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Research Article

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ABSTRACT Serum follicular-stimulating hormone (FSH) and luteinizing hormone (LH) as determined by radioimmunoassay, were correlated with sexual development in 29 patients with hypopituitarism (ages 14.2–29.9 yr).

16 of 25 idiopathic hypopituitary patients (20 males and 5 females) exhibited some degree of sexual development. Stage III of sexual development or beyond was achieved by 12 of the 16. Of 13 patients with growth hormone (GH), adrenocortical-stimulating hormone (ACTH), and thyroid-stimulating hormone (TSH) deficiency, 8 did not develop beyond stage I. In contrast, five of six patients with GH deficiency without ACTH or TSH deficiency developed to stage III of sexual development or beyond. The mean (±SD) serum LH concentration while in stage I (4.3 ±0.9 mIU/ml) of eight patients (seven males and one female) who developed beyond stage I was significantly ($P < 0.005$) greater than the mean serum LH concentration (2.3 ±0.9 mIU/ml) in nine patients (seven males and two females) who had not developed beyond stage I. Mean serum FSH concentrations were not different.

Three of four males with organic hypopituitarism did not develop beyond stage I of sexual development.

Serum FSH and LH concentrations in the idiopathic and organic hypopituitary patients were more compatible with stage of sexual development than with age. A serum LH concentration below the range of normal for stage I of sexual development in a prepubertal patient suggests that the patient will remain sexually infantile as an adult.

INTRODUCTION

The intent of this investigation was to determine if serum follicular-stimulating hormone (FSH)[1] and luteinizing hormone (LH) concentrations in subjects with hypopituitarism correlated with their state of sexual development, and to determine, if possible, in prepubertal patients whether one could predict by determining serum FSH and/or LH concentrations whether sexual development would occur.

METHODS

Serums from 25 patients (20 males and 5 females) with idiopathic hypopituitarism and 4 males with organic hypopituitarism were obtained (1963–1970) and stored at −20°C. The patients ranged in age from 14.2 to 29.9 yr. The radioimmunoassay techniques for determining FSH and LH have been previously reported (1–8) as have the normal values utilized in this manuscript (4, 8, 9). Results are reported as milli International Units (mIU) of the second international reference preparation of human menopausal gonadotropin (2nd IRP-HMG). The standard deviation (SD) for FSH in multiple assays is ±1.1 mIU/ml at a level of 7.1 mIU and ±0.4 mIU at 2.3 mIU/ml. The SD for LH in multiple assays is ±1.2 mIU at a level of 8 mIU/ml and ±0.4 mIU at 1.4 mIU/ml.

Staging of sexual development in males was according to the system of Tanner (10). Boys in stage I were completely prepubertal; those in stage II had enlargement of

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[1] *Abbreviations used in this paper:* FSH, follicular-stimulating hormone; GH, growth hormone; LH, luteinizing hormone; 2nd IRP-HMG, second international reference preparation of human menopausal gonadotropin.

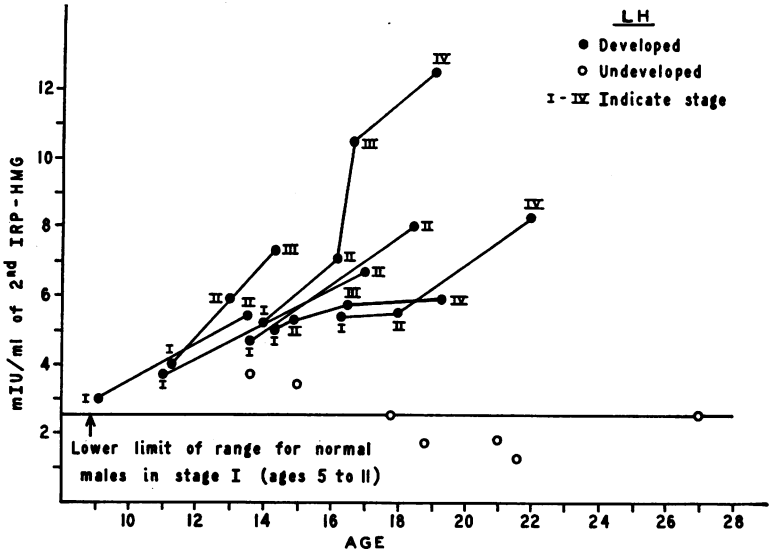

FIGURE 1 Serum LH concentrations in 14 idiopathic hypopituitary males first observed with stage I sexual development. 7 of the 14 developed beyond this stage. Increase in serum LH concentration by stage is apparent in the individual patient. Three of the undeveloped patients had serum LH concentrations which were less than the LH concentration range of normal males in stage I.

