

## 183 ETIOLOGY OF DELAYED PUBERTY IN 137 CHILDREN EVALUATED OVER A 9.5 YEAR PERIOD. Patricia L. Krausz, Cheryl E. Hanna, Stephen H. LaFranchi, Oregon Health Sciences University, Department of Pediatrics, Portland, Oregon, USA.

To determine causes of delayed puberty in a referral population, we analyzed 137 children seen between 1975-84. Pubertal delay was defined in males as testicular volume <2cc beyond age 14 and in females as lack of breast development by age 13 or failure of menarche by age 15 years. Common complaints at clinical presentation included short stature or decreased growth in 82%, delayed puberty in 35%, amenorrhea in 28% of females, signs of intracranial tumor in 3.6%, and evidence of chronic disease in 12%. We obtained height, weight, growth rate, body proportions, parental heights, family history of delay, and Tanner staging. When indicated we measured thyroid function, bone age, gonadotropin and sex hormone levels, growth hormone responses and performed chromosome analysis, skull X-ray or CT scan. 65 patients had a final diagnosis of constitutional pubertal delay; 40% of these had a family history of delay. 46 children had delayed puberty secondary to hypothalamic-pituitary dysfunction. Of 24 who were idiopathic, 7 had isolated gonadotropin deficiency and 17 had other pituitary abnormalities. Six others had congenital anomalies such as septo-optic dysplasia or Kallman's syndrome. The remaining 16 patients had tumors in the pituitary region, of which 7 were craniopharyngiomas. Eleven children had primary gonadal failure with 6 having Turner's syndrome. Two girls with amenorrhea presented with genital tract anatomic anomalies. The last 13 patients had delayed puberty secondary to associated medical problems or chronic disease. Delayed puberty appears most often to be due to constitutional delay, associated with a positive family history, and to idiopathic involvement of the hypothalamic-pituitary axis.

## METOCLOPRAMIDE TEST DIFFERENTIATES HYPOGONADOTROPIC HYPOGONADISM FROM DELAYED PUBERTY

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To evaluate whether metoclopramide-releasable prolactin response had diagnostic values in the differentiation between hypogonadotropic hypogonadism (HH) and constitutional delay of puberty (D) the serum responses of prolactin, LH and FSH to metoclopramide-GnRH were studied in 9 boys with HH, 7 boys with D and 15 controls. Metoclopramide increased prolactin levels in all groups (Table).

Table. Basal and maximal prolactin levels (mIU/l).

	Basal x̄ (range)	Maximal x̄ (range)
Controls	199 (128-572)	3304 (2166-4641)
Delay	243 (186-361)	3308 (2676-4514)
HH	239 (129-391)	1440 (840-2107)

In the boys with HH, the maximal serum levels of prolactin were completely separate from the levels of the controls. Nevertheless, the maximal levels of prolactin were subnormal (=below the 90% confidence ranges of the controls) in 8/9 boys with HH. All the boys with D had normal maximal levels of prolactin. The maximal levels of LH were subnormal in only 3/9 boys and those of FSH in 0/9 boys with HH. Metoclopramide test appears to be effective in further improving the differentiation of HH and D.

A search for the lowest dose of oxandrolone which is effective for the treatment of constitutional delay of growth and puberty in boys.

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24 boys, mean age 14.8 yrs, with a delayed pubertal growth spurt were treated with oxandrolone 2.5 mg daily for a mean of 0.3 yr (range 0.21 to 0.65 yr). Mean increment of growth velocity, compared with pretreatment values, was 4.4 cm/yr during the treatment period and 3.7 cm/yr following cessation of treatment. This effect was not due to a spontaneous growth acceleration as mean testicular volume at the start of treatment was 8.4 ml and 9.3 ml at the end of treatment. There was no significant change in height for bone age SDS and no side effects. All patients had normal pubertal progression during and after treatment.

Following this experience we have used an even lower dose of oxandrolone, 1.25 mg daily, for a mean period of 0.26 yr (range 0.22 - 0.38 yr) with an additional 15 boys, mean age 14.7 yr, with similar results. Although we have still not yet defined the minimum dose, 1.25 mg daily for 3 months is safe, effective and much less than has previously been recommended.

We have investigated the mode of action of oxandrolone using 24 hour serum profiles of GH, gonadotrophins and testosterone.

