LRH; 2) a normal or intermediate (≥75 mIU/ml·90 min) LH IR for BA; 3) a normal adrenarche for BA; 4) a height age below BA; and 5) isolated GH or GH plus TSH deficiencies. A significant linear correlation was found between LH IR and the logarithm of plasma testosterone. The slopes and levels were similar in controls and hypopituitary boys without gonadotropin deficiency. In IDP, the level was significantly higher. All data obtained in these patients show that the increase in plasma testosterone and the clinical onset of puberty are delayed for the observed pubertal pattern of LH responsiveness.

It is concluded that the study of several clinical and biological features, especially the gonadotropin IR to LRH, are of predictive value for the diagnosis of normal or deficient gonadotropic function in prepubertal patients with IDP and hypopituitarism. (*J Clin Endocrinol Metab* **54:** 733, 1982)

WELL defined criteria have been established in order to document a deficiency of GH and TSH (1–5). The diagnosis of gonadotropin deficiency, however, remains difficult, especially in prepubertal patients (6). This may be explained by the fact that the hypothalamo-pituitary-gonadal axis is quiescent during prepuberty. Consequently, physicians generally wait until patients reach a pubertal bone age (BA) before suspecting the possibility of gonadotropin deficiency.

In most patients with isolated GH deficiency, spontaneous puberty may be expected, whereas in hypopituitary patients with multiple deficiencies, the occurrence of puberty remains uncertain.

In 55 hypopituitary patients, several clinical and biological parameters related to puberty were studied longitudinally: growth velocity; bone maturation; plasma levels of dehydroepiandrosterone sulfate (DHEA-s), testosterone, or estradiol; and pituitary responsiveness to LRH. Clinical follow-up in these patients either showed spontaneous puberty or led to hormonal treatment to induce pubertal development. Clinical and biological data were analyzed in retrospect in an attempt to further determine some predictive features associated with gonadotropin deficiency during the prepubertal period. In addition, data obtained in patients with idiopathic delayed puberty (IDP) were compared with those obtained in hypopituitary boys who subsequently went into spontaneous puberty.

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Materials and Methods

Subjects

The control subjects (46 boys and 32 girls) showed no evidence of any disorders of the hypothalamo-pituitary axis. They were considered as controls only when growth and puberty proceeded within normal limits. Formal consent of the parents was obtained for all subjects. The boys and girls were both divided into 3 groups according to the genital development (G) and breast development (B) stages of Tanner (7). G1 consisted

of 23 boys, aged 7–10.8 yr; G2 consisted of 13 boys, aged 11.5–14 yr; and G3 consisted of 10 boys, aged 12.5–16.4 years; 14 girls, aged 7.0–11.6 yr, were in B1; 4 girls, aged 9.4–12.7 yr, were in B2; and 4 girls, aged 11.0–13.5 yr, were in B3.

Fifty-five hypopituitary patients (43 boys and 12 girls) were studied longitudinally. All patients were shown to have blunted responses of GH (<5 ng/ml) to appropriate stimuli, including both insulin (0.1 U/kg, iv) and glucagon (0.1 mg/kg, im) (8). All patients were treated with human GH (Crescormon; supplied by Kabi; Stockholm, Sweden, 4 IU, 2–3 times a week). Treatment was approved by the Comittee for Treatment of Pituitary Growth Retardation appointed by the National Ministery of Health. All patients were receiving human GH (hGH) therapy at the time of the study, and showed a sustained improved growth velocity.

Plasma levels of thyroid hormones and the responses of TSH to TRH were evaluated before hGH treatment. Among the 55 patients, 40 had secondary or tertiary hypothyroidism. Corticotropic function was evaluated by measuring the response of plasma cortisol to the insulin and glucagon tests. Decreased responses were observed in 16 of 55 patients. Appropriate substitutive therapy with T_4 was given if required, and dosages were adjusted individually in order to keep serum T_4 levels within normal limits, as measured every 3 months. ACTH-deficient patients were given hydrocortisone in a dosage which did not exceed 15 mg/m^2/day.

The etiology of hypopituitarism was assumed to be idiopathic in 47 patients. Organic hypopituitarism was attributed to head injury in 1 patient (no. 47), a tumor in 1 (no. 45), and craniopharyngioma in 6 (no. 7, 8, 26, 32, 46, and 65).

Hypopituitary patients were divided into 2 groups depending on subsequent evolution (whether or not they came into puberty spontaneously). The first group consisted of 23 patients (20 boys and 3 girls) studied before and during spontaneous puberty and therefore considered as having no gonadotropin deficiency (Table 1). Among these patients, 5 did not yet show spontaneous puberty at the time of the study, but were not considered to be gonadotropin deficient because of isolated GH deficiency. Moreover, 3 of the 5 had familial GH deficiency. In the 2 remaining patients (no. 11 and 14), prepubertal ages did not allow confirmation of normal gonadotropic function at the time of the study. The second group consisted of 32 patients (23 boys and 9 girls) who were assumed to be gonadotropin deficient (Table 2). Subsequent requirement of hormone administration in order to induce pubertal develoment was based upon the following criteria: a decreased height velocity (<4 cm/yr) despite hGH therapy, and a BA of at least 11.3 yr in males (mean, 12.4 yr) and 10.5 yr in females (mean, 11.9 yr). They were studied before and during puberty induced by the administration of testosterone enanthate (100 mg/month, im) in boys and ethinylestradiol (10 μg/day, orally) in girls.

Fifty-three male patients with IDP were also included in this study. At the time of the endocrine investigation, all patients had a chronological age of at least 14.0 yr. A prepubertal genital score (G1) was observed in 35 patients, whereas 18 were G2. Clinical follow-up has shown subsequent spontaneous puberty in all patients. Some of them were included in a previous study (9).