the scrotum and testis; those in stage III had enlargement of the penis; those in stage IV had further enlargement of the penis and scrotum and growth of the prostate; and those in stage V had genitalia adult in size. In females, stage I was defined as completely prepubertal, stage II as the presence of glandular breast tissue only, stage III as the presence of both breast tissue and sexual hair, and stage IV as the presence of breast tissue, sexual hair, and menarche.

Growth hormone (GH) deficiency was defined as a GH response of < 5 ng/ml to hypoglycemia and arginine infusion; thyroid-stimulating hormone (TSH) deficiency as a radioactive iodine (RAI) uptake of $< 15\%$ and/or a T_4 iodine of < 2.9 μg/100 ml;[2] and adrenocortical-stimulating hormone (ACTH) deficiency as a response of < 5 mg/m^2

[2] TSH stimulation tests and serum TSH levels were not done.

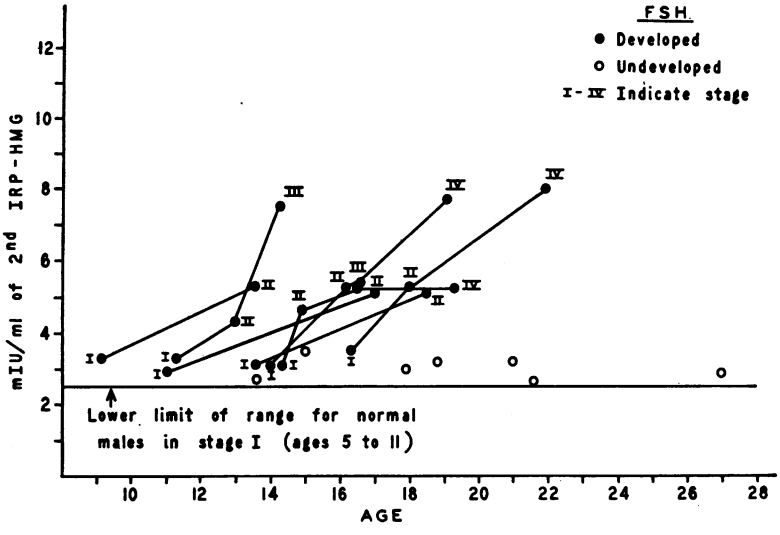

FIGURE 2 Serum FSH concentrations in 14 idiopathic hypopituitary males first observed with stage I sexual development. 7 of the 14 developed beyond this stage. Increase in serum FSH concentration by stage is apparent in the individual patient.

TABLE I
Idiopathic Hypopituitary Males

Stage		Developed									
		B. R.	S. L.	H. P.	B. D.	G. S.	K. D.	S. D.	A. R.	B. A.	S. H
I	Age (yr)	11.1	13.6	9.1	11.3	14.0	14.3	16.3			
	FSH	2.9	3.1	3.3	3.3	3.1	3.1	3.5			
	LH	3.7	4.7	3.0	4.0	5.4	5.0	5.4			
II	Age	17.0	18.5	13.5	13.0	16.2	14.9	18.0	15.2	14.4	15.9
	FSH	5.1	5.1	5.3	4.3	5.3	4.7	5.3	5.0	5.3	5.8
	LH	6.7	8.1	5.4	6.1	7.1	5.3	5.5	2.7	7.6	4.5
III	Age			14.2*	14.3	16.6	16.5			18.9*	17.3
	FSH				7.5	5.4	5.3				8.3
	LH				7.3	10.5	5.7				5.9
IV	Age					19.1	19.3	22.3			
	FSH					7.7	5.3	8.0			
	LH					12.5	5.9	8.3			
V	Age										
	FSH										
	LH										

* Serum not available.
‡ Also in stage I at 16.9 yr.
§ P of <0.01 for difference from mean of preceding stage.
‖ P of <0.05 for difference from mean of preceding stage.

of urinary 17-hydroxycorticosteroids per 24 hr after the administration of Metopirone (SU-4885) at a dosage of 300 mg/m^2 orally every 4 hr for 24 hr.

