Pubertal growth in patients with androgen insensitivity: Indirect evidence for the importance of estrogens in pubertal growth of girls

Spontaneous pubertal growth was studied in eight patients with the syndrome of androgen insensitivity to obtain information on the growth-promoting action of estrogens. In one additional patient (who had a gonadectomy before puberty), the effect of exogenous estrogens was studied. Mean age at peak height velocity (12.7 years) was closer to that in normal girls than to that in normal boys. Mean peak height velocity (7.4 cm/yr) was as in normal girls (7.3 cm/yr), but was lower than in normal boys (9.3 cm/yr). Bone age corresponded better to male standards. Mean adult height (172.3 cm) was lower than in normal men (−0.6 SD), but higher than in normal women (+1.4 SD). In the patient who had a gonadectomy, estrogen replacement caused a higher peak height velocity (12 cm/yr), but lower adult height (160.5 cm) than in the patients with intact gonads who received no treatments. We conclude that in normal girls, the pubertal growth spurt also results from the action of estrogens rather than of adrenal androgens. To ensure normal pubertal growth, physiologic estrogen replacement in hypogonadal females should be started at a bone age of about 11 years, and should not be delayed in the hope of achieving a greater mature height. (J PEDIATR 1986;108(1):694-697)

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Patients with the syndrome of androgen insensitivity (testicular feminization, peripheral resistance to the action of normally produced androgens) are known to be tall as adults,[1,2] but little knowledge exists concerning the timing and magnitude of their pubertal growth spurt. We present pubertal growth data of eight patients with AI who received no treatment, and of one patient who had a gonadectomy and estrogen treatment. Because it is likely that the androgen receptor, which is defective in sexual tissues of patients with AI, is necessary also for the growth-promoting effects of androgens on bone, the syn-

AI	Androgen insensitivity
FSH	Follicle-stimulating hormone
hCG	Human chorionic gonadotropin
LH	Luteinizing hormone
LHRH	Luteinizing hormone releasing hormone
PHV	Peak height velocity

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Table. Measurements at last examination and clinical remarks in nine patients with androgen insensitivity

Patient	CA (yr)	Height			Weight			Remarks
		cm	SDSm	SDSf	kg	SDSm	SDSf	
1	17.2	169.4	−1.0	+0.8	67	+0.5	+1.4	Gonadectomy after puberty
2	17.4	178.7	+0.3	+2.4	69	+0.6	+1.6	Late diagnosis
3	19.2	169.4	−1.2	+0.8	58	−0.9	+0.2	Gonadectomy after puberty
4	15.0	162.8	−0.9	+0.1	55	+0.1	+0.3	Twin
5	17.3	176.5	+0.1	+2.1	78	+1.6	+2.7	Hypofibrinogenemia
6	15.7	169.6	−0.5	+1.0	57	−0.2	+0.4	Treatment with high doses of estrogens for tall stature after 14.6 years; gonadectomy after puberty
7	18.2	170.1	−1.1	+1.0	59	−0.7	+0.4	
8	15.0	164.3	−0.7	+0.3	54	−0.1	+0.2	Twin
9	17.3	160.5	−2.4	−0.7	47	−1.9	−1.1	Gonadectomy at age 3 years; treatment with estrogens in puberty

CA, Chronologic age; SDS, standard deviation score, m for male standards, f for female standards.

drome provides a model to study the effects of estrogens on pubertal growth in general.

METHODS

Nine patients with "complete" AI, whose growth data were sufficient to evaluate the pubertal spurt, were observed (Table). In all of them, there were female external genitalia and completely absent or extremely scant pubic hair, and a buccal smear was chromatin negative. In three patients, the diagnosis was made in early childhood because of the presence of inguinal hernias. Diagnosis was made in two others before puberty because of an affected sister. In the remaining four patients, evaluation was carried out because of absence of pubic hair and primary amenorrhea, but previous growth data were available. Patients 1 and 9, and patients 4 and 8 are sisters (patients 4 and 8 are monozygous twins). Patients 3 and 5 each have an affected sister, who is not included in the present study because of insufficient data.