Methods

Pertinent clinical and biochemical data on hypopituitary patients are listed in Tables 1 and 2. Full data on IDP patients can be obtained from the authors on request. Height was measured using the Harpenden's stadiometer. Height ages were calculated according to the growth standards of Tanner *et al.* (10). Testicular volumes were measured using the orchidometer of Prader (11). Pubertal stages for axillary hair (A), pubic hair (P), genital score (G), and breast development (B) were estimated according to the criteria of Tanner (7). BA was evaluated according to the criteria of Greulich and Pyle (12).

Plasma levels of testosterone and DHEA-s were measured by specific RIA, the limits of detection being 0.1 and 30 ng/ml, respectively. Pituitary gonadotropins were measured by RIA in blood collected 30 and 5 min before and 15, 30, 60, and 90 min after the iv bolus injection of 25 μg/m^2 body surface LRH (Hoechst A.G. Frankfurt A.M., Germany). The mean basal level (mean of −30 and −5 min values), the peak value of increment above the basal level (Δ response), and the area of response above the basal level [integrated response (IR)] were calculated for FSH and LH. For both gonadotropins, Δ responses and IRs were expressed in milliinternational units per ml and milliinternational units per ml/90 min, respectively, with reference to MRC standard preparations (68/39 and 68/40 for FSH and LH, respectively). The RIA techniques have been previously described (13, 14). The limit of sensitivity of the assays was 0.3 mIU/ml for both gonadotropins. Intra- and interassay coefficients of variation were, respectively, 6.8% and 8.8% for FSH and 5.4% and 8.7% for LH.

During induced puberty in boys, the LRH test was performed 2 weeks after the last testosterone injection. At that time, plasma testosterone was measured, and the data obtained are given in Table 2.

Significance of differences between control and patient groups was calculated using Student's *t* test.

Results

IRs vs. Δ responses of gonadotropins to LRH

Figure 1 represents the individual values of Δ responses of FSH and LH to LRH in relation to the integrated responses (IR) in control subjects (Fig. 1, *left panel*) and in patients with IDP and hypopituitarism (Fig. 1, *right panel*). The correlation was studied for FSH and LH in control boys and girls. No significant differences were found for either sex or gonadotropin levels. Consequently, the data were pooled. A highly significant correlation was found ($y = 55.1x + 1.9$; $r = 0.89$; $P < 0.001$). The mean ± 1 SD of control values was calculated (as represented in the figures by the *straight lines* and *shaded area*).

In IDP, gonadotropin-deficient hypopituitary patients, and those without gonadotropin deficiency, correlations were $y = 36.3x + 24$, $r = 0.76$, and $P < 0.001$; $y = 33.4x + 2.6$, $r = 0.78$, and $P < 0.001$; and $y = 42.60x + 14.8$, $r = 0.85$, and $P < 0.001$, respectively. It should be stressed that in several patients, the Δ response was higher than

TABLE 1. Pertinent data on hypopituitary patients without a gonadotropin deficiency

Patient no.	CA	BA	HA	Pub. st.	TV	IR FSH	IR LH	T/E_2	DHEA-s	Deficiencies		
										GH	TSH	ACTH
Males												
1	15.1	13.5	11.4	A1 P3 G3	10	133	565	5640	136	+	+	—
	16.1	14.5	12.8	A2 P5 G5	12	131	531	9130	300			
	17.1	15.0	13.4	A2 P5 G5	15	118	482	8170	730			
	18.1	16.0	13.6	A2 P5 G5	15	200	1596	7190	1300			
2	9.6	7.0	6.4	1	2	23	74		210	+	+	—
	16.2	13.0	11.1	A1 P1 G2	6	5	248	470	1200			
3	17.2	12.5	11.7	1	4	67	156	620	1200	+	+	—
	18.1	13.5	12.6	A1 P2 G3	6	129	114	550	840			
4	8.1	4.0	5.1	1	1	104	150	<100	200	+	—	—
	13.7	11.3	11.3	A1 P3 G3	8	57	249	3730	1560			
	15.7	14.0	12.4	A1 P5 G5	12	54	534	6070	2100			
5	16.7	16.5	12.1	A3 P5 G5	15	65	537	1100	855	+	—	—
6	13.2	9.3	7.8	1	3	293	262	230	377	+	—	—
	15.9	12.3	10.9	A1 P2 G2	5	63	133	185	1800			
7	20.8	14.0	11.9	A2 P2 G2	5	315	141	1120	800	+	—	—
8	19.6	14.0	13.7	A1 P3 G3	5	72	1106		3600	+	+	—
9	17.2	11.5	9.9	1	4	125	130	600	145	+	+	—
10	16.0	12.5	8.7	1	4	77	386	250		+	—	—
11	9.0	7.5	6.2	1	2	76	14	260	174	+	—	—
12	13.6	10.0	9.6	1	2	113	402		30	+	+	—
13	14.2	12.0	11.3	1	2	140	91		1500	+	—	—
14	8.0	4.5	5.0	1	2	108	91	<100	<30	+	—	—
15	12.8	8.0	6.5	1	2	458	188		260	+	—	—
16	12.5	9.0	10.1	1	2	29	63	100	420	+	—	—
	13.5	10.5	10.9	1	2	20	115	<100	440			
17	17.2	11.0	9.7	1	3	155	1094	875	180	+	—	—
18	15.9	10.5	8.9	1	3	451	143	1115	80	+	—	—
19	20.1	12.5	11.5	1	3	36	77	200	649	+	—	—
	21.1	13.5	12.3	A1 P4 G4	8	71	230	3380[a]	568			
	22.5	16.8	13.8	A2 P5 G4	10	72	281	3220[a]	2240			
	23.0	17.0	13.8	A2 P5 G5	12	29	840	3040	2200			
20	18.9	13.0	11.8	1	2	11	17	200	850	+	+	—
	20.0	13.8	13.1	A1 P3 G4	4	26	63	910[a]	1130			
	21.0	14.5	13.6	A1 P4 G5	6	52	104	1330[a]	3000			
	21.9	15.0	14.1	A2 P5 G5	8	11	90	1700[a]	2000			
	23.5	15.0	14.2	A2 P5 G5	10	47	282	650	2304			

