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Isolated Pituitary Gonadotrophin Deficiency: Gonadotrophin Secretion after Synthetic Luteinizing Hormone and Follicle Stimulating Hormone-releasing Hormone

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Summary

The responses of serum immunoreactive luteinizing hormone (LH) and follicle stimulating hormone (FSH) after intravenous injection of 100 μg of synthetic LH/FSH-RH have been studied in 14 patients with the syndrome of isolated pituitary gonadotrophin deficiency. Nine of the patients showed a rise of both hormones, two a small rise of FSH only, and three were unresponsive. In two of the unresponsive patients injection of a 500-μg dose produced a small rise of LH only. Of the patients who responded, four had LH and FSH responses within the normal adult range, while in the others the responses were smaller and delayed. It is suggested that this syndrome is due to a lack of the hypothalamic-releasing hormone itself, rather than to a pituitary deficiency. However, repeat assessment after prolonged administration of the releasing hormone will be necessary before a pituitary disorder can be excluded in all patients. The synthetic LH/FSH-RH, preferably as a depot preparation, may provide a means of treating these patients to induce the development of puberty and subsequent fertility.

Introduction

With the availability of sensitive radioimmunoassays for luteinizing hormone (LH) and follicle stimulating hormone (FSH) the condition of isolated pituitary gonadotrophin deficiency (hypogonadotrophic hypogonadism) has been increasingly recognized as a cause of partial or complete failure of puberty. The condition may occur alone or be associated with other developmental abnormalities such as anosmia, harelip, cleft palate, and craniofacial asymmetry (Kallman *et al.*, 1944). These patients have low or low-normal serum gonadotrophin levels which do not rise after clomiphene administration. Pituitary function is otherwise normal, though blunted growth hormone responses to hypoglycaemia have been described (Odell *et al.*, 1967; Hornichter *et al.*, 1968; Bardin *et al.*, 1969; Anderson *et al.*, 1972).

It remains unclear whether the primary defect in this condition is at a hypothalamic or pituitary level, though the former site has been more often postulated, and histological abnormalities in the hypothalamus have been described (De Morsier and Gauthier, 1963). This view is supported also by the recent report of Naftolin *et al.*, (1971) who found a small increase in serum LH in two patients after administration of a purified ovine hypothalamic extract.

The hypothalamic-releasing hormone for LH/FSH has recently been isolated and shown to be a decapeptide (Schally *et al.*, 1971). The decapeptide has now been synthesized, and by using this material Besser *et al.* (1972) have shown that it releases LH and to a lesser extent FSH in normal men and women.

The aim of the present study was to establish whether patients with isolated gonadotrophin deficiency were able to secrete LH or FSH from the pituitary in response to an injection of LH/FSH-RH, and to assess the potential therapeutic value of the releasing hormone in such patients.

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Patients and Methods

Fourteen patients (10 men and four women) were studied, and details of clinical features, previous therapy, and basal investigations are shown in the Table. The patients presented with complete or partial failure of puberty and the women with primary amenorrhoea. All had a eunuchoid habitus, a normal chromosome karyotype, and normal pituitary fossa radiographs. By using the criteria suggested by Hall *et al.* (1972), all the patients had normal pituitary function with respect to growth hormone and adrenocorticotrophic hormone (assessed by responses to insulin-induced hypoglycaemia) and thyroid stimulating hormone as judged by protein bound iodine and ^{131}I uptake. Case 4, however, had an impaired growth hormone response, peak value 14 ng/ml (M.R.C. standard A HGH). Basal LH levels (mean of three to four estimations) were low in all patients and serum FSH was low in all but two (Cases 3 and 7). None of the subjects showed a rise of serum LH or FSH during a clomiphene test confirming the gonadotrophin deficiency, and all the men had low basal plasma 17β-hydroxyandrogen levels which rose during a human chorionic gonadotrophin stimulation test, indicating the presence of testicular Leydig cells (Anderson *et al.*, 1972).