Spontaneous pubertal growth was followed in eight patients: in one (patient 9), the effect of exogenous estrogens after gonadectomy was studied. Patient 6 was given high doses of estrogens for tall stature before gonadectomy, but only after most of the spontaneous pubertal growth spurt had been completed. Because the patients were selected on the basis of the availability of sufficient growth data, and because the study was mostly retrospective, laboratory data are incomplete, but are in accordance with the diagnosis of classic AI: The serum gonadotropin values before and after stimulation with LHRH were normal or high before puberty, and high during puberty[3]; FSH values tended to be higher than those for LH[4]; serum testosterone concentrations corresponded to normal or high values for normal males,[5] and responded normally to hCG[6]; the estrogen values in plasma were normal or high for males, and the adrenal androgen values were normal. In three patients, the urinary 15N-nitrogen balance, studied during prepuberty, did not change after administration of testosterone,[7] demonstrating a lack of metabolic effect of testosterone. Standard deviation scores were calculated as previously described,[8] and the normal values from the Zurich longitudinal growth study were used.[9] Generally, only height and weight were available from the retrospective data; sitting height measurements had been made in three patients only. Bone age[10] was rated separately, with male and female standards.

RESULTS

Pubertal growth spurt. In all eight patients with intact gonads who had no treatment; a marked increment of height velocity occurred at a pubertal chronologic age (Figure), as would be expected in normal girls. The mean PHV was 7.4 cm/yr (SD not indicated because of skewed distribution) and occurred at a mean chronologic age of 12.7 years. Magnitude and timing of PHV thus resembled those of normal girls (7.3 cm/yr, chronologic age 12.4 years) rather than those of normal boys (9.3 cm/yr, chronologic age 13.9 years[9]). In the patient who had a gonadectomy, estrogen treatment (Premarin; Ayerst Laboratories, New York) was started at the earliest chronologic age appropriate for female puberty (10.3 years), at a dosage of 0.625 mg three times a week. The PHV in this patient was higher than the spontaneous velocities in the other patients, and possibly bone maturation was also

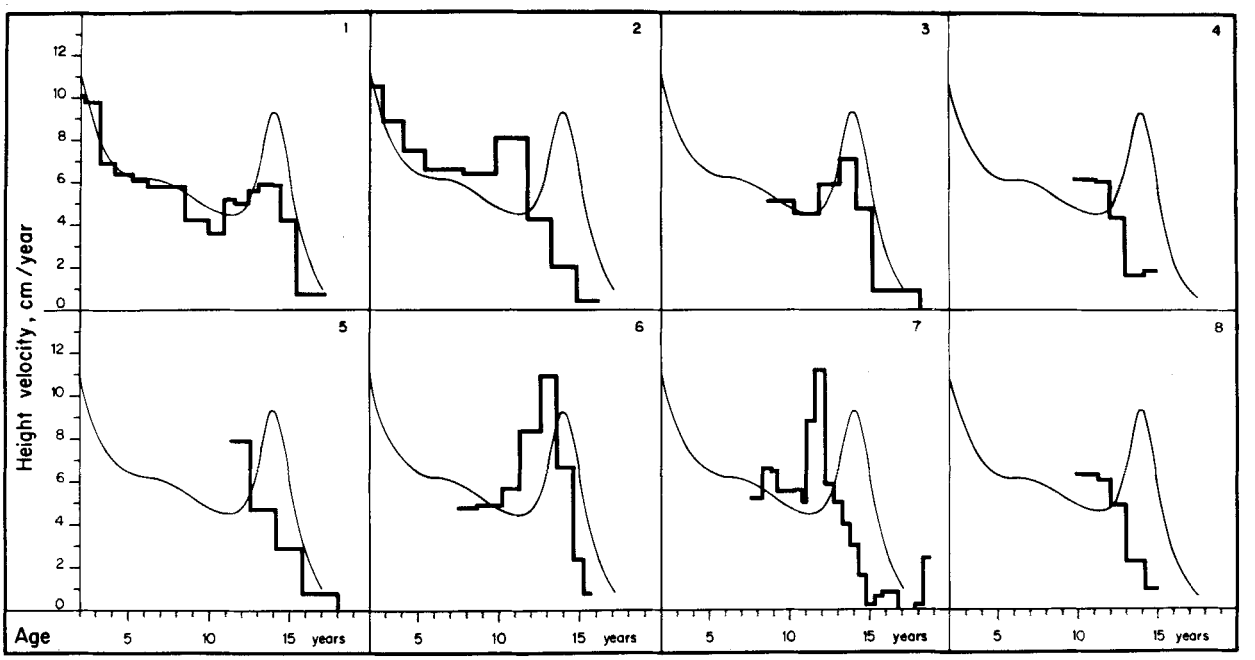

Fig. 1. Growth velocity curves in eight patients with androgen insensitivity. *Thin line,* Normal median value of boys from Zurich longitudinal growth study.[9]