TABLE 1—*Continued*

Patient no.	CA	BA	HA	Pub. st.	TV	IR FSH	IR LH	T/E_2	DHEA-s	Deficiencies		
										GH	TSH	ACTH
Females												
21	18.1	11.5	11.1	A1 P3 B3		284	416	33	899	+	—	—
	19.1	12.5	11.9	A2 P3 B3		376	791	63	542			
	20.0	13.3	12.5	A2 P3 B3		659	1216	65	1650			
	21.0	13.8	12.6	A2 P4 B3		551	1407					
22	13.7	9.0	7.0	1		395	173	5	30	+	—	—
23	15.1	14.0	11.0	A2 P4 B4		357	1582	45	2000	+	+	—

CA, Chronological age; HA, height age (years and tenths of years); Pub. st., Pubertal stage according to Tanner; A, axillary hair; P, pubic hair; G, genital score; B, breast development; TV, testicular volume (milliliters); IR FSH and LH, IRs to LRH (milliinternational units per ml/90 min); T/E_2, plasma levels of testosterone (male) or estradiol (female) in picograms per ml; DHEA-s, plasma levels of DHEA-s (nanograms per ml); +, present; —, absent.

[a] During testosterone therapy.

that expected for IR. In fact, the Δ response may overestimate the actual increase in gonadotropin release because one single increased value may be observed during the test, without a sustained response. The IR, taking into account the variations of gonadotropin response according to time, was thus assumed to better reflect the actual pituitary responsiveness than the Δ response. We, therefore, chose to study the IR in patients.

Gonadotropin IR in control subjects

In Table 3 are summarized gonadotropin IRs according to pubertal stages in control boys and girls. Since the distribution of control values has a log-normal pattern, geometric mean and SDs were calculated after logarithmic transformation of IR. The mean FSH IR was significantly ($P < 0.005$) higher than mean LH IR in prepubertal boys and girls. The mean FSH IR was higher in girls than in boys before ($P < 0.001$) as well as during puberty ($P < 0.005$). When puberty occurs, the mean FSH IR did not change significantly, whereas the mean LH IR increased markedly in boys ($P < 0.001$) and girls ($P < 0.01$), as previously described (15).

FSH IR in patients

The individual values of FSH IR to LRH obtained in hypopituitary patients according to pubertal stage are shown in Fig. 2. Patients were grouped according to their subsequent clinical evolution. In 22 prepubertal male patients who subsequently needed hormonal induction of puberty, 30 FSH IRs were obtained; in 17 of these patients, the FSH IRs (21 of 30 responses) were below the normal limits. Similarly, all FSH IRs observed in 9 prepubertal girls subsequently requiring treatment were below the normal limits. Thus, in 26 of 31 prepubertal patients in whom gonadotropin deficiency was suspected, the FSH IR to LRH was lowered. It is noteworthy that 2 patients (no. 36 and 41; Table 2) had normal prepubertal responses of FSH at the first investigation but blunted responses 1 yr later. In 16 prepubertal male patients in whom spontaneous puberty subsequently occurred, 17 FSH IRs were obtained. In 12 of these patients, the FSH IRs (13 of 17 responses) were at least within normal prepubertal limits. The only prepubertal girl studied under the same conditions also had a FSH IR within normal limits. In hypopituitary patients during spontaneous or induced puberty, the same patterns of FSH IR were observed as those obtained before puberty.

LH IR in patients

Figure 3 represents the individual values of LH IR observed in male subjects, in relation to chronological age in controls and to BA in patients with IDP and hypopituitarism who either entered puberty spontaneously or required testosterone. The *shaded rectangles* in Fig. 3 represent the normal limits (2 SD around the mean) of the data obtained in control boys according to genital stages. It is assumed that in control subjects, chronological age correlates well with BA.

Among 22 prepubertal hypopituitary boys in whom puberty was induced subsequently, 19 were studied at a BA of 11 yr or more. All of these patients had lowered LH IRs for BA, whereas most values were within the prepubertal control range. During induced puberty, LH IRs were not significantly changed compared with those seen before puberty.

In 14 prepubertal hypopituitary boys in whom puberty occurred spontaneously afterwards, LH IRs were either in the upper prepubertal (8 of 14) or even pubertal (4 of 14) control limits. In 12 of 14 patients, LH IRs were above 75 mIU/ml·90 min, the upper limit of LH IR observed in gonadotropin-deficient boys. During spontaneous puberty in 6 of 8 patients, the LH IR increased