Assay Systems.—Serum LH and serum FSH were each measured in triplicate in two different radioimmunoassay systems, details of which have been given previously (Besser *et al.*, 1972; Marshall *et al.*, 1972). Results in the different assays for each hormone were essentially the same, and for clarity values from one system only are presented here (assay 2, Besser *et al.*, 1972). For comparison purposes the same standard preparation M.R.C. 69/104 (derived from LER 907) was used

for both the LH and FSH assays and results expressed as mIU/ml. For LH, 1 ml M.R.C. research standard A = 2 mIU M.R.C. 69/104. In the assays a change of greater than 0·5 mIU/ml for either LH or FSH was significant. When using this standard the normal ranges for adult subjects were: men, LH 3·6-8·2; FSH 1·5-8·4 mIU/ml; women (follicular phase), LH 3·6-9·0; FSH 2·0-8·2 mIU/ml. Plasma 17β-hydroxyandrogens were measured in the men by the method of Anderson (1970). The normal range for men at 9 a.m. was 4·9-21·5 ng/ml.

Test Procedure.—A 100-μg sample of synthetic LH/FSH-RH (Hoechst) in 4 ml of sterile water was given to the recumbent, non-fasted patients between 9 a.m. and 10 a.m. by rapid intravenous injection. Samples for LH and FSH assay were taken 15 minutes and immediately before the injection, and at frequent intervals during the subsequent two hours. In two patients a dosage of 500 μg intravenously was also given. Previous therapy had been discontinued for at least two months before administration of LH/FSH-RH with the exception of Case 2, when the interval was four weeks. All the men had noted a reduction in libido after treatment was stopped.

Control Subjects.—These were 18 normal men, and five women during the follicular phase of the menstrual cycle. Details of the LH and FSH responses are given elsewhere (Besser *et al.*, 1972). Informed consent was given by all patients and control subjects.

Results

Serum LH and FSH levels before and after injection of 100 μg LH/FSH-RH in the 14 patients are shown in Fig. 1. Nine patients showed a rise of both LH and FSH, two (Cases 2 and 4) showed an FSH rise only, and three (Cases 5, 8, and 10) showed no change in the levels of either hormone during the test period.

In four patients (Cases 1, 3, 7, and 9) responses of both hormones were within the range seen in normal adult subjects,

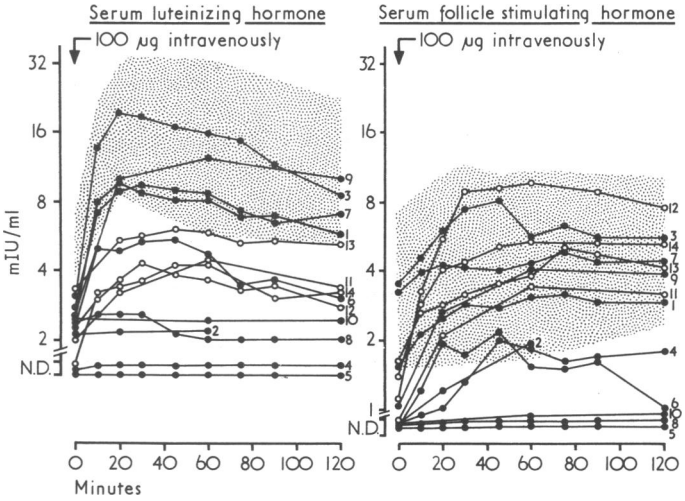

FIG. 1—Responses of serum LH and FSH in 14 patients after intravenous injection of 100 μg LH/FSH-RH. Case numbers as listed in Table. Shaded areas indicate range of response seen in normal subjects. ● = Males. ○ = Females. Mean of the − 15 and 0-minute values is shown. ND = Not detectable in the assays used. A logarithmic scale of gonadotrophin levels is used for clarity.