Except for androgens or estrogens, all patients were on appropriate hormonal replacement therapy.

RESULTS

Idiopathic hypopituitary subjects

A. Males. 10 of the 20 males had developed to stage III of sexual development or beyond when last seen (Tables I and II). Four of five males with GH deficiency without ACTH or TSH deficiency developed to stage III; and three of the four progressed to stage IV of sexual development (Table II). In contrast, sexual development to stage III or beyond had occurred in only 3 of 10 males with GH deficiency associated with ACTH and TSH deficiency (Table II). Mean serum FSH and LH concentrations for all age groups were significantly ($P < 0.01$) lower than the mean levels of normal males (Table III). Though the mean serum concentration of FSH for stages I and II were significantly ($P < 0.03$) lower than that of normal males, mean serum FSH and LH concentrations increased progressively by stage (Table III). The increase in serum FSH and LH concentration by stage is apparent in the individual patient (Table I; Figs. 1 and 2).

B. Females. Sexual development to stage III had occurred in two of the five females when last seen (Table II, The females in stage I were 16 and 18 yr of age, the one in stage II was 18 yr of age, and the two in stage III were 15.3 yr of age). Two of three females with GH, ACTH, and TSH deficiency had not developed beyond stage I (Table II). Mean FSH and LH concentrations of the 15–16 yr age group were not significantly different ($P < 0.3$) from the mean of normal females (Table IV). However, the mean serum FSH concentration of stage I was significantly ($P < 0.03$) lower than that of normal females, and the mean LH concentration of stage III was significantly ($P < 0.01$) greater than that of normal females (Table IV). A progressive increase in mean serum FSH and LH concentrations by stage was observed (Table IV).

C. Comparing stage I mean LH and FSH concentrations respectively. The mean (±SD) serum LH concentration while in stage I (4.5 ±0.9 mIU/ml) of seven males who developed beyond statge I was significantly ($P < 0.005$) greater than the mean stage I LH concentration (2.4 ±0.7 mIU/ml) of seven males who had not developed beyond this stage (Table I). Similarly when this comparison was made for males and females combined (seven males and one female having a mean LH of 4.3 ±0.9 mIU/ml compared with seven males and two

(*FSH and LH in mIU/ml*)

Developed			Undeveloped								
P. J.	B. J.	J. W.	B. C.	B. W.	E. W.	H. D.‡	L. M.	T. W.	V. J.	Mean	SD
			15.0	21.0	21.6	13.6	18.8	17.9	27.0		
			3.5	3.2	2.6	2.7	3.2	3.0	2.9	3.1	0.3
			3.4	1.8	1.5	3.7	1.7	2.5	2.5	3.6	1.4
14.8	13.3										
4.8	5.3									5.1§	0.4
5.7	5.3									5.8§	1.5
15.6	14.7	18.0									
5.3	6.1	5.9								6.3§	1.2
8.7	6.2	7.0								7.3‖	1.8
17.3	15.5										
6.8	6.0									6.8	1.1
10.3	5.9									8.6	2.9
	15.9										
	7.6									7.6	
	5.5									5.5	

females having a mean LH of 2.3 ±0.9 mIU/ml) the difference between the mean LH concentrations was significant ($P < 0.005$). Mean serum FSH concentrations in these groups of patients were not different (3.1 ±0.2 mIU/ml compared with 3.1 ±0.3 mIU/ml). Three of the seven males who had not advanced beyond stage I had serum LH concentrations (1.5–1.8 mIU/ml) which were less than the LH concentration range (2.5–5.8 mIU/ml) of normal males in stage I (Table I patients B. W., E. W., and L. M. and Fig. 1).

Organic hypopituitary subjects

One of four males had progressed beyond stage I of sexual development (Table II). Two of the three who had not progressed beyond stage I were older than 21 yr and the third patient (15.9 yr) showed a regression in sexual development to stage I. The one patient who progressed sexually did so from stage I at age 12.2 yr to stage III at 18.2 yr (Table III, this patient was also in stage I at 14 yr, in stage II at 14.7 yr, and in stage III at 18.2 yr).