TABLE 2. Pertinent data on gonadotropin-deficient hypopituitary patients

Patient no.	CA	BA	HA	Pub. st.	TV	IR FSH	IR LH	T/E_2	DHEA-s	Deficiencies		
										GH	TSH	ACTH
Males												
24	22.4	15.5	12.0	A1 P3 G3	4	46	140	380	30	+	+	+
25	18.1	11.3	13.0	1	2	7	18	100	30	+	+	+
	19.2	13.5	14.1	A2 P3 G4	2	0	29		60			
26	16.2	12.0	11.7	1	2	3	14	200	30	+	+	+
	18.2	13.5	13.3	A2 P2 G3	2	11	13	2600	30			
27	18.4	13.5	13.1	1	1	46	0	100	30	+	+	+
	19.5	14.5	14.0	A1 P3 G3	1	12	84	2640	30			
	20.6	16.5	14.6	A2 P4 G5	1	36	48	2750	30			
28	17.9	11.5	12.6	1	2	3	24	100	304	+	+	—
	19.0	13.5	13.9	A1 P2 G4	3	35	21	2580	380			
	19.8	14.0	14.8	A1 P3 G5	3	36	38	7570	490			
	20.8	14.8	14.9	A2 P3 G5	3	41	35	2950	700			
29	19.7	12.5	13.4	1	2	0	77	100	33	+	+	—
	20.7	14.5	14.5	A1 P2 G3	3	29	50	1690	99			
	21.7	16.3	16.4	A1 P3 G4	3	6	72	350	160			
30	19.1	12.5	11.7	1	1	61	61	100	400	+	+	—
	20.1	13.5	12.9	A2 P3 G4	2	28	3	1786	1000			
31	19.1	12.0	10.0	1	1	2	4	100	150	+	+	+
	20.1	13.8	11.3	A1 P3 G4	1	5	8	5200	320			
32	19.0	12.5	13.7	1	2	5	41	100	148	+	+	—
33	13.5	11.0	9.3	1	1	48	3	160	186	+	+	—
34	17.5	11.5	12.6	1	2	0	29	100	140	+	+	—
	19.1	13.5	13.8	A1 P2 G4	3	3	35	1608	100			
35	18.0	12.5	13.2	1	1	15	29	130	1400	+	+	—
	19.0	14.0	14.2	A2 P4 G5	3	11	23		1100			
36	18.4	10.5	12.3	1	2	48	56	110	30	+	+	+
	20.3	12.0	13.4	1	2	0	26	120	30			
37	21.1	13.0	14.0	1	2	2	6		94	+	+	+
	22.0	15.0	15.1	A1 P3 G3	3	59	18	590	61			
38	20.9	14.0	12.2	1	2	30	13	400	30	+	+	+
39	18.7	13.0	12.5	1	3	20	17	270	300	+	+	—
40	19.9	13.0	11.7	1	2	0	45	170	90	+	+	—
41	15.5	12.3	8.4	1	4	53	94	130	700	+	+	—
	16.5	13.5	9.7	1	4	0	9	100	1600			
42	12.8	11.0	8.1	1	2	9	2	100	30	+	+	+
	13.7	11.3	9.3	1	2	47	5	200	30			
	14.8	11.8	10.1	1	2	57	12	100	100			
	15.8	12.3	10.2	1	2	35	23	120	624			
43	22.0	11.5	11.1	1	2	21	16	100	75	+	+	+

TABLE 2—*Continued*

Patient no.	CA	BA	HA	Pub. st.	TV	IR FSH	IR LH	T/E_2	DHEA-s	Deficiencies		
										GH	TSH	ACTH
Males												
44	14.0	9.5	9.3	1	1	24	5	100	50	+	+	+
	15.0	10.0	9.9	1	1	0	69	100	80			
45	13.1	10.0	10.5	1	1	70	24	100	30	+	+	+
46	7.4	4.8	6.3	1	2	12	36	100	30	+	+	+
	8.4	6.0	8.1	1	2	17	43	100	30			
	10.4	9.0	10.7	1	2	4	27	100	30			
Females												
47	20.0	12.5	11.1	1		0	11	1	30	+	+	+
	21.1	12.8	11.3	A1 P1 B3		9	34	23	50			
48	19.4	13.3	10.9	1		36	0	13	35	+	+	—
	21.0	13.8	12.3	1		13	15		90			
49	18.5	12.0	11.6	1		2	11	23	80	+	+	—
	19.5	13.5	12.5	A1 P1 B4		0	37					
50	19.9	10.5	11.2	1		91	8	15	112	+	+	—
	20.9	11.0	11.9	1		45	4	31				
	21.9	14.5	12.5	A2 P2 B5		23	35	16				
51	18.5	10.5	12.6	1		65	15	7	30	+	+	+
	19.5	13.0	13.9	A1 P1 B3		33	25	21	84			
52	16.6	12.0	12.4	A2 P2 B1		9	15	10	676	+	+	—
	17.6	12.5	13.8	A2 P2 B1		36	99	20	680			
	18.6	13.0	16.3	A3 P3 B4		5	22	7	820			
53	20.8	11.0	12.5	1		40	0	1		+	+	—
	21.8	13.5	13.3	A1 P1 B5		36	0	56	120			
54	16.9	12.0	10.8	1		27	83	25	30	+	+	—
	17.9	13.0	11.2	1		23	52		60			
55	17.8	11.5	11.4	1		26	33	10	70	+	+	+

See Table 1 for definition of symbols and abbreviations.

to the pubertal control range.

In boys with IDP, either in stage G1 or G2, almost all LH IRs were within pubertal control limits, regardless of their clinical development. Thus, in prepubertal boys with IDP, the LH IRs were increased before the clinical symptoms of puberty occurred.

In nine gonadotropin-deficient hypopituitary girls (Table 2), LH IRs were lower than those observed in three hypopituitary girls without gonadotropin deficiency (Table 1).

LH IR in relation to plasma testosterone

The correlation between plasma testosterone levels, on the one hand, and gonadotropin basal values or IRs, on the other hand, was calculated in control boys and patients. Plasma testosterone levels were not significantly related to basal FSH, basal LH, and FSH IR to LRH. In contrast, a significant positive correlation was found between the LH IR to LRH and logarithms of plasma testosterone levels, as shown in Fig. 4. The following equations were obtained, with y being the IR of LH and x the logarithm of plasma testosterone levels: for control boys, $y = 182x - 145$, $r = 0.74$, and $P < 0.001$; for hypopituitary boys in whom spontaneous puberty occurred, $y = 154x - 666$, $r = 0.63$, and $P < 0.001$; an for boys with IDP, $y = 167x - 620$, $r = 0.61$, and $P < 0.001$. There was no significant difference in the slopes of the three groups. However, the level was significantly higher for boys with IDP than for controls ($t = 1.99$; $P = 0.05$) and hypopituitary boys ($t = 2.10$; $P < 0.05$). In controls and hypopituitary boys, similar plasma testosterone levels were found in the presence of similar LH IRs. In