Clinical Details of Patients Studied

Case No.	At Presentation		Testicular Size (cm)	Bone Age	Testicular Biopsy		Basal Hormone Levels			Therapy Before Presentation	Therapy before Administration of LH/FSH-RH†
	Age	Clinical Features*			Leydig Cells	Spermatozoa	LH (mIU/ml)	FSH ml (U/ml)	17β-hydroxy-androgen (ng/ml)		
Men:											
1 ..	26	Prepubertal	2·5 × 1·5 × 1·0	15	Occasional	None	<2·0	<1·0	1·6	Nil	HCG 1,000 IU for 17 months
2 ..	21	Stage II puberty	1·5 × 1·0 × 1·0	15	—	—	2·1	<1·0	3·2	Nil	HCG 500 IU for 2 months
3 ..	26	Stage III puberty	3·5 × 2·0 × 2·5	17	None	Occasional	3·4	3·0	3·9	Nil	HCG 1,000 IU for 18 months
4	25	Stage II puberty	2·0 × 2·0 × 1·5	15	None	None	<2·0	<1·0	1·4	HCG for 6 weeks, intramuscular testosterone for 6 months	HCG 1,000 IU for 19 months
5 ..	19	Prepubertal	2·0 × 2·0 × 1·5	—	None	None	<2·0	<1·0	1·0	Nil	HCG 2,000 IU for 12 months
6 ..	19	Prepubertal	2·0 × 1·0 × 1·0	15	—	—	2·6	<1·0	1·3	Nil	HCG 2,000 IU for 6 months
7 ..	18	Prepubertal	2·0 × 1·0 × 1·0	12	None	None	2·4	2·7	0·8	Nil	HCG 2,000 IU for 12 months
8 ..	30	Normal male hair. Voice broken	2·5 × 1·5 × 1·0	Adult	None	None	2·0	<1·0	2·5	Intramuscular testosterone for 10 years	None for 2 months
9 ..	21	Stage III puberty	2·0 × 1·0 × 1·0	17	None	None	2·2	<1·0	1·3	HCG for 2 months, Intramuscular testosterone for 7 months	None for 3 months
10 ..	25	Stage II puberty	1·5 × 0·5 × 0·5	16	None	None	2·6	<1·0	1·7	Intermittent testosterone for 2 years	HCG 500 IU, Pergonal for 12 months 300 IU
Women:											
11	26	1° amenorrhoea. Small uterus. Normal pubic hair. Small breasts	—	17	—	—	2·0	<1·0	—	Oral oestrogens for 2 years	None for 8 years
12 ..	22	1° amenorrhoea. Small uterus. Normal pubic hair. Small breasts	—	18	—	—	<2·0	<1·0	—	Oral oestrogens for 5 months	Minovlar for 18 months
13 ..	22	1° amenorrhoea. Small uterus. Normal pubic hair and breasts	—	18	—	—	<2·0	1·2	—	Oral oestrogens for 1 year	Minovlar for 6 months
14 ..	24	1° amenorrhoea. Small uterus. Normal pubic hair and breasts. Anosmic	—	Adult	—	—	<2·0	<1·0	—	Oral oestrogens for 18 months	Volidan 21 for 4 months

*Puberty stages according to Tanner (1962).
†This therapy was discontinued for at least two months before administration of LH/FSH-RH, except in Case 2 when the interval was four weeks.
HCG = Human chorionic gonadotrophin. For therapy the dose of HCG indicated was given twice weekly and Pergonal three times a week.

though basal values were low. In five (Cases 6, 11, 12, 13, and 14) who had low basal values and an LH response, the LH rise was smaller and delayed, maximum values being seen 45-60 minutes after the injection. In general, the patients with a good LH response showed a noticeable FSH rise. In the four women patients, however, an appreciable increase in FSH was seen, while the LH rise was small and delayed.

Repeat Tests.—Repeat injections with the same dose of LH/FSH-RH were given to four patients (Cases 1, 12, 13, and 14) between three and six weeks after the first injection. In all four the LH and FSH responses were reproducible, being of similar magnitude and time course to those seen after the first injection. LH and FSH responses during these tests in Case 12 are shown in Fig. 2. No progressive increase in the response of