somewhat faster. This may explain why this patient is shorter as an adult than the other patients; the estrogen dose was probably too high for early puberty. Although the doses of ethinyl estradiol and of conjugated estrogens are difficult to compare, the potency of the Premarin dose seems to be higher than the daily dose of, for example, 0.005 to 0.01 mg ethinyl estradiol, which at present is thought to be sufficient for physiologic replacement during early puberty.

Adult height. The mean adult height of five patients who could be evaluated for this measurement was 172 ± 4.1 cm, which corresponds to +1.4 ± 0.8 SD for women, and −0.6 ± 0.7 SD for men.

Bone maturation. Repeated radiographs of the hand and wrist were available in four patients; 23 radiographs could be evaluated. The bone age values obtained corresponded better to the standards of boys than to the standards of girls. Thus bone age in our patients with AI was slightly advanced for boys, and slightly retarded for girls.

DISCUSSION

Our results indicate that, in patients with androgen insensitivity, (1) a spontaneous pubertal growth spurt takes place; (2) the spurt is quantitatively equal to that in normal girls; (3) it occurs at an appropriate chronologic age for girls, but early for boys, and (4) bone maturation corresponds better to chronologic age when the standards of boys rather than those of girls are used.

These observations are not only of interest for the natural history of AI, but appear to be of more general importance for the understanding of the mechanisms involved in pubertal growth of normal girls, and for the selection of appropriate time and dosage of estrogen replacement in hypogonadal females. Because in the classic, complete form of AI with female external genitalia, to which all our patients belong, the patients have complete resistance to the action not only of testosterone, but also of other androgens,[11] the syndrome provides an unique model for the study of the effects of estrogens on pubertal growth.

The normal male pubertal spurt can be quite satisfactorily explained by the combined action of testosterone and growth hormone,[12,13] but the mechanisms involved in the female spurt are incompletely understood. Estrogens have formerly been considered to be of minor importance, and more influence has been attributed to adrenal androgens. However, more recent observations in girls with Turner syndrome who were given estrogen,[14,15] in other conditions[16] and in our patients suggest that adrenal and gonadal androgens are not required for a normal female growth spurt. Because the spurt in our patients was quantitatively equal to that in normal girls, our results rather suggest that estrogens alone are sufficient. That estrogens and not some other factors are actually causing the growth spurt in patients with AI is also suggested by the response to exogenous estrogens of the patient who had a gonadecto-

my. Experience from other patients with AI shows that plasma estrogen concentrations tend to be lower than in normal girls of the same age; it is therefore somewhat surprising that the growth rate in these patients is equal to that in normal girls. In this respect, the absence of androgen activity at the receptor site may play a role; not only the quantity of secreted estrogens, but also the ratio between active androgens and estrogens seem to be of importance for the estrogen effects. This conclusion is also suggested by the fact that patients with AI have well-developed breasts, whereas females with congenital adrenal hyperplasia (21-hydroxylase deficiency) who have had no treatment have minimal or no breast development in the presence of even larger quantities of estrogens. A high sensitivity to very low quantities of estrogens is also indicated by the observation of spontaneous breast development in patients with AI who have had gonadectomies.[17,18] It thus is likely that patients with AI are more sensitive to the action of estrogens, possibly because of the androgen insensitivity. Normal girls seem to need more estrogens in the presence of active adrenal androgens to reach the same breast development stage and PHV.

Our observations support the view that estrogens are the most important cause of the pubertal growth spurt, not only in patients with AI, but also in normal girls. Another conclusion, which also has been derived from patients with Turner syndrome,[19] is that to ensure normal pubertal growth, physiologic estrogen replacement in hypogonadal females should be started at the appropriate bone age of about 11 years, and should not be delayed in the hope of achieving a greater mature height.

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