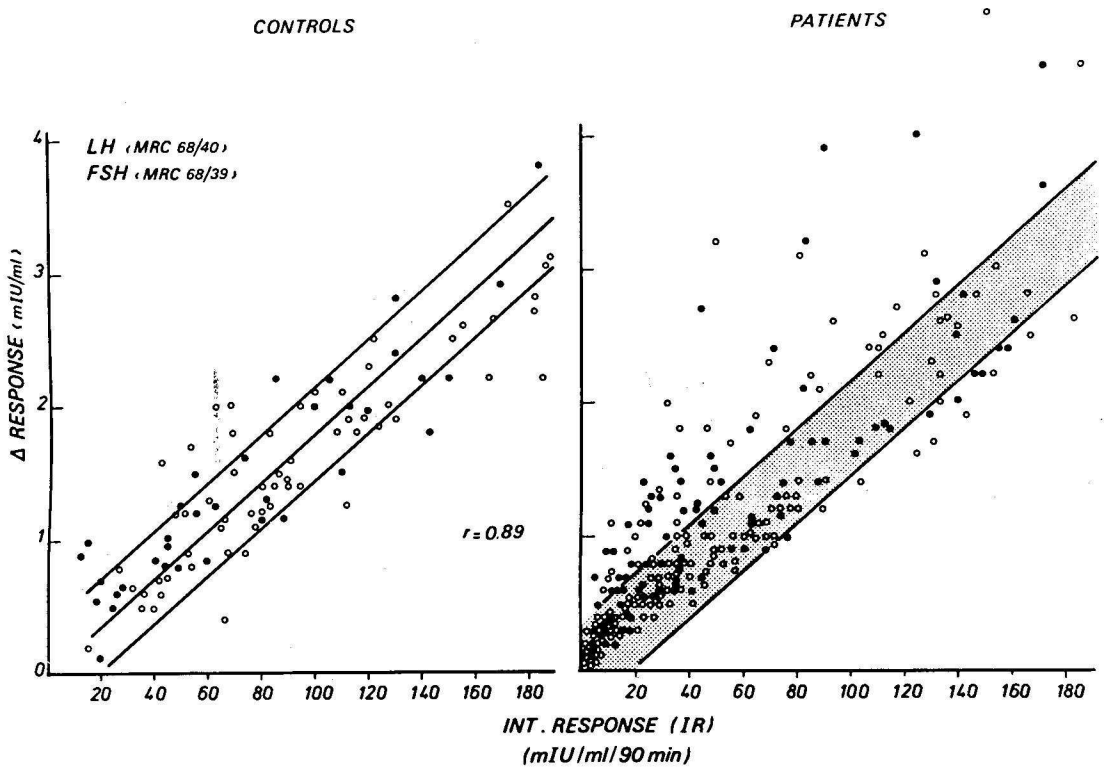

FIG. 1. IRs of FSH (*open circles*) and LH (*closed circles*) to LRH in relation to Δ responses in control subjects (*left panel*) and in patients with hypopituitarism and IDP (*right panel*). The *straight lines* and *shaded area* represent the mean ± 1 SD of control values. (MRC standards used were 68/39 for FSH and 68/40 for LH).

TABLE 3. Gonadotropin IRs to LRH in control subjects (milliinternational units per ml/90 min)

	Boys			Girls		
Pubertal stage	G1	G2	G3	B1	B2	B3
n	23	13	10	14	4	4
FSH IR						
Geometric mean	96	90	74	289	243	235
Upper limit (+2 SD)	307	299	446	854	611	692
Lower limit (−2 SD)	30	27	12	98	97	80
LH IR						
Geometric mean	60	344	556	77	299	731
Upper limit (+2 SD)	212	544	1261	460	936	1531
Lower limit (−2 SD)	17	217	245	13	96	349

boys with IDP, however, a higher LH responsiveness was observed.

Spontaneous puberty during testosterone therapy

In 2 patients (no. 19 and 20; Table 1), spontaneous puberty occurred during testosterone therapy. At 20.1 and 18.9 yr of chronological age, the patients had BAs of 12.5 and 13.0 yr and were clinically still prepubertal. Their FSH IRs were either at the lower limit of the prepubertal control range (patient 19) or less (patient 20). The LH IRs, analyzed according to BA, were below the lower limit of controls. During testosterone therapy, genital and pubic hair development proceeded according to normal standards. Surprisingly, both testicles enlarged, reaching 10 ml after 2.4 yr in patient 19 and 8 ml after 3 yr in patient 20. LRH tests were repeated 2 weeks after the last testosterone injection, at which time a pubertal level of plasma testosterone was achieved. The LH IR was slightly increased in patient 20, and was within the pubertal control range in patient 19. In both patients, reinvestigated 3 months after testosterone therapy had been stopped, the LH IR was within the pubertal control range, and plasma testosterone was at a pubertal level.

Adrenarche in patients

In boys with IDP, biological adrenarche was delayed for chronological age but normal for BA (not shown). Most hypopituitary boys and girls without gonadotropin deficiency showed a normal increase in DHEA-s levels from a BA of 9 yr on. However, four prepubertal patients had still low plasma DHEA-s levels despite BAs between 10.0–11.5 yr. During spontaneous puberty, normal DHEA-s levels were found in all patients but one. This patient (no. 1; Table 1) had a low DHEA-s level (300 ng/ml) for a BA of 14.5 yr, although clinical pubertal development was completed at that time. However, at 16 yr of BA, an increase in DHEA-s up to 1.300 ng/ml was observed.