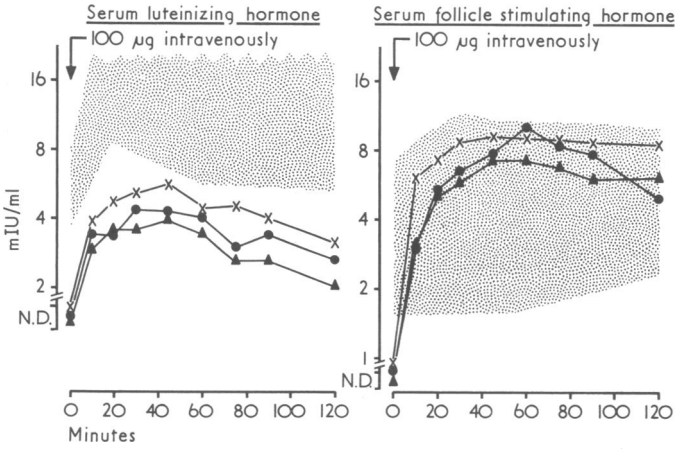

FIG. 2—Responses of serum LH and FSH to three intravenous injections of 100 μg LH/FSH-RH in one patient (Case 12). ● = first injection. × = second injection (three weeks later). ▲ = third injection (five weeks later). Shaded areas indicate range of responses seen in normal subjects.

either hormone was seen during the later two tests. In two patients (Cases 8 and 10) who did not have a hormone response after the first injection, a repeat test with 500 μg LH/FSH-RH was performed. In both a small rise of serum LH was seen (Case 8 <2·0-2·6, Case 10 <2·0-3·0 mIU/ml) but neither patient showed an FSH response (all values <1·0 mIU/ml).

Discussion

The failure of these patients to achieve normal adult development is due to a lack of adequate circulating levels of one or both pituitary gonadotrophins. Hitherto it has not been clear whether this results from a deficiency of releasing hormone secretion by the hypothalamus, or from the inability of the anterior pituitary gland to secrete gonadotrophins. In this study nine of 14 patients showed a response of both LH and FSH after injection of 100 μg LH/FSH-RH, and in another two a small LH rise was seen after the larger dose. This shows that the anterior pituitary cells in these patients are capable of secreting gonadotrophins, and suggests that their hypogonadism results from deficient gonadotrophin-releasing hormone secretion. The degree of response varied, some patients showing a normal rise from low basal values, whereas others had smaller, delayed gonadotrophin response.

Some of the variation in the hormonal responses might be accounted for by the degree of previous stimulation of the pituitary by endogenous releasing hormone. Thus, two of the four patients who had normal hormonal responses to LH/FSH-RH had clinical evidence of partial spontaneous puberty, suggesting that the pituitaries of these patients may have been exposed to some endogenous releasing hormone and that their deficiency was only partial. These patients had also shown a noticeable and early 17β-hydroxyandrogen rise after human chorionic gonadotrophin, suggesting previous stimulation of the testis by endogenous gonadotrophin. In those with absent or small hormonal responses to the releasing hormone, it is not possible at present to decide whether their hypogonadism is simply due to chronic releasing hormone deficiency or whether the pituitary itself is unable to respond. This might be resolved after repeated stimulation with the releasing hormone. If a normal gonadotrophin response develops this would confirm that the pituitary cells had merely been atrophied. Repeat tests with 100 μg in four of the present patients did not show an increased response, but this may be due to the long time interval between injections.

Interpretation of the FSH responses in these patients is difficult, as in normal adults FSH release does not always occur after injection of LH/FSH-RH (Besser *et al.*, 1972). It is of interest to note, however, that in each of the women patients a normal FSH response occurred in the presence of a small delayed LH rise. This may represent a partial failure of the pituitary LH secreting cells only. Alternatively, there could be two rather than one releasing hormone—one each for LH and FSH. While much evidence is available that the synthetic decapeptide releases both LH and FSH, doubt exists as to whether this is the only gonadotrophin-releasing hormone, or whether another, predominantly releasing FSH, is present in the hypothalamus. If this is the case then these subjects could be suffering from a deficiency of the LH-releasing hormone only.

These results indicate that in most cases of isolated pituitary gonadotrophin deficiency there is a failure of hypothalamic-releasing hormone secretion, though results after prolonged administration of the releasing hormone are needed to exclude degrees of pituitary impairment in some patients. Furthermore, these studies suggest that synthetic LH/FSH-RH may prove to be a satisfactory form of treatment in these patients to induce the development of puberty and subsequent fertility.

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