Gonadotrophin release in untreated congenital virilising adrenal hyperplasia

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SUMMARY A 9·9-year-old boy and a 9·8-year-old girl with virilising congenital adrenal hyperplasia were subjected to an IV LH-RH (luteinising hormone-releasing hormone) test ($50 \mu\text{g}/\text{m}^2$) before initiation of therapy with corticosteroids. The pattern of response of LH and follicle-stimulating hormone to LH-RH was found to correspond to the stage of their precocious sexual development and advanced bone age, but not to their chronological age. This finding has implications with regard to the mechanism controlling gonadotrophin secretion at puberty.

The regulation of gonadotrophin secretion in untreated patients with congenital adrenal hyperplasia (CAH) has been a matter of controversy. Stevens and Goldzieher (1968) measuring urinary gonadotrophins found raised luteinising hormone (LH) and follicle-stimulating hormone (FSH) in untreated subjects with CAH. Klingensmith *et al.* (1976), in contrast, found that the development of normal puberty is suppressed until initiation of therapy. Recently the clinical use of luteinising hormone-releasing hormone (LH-RH) has made possible a re-evaluation of this problem (Reiter *et al.*, 1975; Wentz, *et al.*, 1976). We report 2 children with virilising CAH of prepubertal age but with advanced pubertal signs in whom LH-RH tests were performed before initiation of therapy.

Subjects and methods

Case 1. A boy was referred at the age of 9·9 years because of sexual precocity. The parents are distant cousins and new immigrants from the USSR. Another sibling, raised as a boy, at the age of 25 years was found to be suffering from CAH and genetically to be a female. The patient had full sexual development, appearing to be a mature but short young man, pubertal sign P5 according to Tanner (1962). The clinical data are given in Table 1.

Case 2. A girl was referred at the age of 9·8 years because of an enlarged clitoris known to be present

since birth. The parents are not related and her brother and sister are normally developed. A paternal aunt was reported to be very hirsute, and unmarried. Clinical examination showed a tall girl with pubertal signs corresponding to P2-3 (Tanner, 1962) (Table 1).

In both patients laboratory investigation proved the diagnosis of CAH due to 21-hydroxylase deficiency of the nonsalt-losing type (Table 2). It is notable that in the boy (Case 1) the plasma testosterone was only partially suppressed by dexamethasone, indicating that most of the testosterone was produced by his prematurely developed testicles.

Plasma LH and FSH were measured by radioimmunoassay before and in response to IV administration of LH-RH, $50 \mu\text{g}/\text{m}^2$, in a single bolus injection. The results were rated from P1 (prepubertal) to P5 (fully mature) according to the standards obtained by Dickerman *et al.* (1976) for normal boys and girls. Before referral and investigation neither of the patients had been treated.

Table 1 *Clinical data of 2 children with CAH*

Case no.	Sex	CA (years)	BA (years)	Height (cm)	Pubertal rating*	
					G/B	PH
1	Male	9·9	17	150	5 (TV 15 ml)	5
2	Female	9·8	11	147	2	3

CA = chronological age; BA = bone age.

*According to Tanner (1962): G/B = genital or breast; PH = pubic hair; TV = testicular volume.

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Table 2 Laboratory findings in 2 children with CAH

Case no.	Urine				Plasma							
	17 ketosteroids (mg/24h)		Pregnanetriol (mg/24h)		ACTH (pg/ml)		Progesterone (ng/ml)		Oestradiol (pg/ml)		Testosterone (ng/100 ml)	
	Basal	Dex	Basal	Dex	Basal	Dex	Basal	Dex	Basal	Dex	Basal	Dex
1	21.7	4.5	30.0	3.0	140	16	3.7	0.1	25	19	350	230
2	9.0	2.0	7.1	0.3	300	45	13.5	0.16	78	29	97	16

Dex=Dexamethasone suppression, administration of dexamethasone orally, 1 mg (Case 1), 0.5 mg (Case 2), every 6 hours for 3 days.

Conversion: Traditional units to SI—17-ketosteroids: 1 mg/24 h $\approx$ 3.47 μ mol/24 h. Pregnanetriol: 1 mg/24 h $\approx$ 2.97 μ mol/24 h. Progesterone: 1 ng/ml $\approx$ 3.178 nmol/l. Oestradiol: 1 pg/ml $\approx$ 3.671 pmol/l. Testosterone: 1 ng/100 ml $\approx$ 34.67 nmol/l.