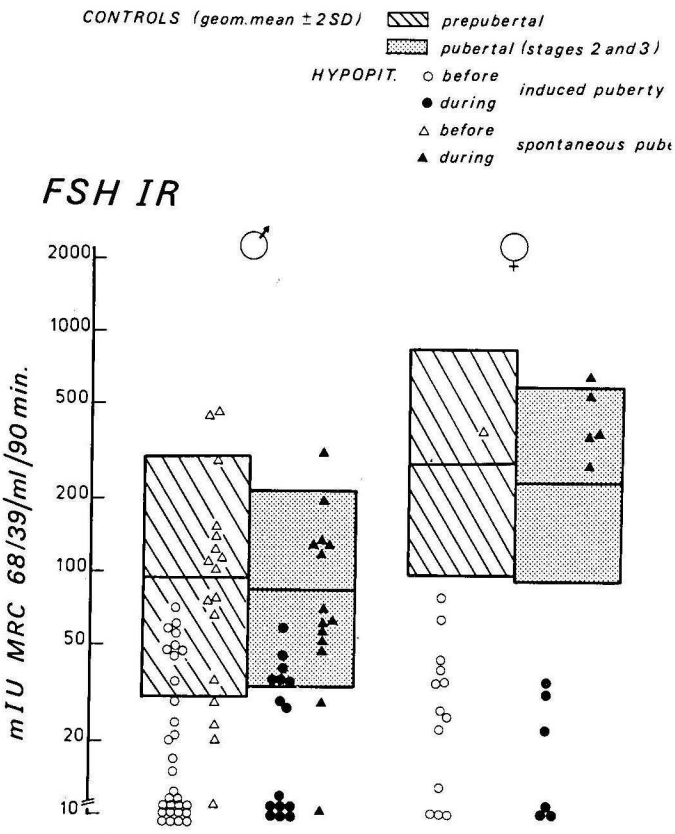

FIG. 2. FSH IRs to LRH (logarithmic scale) according to pubertal development in male and female controls and in hypopituitary patients. The areas represent geometric means ± 2 SD of prepubertal (▨) and pubertal (*shaded areas*) controls. Individual values of prepubertal (*open*) and pubertal (*closed symbols*) hypopituitary patients are shown according to their evolution into spontaneous puberty (*triangles*) or persistent prepubertal stage and subsequent substitutive therapy (*circles*). The MRC standard used was 68/39 for FSH.

Only 6 of 31 gonadotropin-deficient hypopituitary patients of both sexes with BAs of 11 yr or more had increases in plasma DHEA-s. These occurred independently of induced pubertal development and were delayed for BA. Indeed, increased DHEA-s levels were found only after 12 yr of BA, later than in patients without gonadotropin deficiency. Among 13 ACTH-deficient patients with a BA of at least 11 yr, 2 had a biological adrenarche.

In Table 4 are summarized the number of patients (boys and girls) with or without biological adrenarche in relation to pituitary hormone deficiencies. Adrenarche was considered to be present when plasma DHEA-s levels of at least 200 ng/ml were obtained at a bone age of 11 yr or more. The absence of adrenarche did not seem to be related to a known specific pituitary deficiency. However, the greater the number of pituitary hormone deficiencies found, the larger was the percentage of patients lacking adrenarche.

Skeletal maturation in relation to height in prepubertal and pubertal male patients

In Fig. 5 are represented individual values of height for BA in patients studied longitudinally in comparison with the 50th percentile height curve of Tanner *et al.* (10). This allows an evaluation of the height ages. In hypopituitary patients, only BAs obtained during hGH therapy are shown. In this study, four patients were not taken into account [patients 19 and 20 (Table 1) since spontaneous puberty occurred during testosterone therapy, patient 41 since he had previously received treatment with hCG resulting in a slight increase in testicular volume and a possible advance in bone maturation, and patient 24 because he had received oxandrolone before hGH therapy].

The mean height for BA was calculated for each yearly interval of BA and is represented by the *dotted lines* in Fig. 5. In gonadotropin-deficient hypopituitary boys, height for BA was close to normal before and during treatment with testosterone. On the contrary, hypopituitary boys without gonadotropin deficiency were already small for BA before puberty started. In these patients, spontaneous puberty occurred at a mean BA (±1 SD) of 11.4 ± 1.0 yr. Bone maturation accelerated more than expected for height velocity, resulting in mean height age (±1 SD) of 12.8 ± 0.7 yr for a mean BA (±1 SD) of 15.0 ± 1.2 yr.

Discussion

Adults with hypogonadotropic hypogonadism have been studied extensively (16–21). Only few studies are available on gonadotropic function in prepubertal hypopituitary patients (22–25). Furthermore, it has been stressed that the lack of follow-up data on the presence or absence of subsequent puberty in these patients has hampered the conclusions on the diagnostic value of biological investigations. Therefore, we have investigated some parameters related to puberty in GH-deficient patients during hGH therapy. Follow-up of these patients revealed whether puberty occurred or not. Boys with IDP were also studied.

The data obtained show that prepubertal hypopituitary patients with gonadotropin deficiency may be characterized by the following features: 1) the FSH IR to LRH is lowered in most boys and all girls, 2) the LH IR is low for BA, 3) biological adrenarche is frequently absent or occurs at a time that is delayed for BA, 4) height age is close to BA, and 5) all patients have several pituitary deficiencies.

In contrast, the following features may characterize hypopituitary patients without gonadotropin deficiency: 1) the FSH IR to LRH is usually normal, 2) the LH IR is normal or intermediate for BA, 3) biological adren-

