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Differential Diagnosis of Male Central Hypogonadism by Short-term Pulsatile LHRH Administration

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ABSTRACT

In order to obtain a clinically valuable differentiation of central hypogonadism (CH), 18 male patients, including 13 with permanent gonadotropin deficiency (GD), age 14.3 - 41 yrs, bone age 8.5 - 19 yrs, and 5 with constitutional delay (CD) of puberty (age 15.3 - 20, bone age 12.5 - 15 yrs) were studied. Among the GD patients, there were 4 with anosmia (Kallmann's syndrome, KS), 6 with idiopathic hypopituitarism (HP) and 3 with isolated hypogonadotropic hypogonadism (HH).

The spontaneous nocturnal plasma profile of LH and FSH was compared with that during pulsatile LHRH infusion (5 µg iv every 90 min) by a portable micropump (Zyklomat®) for 36 hrs. The pituitary-gonadal response was evaluated by calculating the LH and FSH slopes during pulsatile LHRH and by comparing plasma testosterone (T) before and after.

While spontaneous nocturnal FSH pulses were absent in all patients, between 1 and 4 significant LH pulses were seen in all CD but in none of the GD patients. In all patients, mean FSH was significantly higher during pulsatile LHRH than during sleep. During pulsatile LHRH administration, significantly increasing FSH responses were seen in all KS and HP patients, but in only 2 of the 5 CD and in none of the 3 HH patients. In all CD boys (mean testis vol, 8.6 ml), T rose markedly during pulsatile LHRH (mean, from 168 to 414 ng/dl), whereas in all GD patients (mean testis vol, 2 ml) it did not (19 vs 27 ng/dl).

Conclusions: Pulsatile LHRH for 36 hrs differentiates CD and GD far more exact than was previously possible. A primary hypothalamic defect is present not only in KS and HH patients, but occurs also in classic hypopituitary (HP) patients who thus, too, may have the potential of becoming fertile with pulsatile LHRH therapy.

INTRODUCTION

One of the most difficult diagnostic problems in paediatric endocrinology is the early distinction between permanent gonadotropin deficiency (GD) and severe

constitutional delay (CD) of puberty (4). Unless GD is associated with anosmia, then called the Kallmann syndrome (KS)(2), it cannot readily be differentiated from CD during early and mid-adolescence by either clinical features or laboratory tests, including a LHRH bolus test (3). Moreover, none of these tests is able to differentiate between GD of pituitary and that of hypothalamic origin. We attempted, therefore, to devise a procedure imitating the physiologic changes in hypothalamic function occurring at puberty, with the aim to improve the differential diagnosis between GD and CD, and to track down the site of lesion and the severity of defect in GD.

PATIENTS and METHODS

The 18 hypogonadal male patients are listed in Table 1. In addition to GD, growth hormone deficiency was present in all HP patients. The 3 HH patients had neither olfactory nor additional pituitary deficiencies. There were no obvious differences in CA or in BA-retardation between the 4 groups. However, TVs were significantly higher in the CD boys.

		PATIENTS			
DIAGNOSIS		CA	BA	DIFF	T.V.
KALLMANN-SYNDROME (KS)	1.MG	15:6	14	-1:6	1/1
	2.HB	41	MAT		2/2
	3.MM	17:9	14	-3:9	3/4
	4.JS	17:8	14	-3:8	3/2
IDIOPATH. HYPOPIT. (HP)	1.DC	17:9	8:6	-9:3	2/1
	2.MC	17:11	11	-6:11	1/1
	3.HP	14:3	9	-5:3	1/1
	4.AB	14:3	11:6	-2:9	2/2
	5.HP	16:3	12:6	-3:9	2/2
	6.SW	20:1	14:6	-5:7	4/4
(HH)	1.CR	22:3	15:6	-6:9	4/4
	2.NM	14:6	12:6	-2	4/4
	3.FC	21:2	17:6	-3:8	1/1
CONSTIT. DELAY (CD)	1.JR	17	14	-3	8/8
	2.HL	18:4	14	-4.4	15/7
	3.US	15:4	12:6	-2:8	8/10
	4.RF	16:6	13	-3:6	10/10
	5.CP	20	15	-5	5/5

CA = CHRON AGE BA = BONE AGE T.V. = TESTIS VOLUME(ML)

Table 1

On the evening of the admission day, a flexible indwelling iv cannula was inserted and blood was sampled every 20 min during sleep for plasma LH and FSH determination. The next day, the patient was connected for 36 hrs to a portable micropump (Zyklomat®, Ferring GmbH, Kiel, Germany) delivering a LHRH pulse of 5 µg iv every 90 min. Blood was taken for LH and FSH exactly 30 min after each LHRH pulse. Plasma testosterone (T) and dehydroepiandrosteronesulfate (DHAS) were determined before and after the pulsatile stimulation period.

Analysis of results: A significant spontaneous LH peak was counted from the nocturnal plasma profile when a rise from nadir to peak within 40 min exceeded twice the corresponding intraassay coefficient of variation (19.5, 9.5 and 6.8 % for LH levels of about 2.5, 7.5 and 15.0 mIU/ml, respectively). The mean of all FSH levels during pulsatile LHRH was compared by t-test with that during the spontaneous nocturnal profile ("pump vs noct"). The pituitary response of FSH

during pulsatile LHRH was assessed by linear regression analysis.