Table 3 Gonadotrophin response to IV LH-RH 50 μ g/m² in 2 children with CAH

Case no.	Plasma LH (mIU/ml)						Plasma FSH (mIU/ml)					
	Minutes						Minutes					
	0	15	30	45	60	90	0	15	30	45	60	90
1	1.5	7.5	11.8	11.8	14.2	6.4	3.8	6.9	7.4	12.1	10.1	6.5
2	1.2	4.7	5.9	4.7	4.6	3.6	2.1	3.6	4.4	4.2	5.4	4.4

Results

The basal plasma LH and FSH levels (Table 3) were higher in our 2 patients than in normal children of the same age: prepubertal male (mean $\pm$ SD) LH 0.54 ± 0.1 , FSH 0.6 ± 0.2 ; prepubertal female LH 0.43 ± 0.12 , FSH 0.6 ± 0.3 (Dickerman *et al.*, 1976). The peak response to LH-RH (Table 3) was also greater than that expected in children of prepubertal age, which in our clinic is: male LH 1.3 ± 0.17 , FSH 1.5 ± 0.5 ; female LH 3.03 ± 0.34 , FSH 2.1 ± 0.9 (Dickerman *et al.*, 1976). In the boy (Case 1) the response of LH and FSH corresponded to P5 (full maturity) and in the girl (Case 2) to P3, i.e. corresponding to their clinical pubertal stage and bone age (Table 4) but markedly advanced for their chronological age.

Discussion

The increased secretion of adrenal androgens which starts *in utero* in congenital adrenal hyperplasia

(CAH) raises some questions as to their possible influence on subsequent development, both clinical and psychological (Laron *et al.*, 1974). How do the sex hormones influence the normal function of the hypothalamo-pituitary-gonadal (H-P-G) axis, and how can the oversecretion of gonadotrophins be related to the basic overproduction of adrenal sex hormones? Reiter *et al.* (1975) showed that the regulation of the H-P-G axis was preserved '... both in the maturity-related LH release and in the sex dichotomy of the FSH release evoked by LH-RH'. Other reports, however, provide evidence that in patients with untreated or poorly controlled CAH, gonadotrophin secretion was suppressed (Klingensmith *et al.*, 1976; Wentz *et al.*, 1976) and the H-P-G axis disrupted (Kirkland *et al.*, 1974) by the raised adrenal sex hormones. It has also been reported that in patients treated with suboptimal doses of corticosteroids, treatment with optimal doses which adequately suppressed the abnormally raised sex hormones led to the onset of precocious puberty and menstruation (Penny *et al.*, 1973; Klingensmith *et al.*, 1976).

Our studies in 2 patients of prepubertal age with untreated CAH show that the levels of both basal and readily-releasable pituitary LH and FSH are raised for their chronological age, corresponding to the respective stage of sexual precocity and advanced bone age. These findings are similar to those reported by Stevens and Goldzieher (1968), who measured urinary gonadotrophins, and in contrast to the usual finding of delayed normal pubertal process found in children with CAH (Klingensmith *et al.*, 1976).

Table 4 Correlation between pubertal ratings determined according to the clinical signs and gonadotrophin secretion

Case no.	CA (years)	BA (years)	Pubertal rating			
			Clinical*		Laboratory†	
			G/B	PH	LH	FSH
1	9.9	17	5	5	5	5
2	9.8	11	2	3	3	3

*Tanner (1962). †Dickerman *et al.* (1976).

The relative hypersecretion of gonadotrophins in untreated CAH could be explained either by an overlap mechanism induced by the hypersecretion of ACTH, similar to that encountered in primary hypothyroidism and precocious puberty (Laron *et al.*, 1970), or by a direct effect of the sex hormones on the hypothalamus or pituitary. Reiter *et al.* (1975) raised the possibility that chronologically raised levels of adrenal sex hormones induce precocious maturation of the hypothalamus by lowering its sensitivity to the negative feedback of the sex steroids. This suggestion is reinforced by the acceleration of central precocious puberty observed after initiation of corticosteroid therapy in young children with CAH and advanced bone age (Penny *et al.*, 1973; Reiter *et al.*, 1975).

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