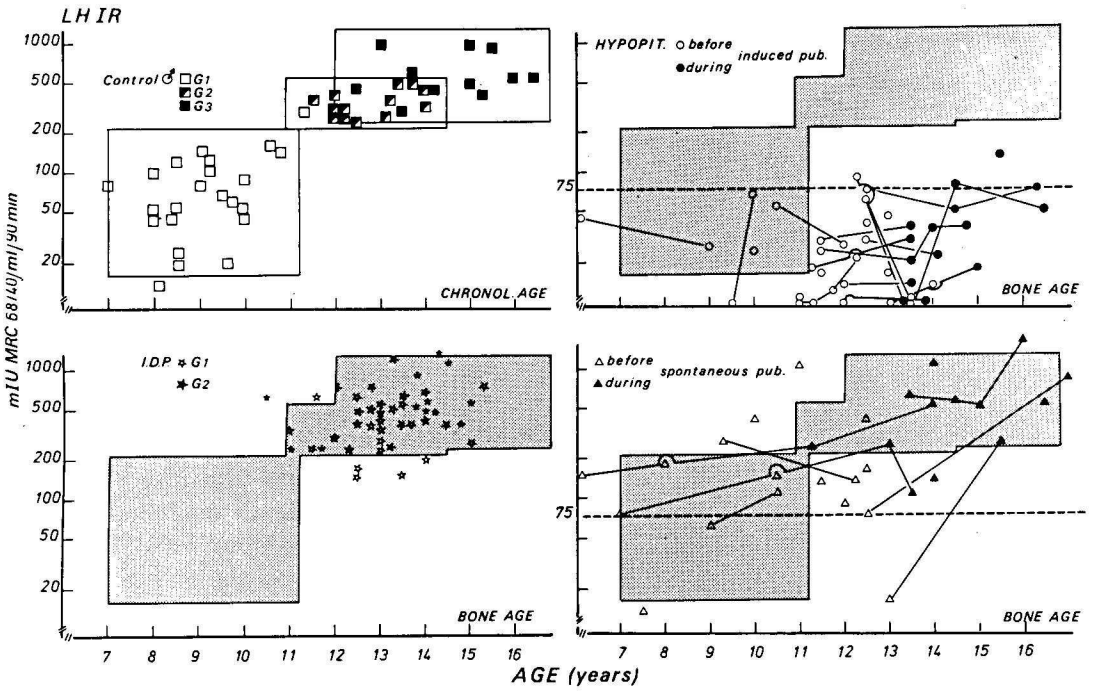

FIG. 3. LH IR to LRH (logarithmic scale) in relation to chronological age in prepubertal and pubertal control boys and to BA in patients with IDP and hypopituitarism. *Shaded areas* represent the mean ± 2 SD of the data obtained in controls according to genital stages. The MRC standard used was 68/40 for LH. Longitudinal data obtained in the same patient are *connected by lines*.

arche occurs at a normal time for BA in most patients, 4) bone maturation is excessive in relation to height age and 5) most patients (two of three) have isolated GH deficiency. Thus, none of the studied parameters, when considered alone, allows the diagnosis of gonadotropin deficiency in prepubertal hypopituitary patients to be made. However, the association of several clinical and biological features can be of predictive value.

Several investigators (22–24) have reported that in most children with multiple pituitary deficiencies, LH responses to LRH are decreased. Grumbach *et al.* (22) have also reported a decreased FSH response in 16 of 18 patients. Our data are in agreement with these findings. However, Chaussain *et al.* (23) and Kelch *et al.* (24) have reported FSH responses not significantly different from those obtained in prepubertal controls. The explanation for these differences remains to be elucidated.

In prepubertal children with isolated GH deficiency, LH responses were also reported to be lowered as in hypogonadotropic patients (24). In contrast, we have observed normal prepubertal LH and FSH IRs to LRH in most patients with isolated GH deficiency. This discrepancy may be explained by the fact that the longitudinal study of our patients allowed us to separate patients with from those without gonadotropin deficiency. In fact, the two types of LH IRs in boys virtually may be separated by concentrations lower or higher than 75 mIU/ml · 90 min. A very low LH IR was found in one patient who showed a subsequent spontaneous puberty during testosterone therapy. This shows the limits of the LRH test (9, 25). It should be stressed that in some patients, the calculation of the areas of gonadotropin responses during 90 min is more useful than Δ responses, whereas the latter were preferred to the former by Kelch *et al.* (24). In fact, peak values may overestimate the gonadotropin responses. In our study, gonadotropin-deficient patients were less clearly distinguishable from controls when Δ responses were used instead of IRs (26).

In hypopituitary boys without gonadotropin deficiency, the correlation between LH IR and plasma testosterone was found to be similar to that in controls, suggesting that in patients treated with hGH, Leydig cell responsiveness to LH is normal. However, in boys with IDP, the level of that correlation is higher. This might suggest some delay or resistance of the testicular response to the stimulating action of LH. This may explain the observation that LH responsiveness to LRH anticipates clinical puberty in IDP patients, as described in some late prepubertal controls (9, 22, 27).

The measurement of plasma DHEA-s levels has been shown to reflect adrenarche (28–31). Although the mechanisms involved in initiating this process have not been elucidated so far, the role of a still unidentified pituitary factor has been suggested (32–35). Consequently, adrenarche was studied in relation to pituitary function. The absence of adrenarche was most frequent in hypopitui-

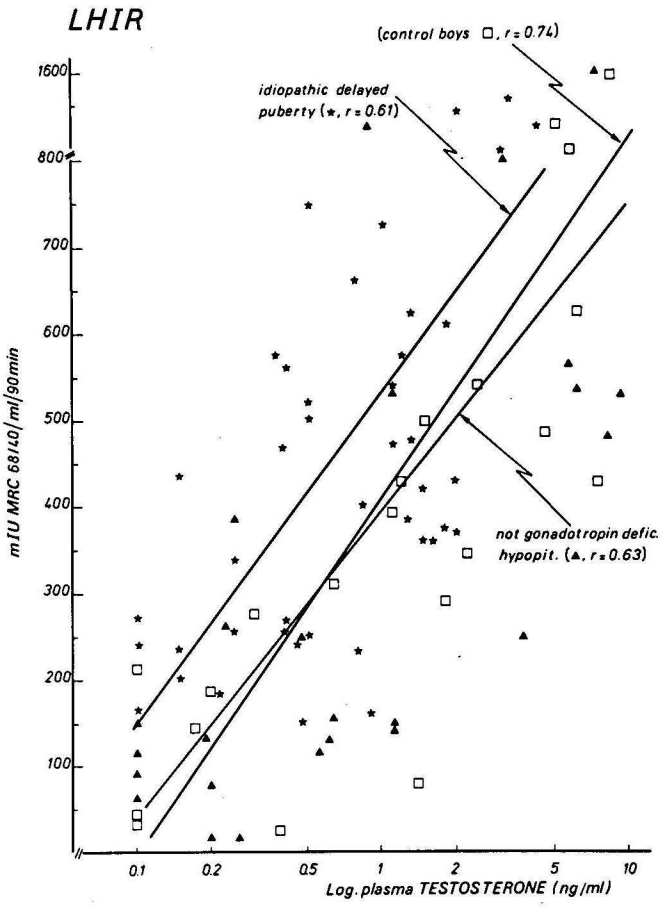

FIG. 4. LH IR to LRH in relation to logarithms of plasma testosterone levels in controls, hypopituitary boys, and boys with IDP. The MRC standard used was 68/40 for LH.