RESULTS and DISCUSSION

Results of plasma gonadotropin changes are listed in Table 2. Significant spontaneous nocturnal LH pulses were observed only in the boys with constitutional delay (CD), but were absent in all 13 patients with GD. This corresponds to the higher testicular volumes (TV) found in the CD group. Whereas spontaneous nocturnal FSH pulses were absent in all 18 patients, mean FSH levels during pulsatile LHRH were significantly increased ("pump vs noct"), indicating that responding pituitary tissue was present in each case, and even in the HP patients. During the 36 hrs of pulsatile LHRH, there was a highly significant rise of the plasma FSH response in all our KS and also in all our HP patients. Such a response could not be seen in the HH and in 3 of the 5 CD patients. These findings indicate rapid maturation of pituitary FSH production in all our Kallmann and hypopituitary patients, whereas this maturational response seems to be slower in severe HH (5) and of variable speed in CD. During the same period, LH responses did not change significantly, suggesting a slower maturation of pituitary LH than FSH production (5).

PLASMA GONADOTROPIN DYNAMICS

		SPONT NOCT LH-PEAKS (N)	FSH-INCREASE "PUMP VS NOCT"	RISE OF FSH-RESPONSE DURING PULSATILE GnRH (36 HRS)		T.V. (ML)
KS	1. MG	0	+*	R = 0.826	P < 0.001	1/1
	2. HB	0	+	0.663	< 0.001	2/2
	3. MM	0	+	0.886	< 0.001	3/4
	4. JS	0	+	0.831	< 0.001	3/2
HP	1. DC	0	+	R = 0.825	P < 0.001	2/1
	2. MC	0	+	0.840	0.001	1/1
	3. HP	0	+	0.862	0.001	1/1
	4. AB	0	+	0.947	0.001	2/2
	5. HP	0	+	0.887	0.001	2/2
	6. SW	0	+	0.821	0.001	4/4
HH	1. KR	0	+	R = 0.232	N.S.	4/4
	2. NM	0	+	-0.354	N.S.	4/4
	3. FC	0	+	0.245	N.S.	1/1
CD	1. JR	2	+	R = 0.326	N.S.	8/8
	2. HL	2	+	0.760	P < 0.001	15/7
	3. US	2	+	0.321	N.S.	8/10
	4. RF	1	+	-0.454	N.S.	10/10
	5. CP	4	+	0.697	P < 0.001	5/5

* SIGNIFICANTLY HIGHER ($P < 0.05$) MEAN FSH DURING PULSATILE GnRH THAN DURING SPONT. NOCTURNAL PROFILE

Table 2

Plasma androgen results are given in Table 3. While testosterone levels did not increase significantly in the 13 patients with permanent GD during the 36 hrs of pulsatile LHRH, they rose markedly (mean, from 168 to 414 ng/dl) in the 5 boys with CD who all had pubertal testes (Table 2). DHAS levels did not change during pulsatile LHRH, but were

PLASMA ANDROGENS

		TESTO (NG/DL)	$\bar{x}$	DHA-S (NG/ML)	$\bar{x}$
KS	1.MG	17-15	20 → 28	1700	1967
	2.HB	31-27		3520	
	3.MM	21-55		2105	
	4.JS	9-16		545	
HP	1.DC	2-2	3 → 4	35	78
	2.MC	2-4		12.5	
	3.HP	2-2		12.6	
	4.AB	2-2		103	
	5.HP	5-6		220	
	6.SW	6-10		86	
HH	1.KR	21-18	48 → 68	1580	1970
	2.NM	21-90		573	
	3.FC	102-98		3755	
CD	1.JR	67-220	168 → 414	2700	1480
	2.HL	95-155		2100	
	3.US	143-689		1165	
	4.RF	389-648		480	
	5.CP	149-360		960	

Table 3

elevated in the KS and HH patients, whereas in the hypopituitary group they were decreased even in relation to bone age (Table 1), as evidence of their lacking adrenarche. DHAS levels in the CD group were appropriate for bone age.

On the basis of these various findings, we would like to propose an improved differential diagnostic scheme of male central hypogonadism (Table 4).

	Spont noct LH-peaks	Significant FSH-increase "pump vs noct"	Significant rise of FSH-response during puls. GnRH (36 hrs)	DHAS for BA	Testo for BA
Isolated hypothalamic GnRH defic. (KS)	0	+	+	↑	↓
Idiopathic hypo-pituitarism (HP)	0	+	+	↓	↓↓
Hypogonado-tropic hypo-gonadism (HH)	0	+	0	↑	↓
Constitutio-nal delay of puberty (CD)	+	+	0	NL	NL

Table 4

CD patients (bottom line) can be differentiated from the three other groups with permanent gonadotropin deficiency both by the presence of significant spontaneous nocturnal LH pulses and by normal plasma testosterone and DHAS relative to bone age. Since the primary lesion in all three hypogonadotropic groups (KS, HP and HH) has been shown to be hypothalamic, the pituitary can respond to even short-term pulsatile LHRH stimulation by a significantly increased FSH production. Pituitary FSH maturation seems at least in our small series to be slightly slower in hypogonadotropic patients without anosmia and in constitutionally delayed puberty. KS and HH patients are further characterised by their elevated adrenal androgen (DHAS) levels in relation to bone age (1).

The most striking observation of these still preliminary studies, however, is the finding that even in classic idiopathic hypopituitarism (HP) the primary site of the lesion is the hypothalamus. This means that HP patients, too, may have the possibility to reach fertility by means of an appropriate substitution therapy using pulsatile LHRH administration.

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