DISCUSSION

Other investigators have reported measurable radioimmunoassayable concentrations of serum FSH and LH in hypopituitary patients (2, 3, 6, 11–15). None, how-

TABLE II
Hypopituitary Subjects

		Stage				
	Subjects	I	II	III	IV	V
	n					
Idiopathic						
Males						
GH; ACTH; TSH deficient	10	6	1	1	1	1
GH deficient only	5	—	1	1	3	—
GH and ACTH deficient	4	1	1	2	—	—
GH and TSH deficient	1	—	—	1	—	—
Total	20	7	3	5	4	1
Females						
GH; ACTH; TSH deficient	3	2	1	—	—	—
GH deficient only	1	—	—	1	—	—
GH and TSH deficient	1	—	—	1	—	—
Total	5	2	1	2		
Organics						
Males	4	3	—	1	—	—

ever, has presented extensive data. The data presented in this manuscript allow certain pertinent observations to be made concenring sexual development and serum gonadotropin concentrations in patients with hypopituitarism. Prognosis for sexual development was better in those patients with only growth hormone deficiency [five of six developed to stage III of sexual development or beyond (Table II; idiopathic hypopituitary patients males and females combined)], as compared with those patients with growth hormone, ACTH, and TSH deficiency [3 of 13 had developed to stage III or beyond (Table II; idiopathic hypopituitary patients males and females combined)]. This finding is in keeping with the reports of sexually mature dwarfs with inherited isolated deficiency of growth hormone (16, 17). Utilization of the immunoassay to measure serum FSH and/or serum LH concentrations in one patient in an effort to predict if that patient will develop sexually is by and large not possible. However, measurement of serum LH concentrations in a group of hypopituitary patients dem-

TABLE III

Hypopituitary Males Compared with Normal Males

Stage	Age	Patients	FSH			LH		
			Range	Mean	SD	Range	Mean	SD
		n		*mIU/ml*			*mIU/ml*	
Normal males								
	9–10	9	3.2–7.1	5.4	1.0	3.5–7.0	4.8	1.2
	11–12	13	3.0–9.0	5.6	1.7	4.0–12.0	6.8§	2.0
	13–14	18	5.0–14.0	8.1§	2.5	5.0–14.0	9.4§	2.5
	15–16	18	5.0–13.0	8.7	4.2	4.0–13.0	9.0	2.1
	17–18	10	4.0–14.0	9.2	3.8	2.5–5.8	14.1§	3.8
	Adult	35	4.4–13.2	7.4	1.9	6.0–23.0	10.9	4.0
I	5–11	25	2.5–7.0	4.5	1.0	2.5–5.8	3.9	1.0
II	10–13	17	3.0–9.0	5.9§	1.2	4.0–12.0	6.8§	2.1
III	12–14	11	2.5–14.0	8.1§	3.0	6.0–11.0	8.5‖	1.7
IV	12–17	18	3.5–15.0	8.5	3.4	4.0–15.5	9.5	3.0
V	15–18	21	4.0–13.0	7.2	2.2	7.0–19.0	11.8	3.7
Idiopathic hypopituitary male subjects*‡								
	9–10	1	—	3.3	—	—	3.0	—
	11–12	2	2.9–2.3	3.1	0.2	3.7–4.0	3.9	0.2
	13–14	12	2.7–7.5	4.4	1.5	3.7–7.6	5.6§	1.1
	15–16	10	3.5–7.6	5.3**	1.2	2.7–10.5	5.9	2.3
	17–18	8	3.0–8.3	5.4	1.8	1.7–10.3	6.0	2.8
	Adult	6	2.6–8.0	5.0	2.4	1.5–12.5	5.5	4.2
I	9–27	14	2.6–3.5	3.1	0.3	1.5–5.4	3.6	1.4
III	13–18	12	4.3–5.8	5.1§	0.4	2.7–7.6	5.8§	1.5
III	14–18	7	5.3–8.3	6.3§	1.2	5.9–10.5	7.3¶	1.8
IV	15–22	5	5.3–8.0	6.8	1.1	5.9–12.5	8.6	2.9
V	15.9	1	—	7.6	—	—	5.5	—
Organic hypopituitary male subjects								
	13–14	2	2.5–5.0	3.4	1.4	2.4–4.1	3.3	1.3
	15–16	1	—	2.8	—	—	1.5	—
	17–18	1	—	7.1	—	—	5.1	—
	Adult	2	2.7–2.9	2.8	0.1	1.5–1.5	1.5	—
I	14–30	4	2.5–2.9	2.7	0.2	1.5–2.4	1.7	0.5
II	14.7	1	—	5.0	—	—	4.1	—
III	18.2	1	—	7.1	—	—	5.1	—

* P of <0.01 for difference from mean of normal males for all ages.
‡ P of <0.03 for difference from mean of normal males for stages I and II for FSH.
§ P of <0.01 for difference from mean of preceding group.
‖ P of <0.03 for difference from mean of preceding group.
¶ P of <0.05 for difference from mean of preceding group.
** P of <0.03 for difference from mean of 11–12 age group.