TABLE 4. Adrenarche in relation to pituitary hormone deficiencies

Pituitary deficiencies	No. of patients (boys and girls)	
	Adrenarche present[a]	Adrenarche absent
GH	7	1
GH + TSH	6	1
GH + TSH + FSH + LH	6	9
GH + TSH + FSH + LH + ACTH	2	11

[a] Plasma DHEA-s, ≥200 ng/ml at a BA of 11 yr or more.

tary patients with multiple deficiencies. In contrast, adrenarche usually occurs normally for BA in patients with isolated GH deficiency as well as in IDP patients (35–38).

In hypogonadotropic hypogonadism, DHEA-s has been reported to be normal or even high for BA (36). Several clinical situations with dissociated gonadarche and adrenarche have been described. (35). Thus, the occurrence of adrenarche seems to be related to pituitary function, although none of the pituitary hormones studied can be considered to be the factor responsible for adrenarche (32–35). However PRL secretion was not investigated in this study.

Hypopituitary boys and girls, investigated during spontaneous puberty show a normal increase in LH IR to LRH. This confirms normal gonadotropic function in these patients. The longitudinal observation of two boys without gonadotropin deficiency to whom testosterone therapy was given is of particular interest; a low testosterone dosage (100 mg/month) did not fully suppress gonadotropin secretion. In fact, in one of them, the LH response increased up to pubertal control ranges, whereas both patients showed testicular growth.

None of our patients was found to have gonadotropin deficiency associated only with GH deficiency. Of note is the fact that such association has been reported in about one fifth of patients with so-called isolated GH deficiency (39). On the other hand, among the patients without gonadotropin deficiency reported in this study, only TSH deficiency has been found to be associated with GH deficiency in some patients. Nevertheless, a normal gonadotropic function has been confirmed in a GH, TSH-, and ACTH-deficient patient who was not included in this study. This patient entered a spontaneous puberty at a BA of 9.7 yr.

Hypopituitary patients entered spontaneous puberty at a normal BA. This is agreement with our previous observations (40) and those of Tanner and Whitehouse (39). However, mean height for BA was low before as well as during puberty. This resulted in a progressive decline of the mean height for BA curve from the 50th percentile. In gonadotropin-deficient boys, a different growth pattern was observed. In fact, the mean height for BA was normal. Testosterone administration resulted in an increase in height velocity during the first year of treatment without excessive BA maturation, as previously reported (16). Consequently, these observations suggest that concomitant therapy using hGH and low dosages of testosterone promotes growth and puberty according to normal standards, at least when started at a BA above that of spontaneous pubertal onset. The discrepancies observed might be due to a different relationship between androgens and GH in the two groups (41–46). It should be noted that during testosterone treatment, the testes remained prepubertal.

It is concluded that the study of several clinical and biological features, and especially the gonadotropin IR to LHRH, are of predictive value for the diagnosis of gonadotropin deficiency in prepubertal hypopituitary patients.

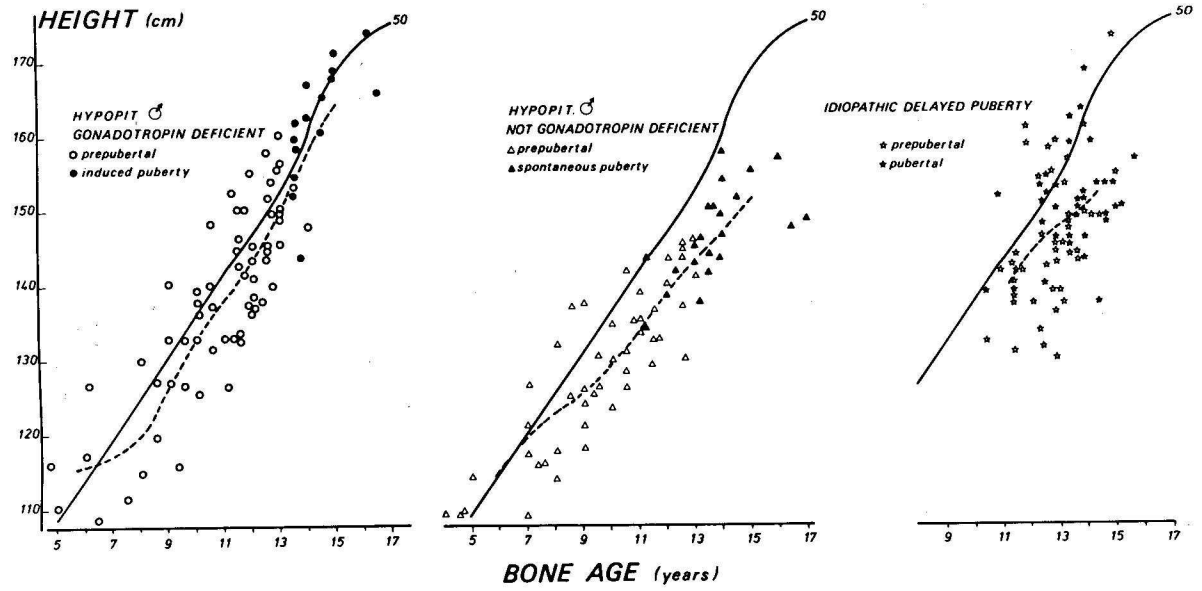

FIG. 5. Height in relation to BA in hypopituitary boys with and without gonadotropin deficiency and in boys with IDP. ——, The 50th percentile of the standard curves according to Tanner *et al.* (10); - - -, the mean curves of height according to BA in the patients.

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