## 186 TREATMENT OF PRECOCIOUS PUBERTY (PP) WITH A MONTHLY INJECTION OF D-Trp<sup>6</sup> LHRH ANALOG (A).

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Nine children with PP (2 boys and 7 girls) have been treated with D-Trp<sup>6</sup> LHRH microcapsules (3mg), given once per month, for a period of 6-12 months. Two of them had congenital adrenal hyperplasia, one had hypopituitary dwarfism with early pubertal development and 6 had idiopathic PP. In all, clinical improvement (decreasing breast size down to fullness from adiposity, or decreasing testicular volume) became evident within two months of treatment. The changes in LH values (basal, during sleep and post IV LHRH), prior to, and 3-5 months of treatment with A, are given below (mean±SEM): mIU/ml

	Mean	Peak	Basal	Mean	Peak	p
Before A	9.2±1.8	13.2±3.4	4.1±0.6	23.7±5	26±6	<0.02
During A	4.4±0.8	5.9±0.9	3.6±0.3	4.8±1	5.7±1.1	N.S.
p :	N.S.	N.S.	N.S.	<0.02	<0.05	

The mean estradiol value (pg/ml) was 35±1.1 before, and 21±5.3 during A (p<0.05). The mean testosterone value (µg/dl) was 257±20 before and 23±5 during A (p<0.001). It is concluded that the A used in this study is effective in inhibiting puberty in boys and girls. It was very well accepted and there were no evident side effects except for temporary local pain. The length of treatment in our subjects does not allow a prediction of the effect on final height, but the clinical and hormonal data in hands are favorable.

## 187 INTRANASAL TREATMENT OF PRECOCIOUS PUBERTY (PP) WITH A LONG-ACTING LH-RH-ANALOGUE.

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5 girls with true PP (4-8 years), demonstrating clinical signs of puberty, accelerated growth velocity, advanced bone age and pubertal LH/FSH levels of gonadotrophins, were treated with an intranasal spray of the LH-RH-analogue D-Ser (TBU)<sup>6</sup>-LH-RH-EA (Buserelin (B)) for 6 to 9 months. Therapy was started with 8x300 µg B/day intranasally (150 µg per puff into each nostril) for 2 weeks, followed by a maintenance dose of 3x300 µg/day. When spontaneous LH/FSH-secretion during the night (20 min. sampling intervals from 0 to 4 a.m.) before and 7 days after beginning of the treatment was compared, 2 girls showed a slight rise of median LH values (3.5 to 6.5 mIU/ml) and to others a decrease (18 to 9 mIU/ml). Only one had 2 spontaneous bursts of secretion that did not occur on B-therapy one week later. Whereas measurements of LH/FSH, E<sub>2</sub> and testosterone after 1, 3, 6 and 9 months of B-treatment suggested continued suppression of the pituitary-gonadal axis, adrenal steroids (DHEA-S) did not change. Clinical signs of puberty were diminished or arrested, including the acceleration of skeletal maturation. Clinical or endocrinological escape phenomena were not observed. Intranasal application of B, therefore, compares favorably to other form of PP-therapy.

## LH RESPONSES TO NALOXONE IN NORMAL PRECOCIOUS AND DELAYED PUBERTY.

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Opioid peptides exert a tonic inhibitory effect on LH secretion, acting at the hypothalamic level in modulating LHRH release. Naloxone, an opiate receptor antagonist, has been used to evaluate the activity of such tonus. Previous data have demonstrated Naloxone inefficacy on circulating LH in prepubertal children. The present study refers the effects of Naloxone (0.08 mg/kg B.W., i.v.) and LH-RH (50 mcg i.v.) in healthy subjects subdivided according to pubertal development, in 5 precocious and in 7 delayed puberty. In the normal controls and in precocious puberty patients, while LH-RH induced a significant rise of LH levels correlated to the pubertal stages, Naloxone induced an LH increase only after P<sub>3</sub> stage (P<0.01). In the group of delayed puberty LH-RH stimulation increased LH levels in all subjects and, on the contrary, Naloxone was unable to modify circulating LH levels in all subjects. These data may suggest that the function of opiate neurons involved in the inhibitory control of LH secretion become active at the more advanced stages of puberty, independently from the age of the subjects or from the age of the onset of puberty. This assumption corroborate the concept that gonadal steroids play a fundamental role in modulating the tonus of central opioid system and support the hypothesis that the opioid system is involved in the neuroendocrine events of pubertal maturation.