TABLE IV

Hypopituitary Females Compared with Normal Females

Stage	Age	Patients	FSH Range	FSH Mean	FSH SD	LH Range	LH Mean	LH SD
		n		*mIU/ml*			*mIU/ml*	
Normal females								
	11–12	20	5.0–12.0	7.5	2.2	2.4–14.0	8.7	3.6
	13–14	19	3.5–13.3	8.0	2.9	4.0–22	8.8	4.5
	15–16	4	5.7–10.4	8.2	2.0	3.8–19	13.5	6.8
	17–18	7	4.4–13.0	8.6	2.4	5.0–29.0	15.3‡	8.5
I	2–12	27	3.1–5.7	4.2	1.0	2.0–7.5	2.9	2.1
II	8–12	13	4.6–7.1/	5.5*	0.7	2.5–11.5	3.9*	2.9
III	9–14	23	5.0–12.0	8.0*	1.9	2.5–14.0	8.4*	2.9
Idiopathic hypopituitary female subjects								
	11–12	1	—	2.9	—	—	3.2	—
	13–14	1	—	5.0	—	—	4.7	—
	15–16	3	2.6–7.3	6.5‖	4.0	1.0–19.6	11.4‖	9.5
	17–18	2	3.1–5.1	4.1	1.0	3.0–4.3	3.7	1.3
I	11–18	3	2.6–3.1	2.9¶	0.3	1.0–3.2	2.4	1.2
II	13–18	2	5.0–5.1	5.1*	0.1	/4.3–4.7	4.5§	0.2
III	15.3	2	7.3–9.5	8.4*	1.1	13.5–19.6	16.6*,**	3.0

* P of <0.01 for difference from mean of preceding group.
‡ P of <0.03 for difference from mean of preceding group.
§ P of <0.05 for difference from mean of preceding group.
‖ P of 0.30 for difference of mean of normal females.
¶ P of <0.03 for difference of mean of normal females.
** P of <0.01 for difference of mean of normal females.

onstrates that a relationship between relative serum LH concentrations and future sexual development does exist. While in stage I the mean serum LH concentration of seven patients who progressed beyond this stage of sexual development were significantly ($P < 0.005$) greater than the mean serum LH concentration of seven patients who had not progressed beyond stage I (see Results, section *C*). Moreover, the fact that serum LH concentrations were less than the range of normal for stage I, in three of the seven patients who had not advanced beyond stage I, suggests that such a finding is consistent with a prediction of no further sexual development (Table I patients B. W., E. W., L. M., and Fig. 1).

Serum FSH and LH concentrations in patients with hypopituitarism are more compatible with their stage of sexual development than with their age (Tables III and IV). A similar pattern has been reported for normal individuals and patients with constitutional delayed adolescence (9). Though 16 of the idiopathic hypopituitary patients and 1 of the oragnic hypopituitary patients exhibited various degrees of sexual development, only 1 patient (Tables I and II) approached the adult state of sexual maturation. In this regard, it is of interest to note the serum LH concentrations (13.5, 19.6 mIU/ml) of the two 15 yr old females in stage III (Table IV). Root, Moshang, Bongiovanni, and Eberlein have indicated that a 17 yr old female with idiopathic hypopituitarism who had a serum LH concentration of 13.7 mIU/ml attained sexual maturity (13).

In conclusion, the data indicate that hypopituitary subjects may attain various levels of sexual development and suggest that in an occasional case full sexual maturity may be achieved. Serum FSH and LH concentrations correlate with stage of sexual development, and the finding of an LH serum concentration in a prepubertal patient which is less than the range of normal for stage I of sexual development strongly suggests that the patient will have sexual infantilism during adult life.

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