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THE RELATION BETWEEN BIOACTIVE AND IMMUNOACTIVE LH DURING PUBERTY. EJ Schroor, MM van Weissenbruch, HA Delemarre-van de Waal. Department of Pediatrics, Free University Hospital, Amsterdam, the Netherlands.

During puberty an increase in LH secretion, as measured by RIA, is observed. Other studies have reported an increasing ratio of bioactivity over immunoactivity of LH during puberty. In order to study the relationship between in-vitro biological (bLH) and immunological (iLH) LH secretion during normal pubertal development, bLH and iLH was measured in 62 normal children (31 boys, 31 girls) in different stages of puberty. Plasma samples were derived at 1 hour intervals during 3 hours daytime and 3 hours nighttime. BLH was measured by the Mouse Leydig Cell Assay (MLCA) and ILH was measured by IRMA. **Results:** Boys: mean bLH and mean iLH significantly increased during puberty, with a maximum at G4 (G1: day + night bLH <0.3 U/l and day + night iLH <0.3 U/l; G4: day bLH 1.36 U/l sd 0.63, night 3.57 U/l sd 1.43; day iLH 1.14 U/l sd 0.62, night 4.33 U/l sd 1.29; Kruskal-Wallis oneway anova,p<0.01). A correlation is found between bLH and iLH, in all samples studied during daytime and nighttime (R=0.85, p<0.01). At daytime, the ratio of the in-vitro bioactivity and the immunoactivity (B/I ratio) is 1.3 sd 0.2 in stages G2-G4, significantly higher compared to B/I 0.7 sd 0.2 in G5 (K-W oneway anova,p<0.05). During night B/I ratio is <1 and does not differ in all stages. Girls: for both bLH and iLH a significant increase during puberty is seen, with a maximum at M4 (M1: day+night bLH, day + night iLH <0.3 U/l; M4: day bLH 1.87 U/l sd 1.03, night 2.63 U/l sd 1.29; day iLH 2.45 U/l sd 1.73, night 5.03 U/l sd 2.37; K-W oneway ANOVA, p<0.01). BLH significantly correlates with iLH (R=0.87, p<0.01). In contrast to boys, no significant changes in B/I ratio are detected in girls during puberty. **In conclusion:** during normal puberty, the changing LH in-vitro bioactivity significantly correlates with iLH. In girls the LH B/I ratio does not change. In boys an increased B/I ratio is found in stages G2-G4 during the day, which may be due to the low daytime testosterone levels, associated with the day-night rhythm.

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PATIENTS WITH CONSTITUTIONAL DELAY OF GROWTH AND PUBERTY (CDGP) DO NOT EXHIBIT AN ABNORMAL PATTERN OF GROWTH HORMONE (GH) SECRETION, INDEPENDENT OF THEIR GROWTH VELOCITY (GV). J. Pozo*, J. Argente, V. Barrios*, S. González-Parra*, M.T. Muñoz*, M. Hernández*. Autonomous University. The Hospital of Niño Jesús. Division of Growth, Endocrinology & Metabolism, 28009 Madrid, Spain.

Children with CDGP exhibit a characteristic pattern of growth during their infancy and childhood. Some of these patients show a severe deceleration of growth velocity before puberty. Although some authors have suggested that a transitory GH deficiency secretory pattern can be observed at that moment, there is not a universal agreement in this matter. To test the hypothesis of whether or not a diminution in GH secretion strikes before puberty in children with CDGP, we studied the spontaneous GH secretory profile by measuring GH plasma levels at 30 minute intervals for 24 hr in 107 prepubertal children (Tanner I stage); 37 children were controls (24 boys and 13 girls) and 70 were patients with CDGP (44 boys and 26 girls). The group of patients with CDGP was divided into two subgroups: 1) Children with diminished growth velocity (DGV) (n=20; 12 boys and 8 girls) and 2) Patients with normal growth velocity (NGV) (n=50; 32 boys and 18 girls). GH values were subjected to a Cluster® analysis program to simultaneously estimate endogenous secretion of GH, frequency and amplitude of GH bursts in 24 hr. No significant differences were found among the different groups of subjects (ANOVA®) regarding the mean levels of GH in 24 hr (MGH), the number of secretory bursts (NB), the height of the maximum peak (MP), the pulsatile area of GH secretion (PA) or in the total area of GH secretion (TA). In addition, the frequency of MGH < 3 ng/ml was similar in all experimental groups (λ^2) (Table).

	MGH* (ng/ml)	NB*	MP* (ng/ml)	PA* (ng/ml)x min	TA* (ng/ml)x min	MGH< 3 ng/ml (%)
NGV (n=50)	3,7±1,1	6±1,1	20,8±8,6	3448±1280	3751±1282	28
DGV (n=20)	3,6±1,5	6±1,5	22,8±12,2	3323±1857	3633±1876	40
Control (n=37)	3,5±1,3	6±1,3	21,4±9,2	3206±1385	3505±1430	43,2

* Mean ± SD

Conclusion: Patients in the prepubertal period of life with CDGP exhibit a spontaneous GH secretion that is quantitatively similar to normal children in the same period of life. Hence, we postulate that the decrease of growth velocity that some patients with CDGP show is not due to a transitory GH deficiency.

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PROSPECTIVE RANDOMISED STUDY OF THE EFFECTS OF TREATMENT WITH EITHER LOW DOSE OXANDROLONE OR TESTOSTERONE OR PLACEBO ON THE PITUITARY-TESTICULAR AXIS IN BOYS WITH CDGP.

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16 boys with CDGP in early puberty (mean(S.D)age 14.2(0.7) years, bone age 11.1(0.9) years, testicular volume 4-6 mls) were randomly assigned to treatment for 3 months with placebo (group 1, n=5), oxandrolone 2.5 mg daily (group 2, n=5) or testosterone 4 weekly 50 mg im injection (group 3, n=6). Assessments were at 0, 3, 6 and 12 months and consisted of pubertal development, and 12 hour overnight hormone profiles with 15 minute samples. LH was assayed using a highly sensitive IRMA (Maiaclone, Serono), each profile in one assay. Testosterone was measured following ether extraction, and inhibin by RIA. LH profiles were analysed using a peak detection programme (Pulsar), Fourier transformation and autocorrelation techniques. RESULTS. Mean testicular volume increased to 6.7, 7.6 and 8.8 mls in Groups 1, 2 and 3 respectively at 12 months (p=0.05, 0.04 and 0.015), group 3 also showed a significant increase at 6 months (p=0.04). There was a progressive increase in mean LH concentration, area under the curve (AUC) and number of LH peaks in group 1 over 12 months, but LH profiles in Groups 2 and 3 showed a decrease in these parameters at 3 months. Mean LH, number of LH peaks and AUC increased significantly between 3 and 6 months in group 3 (p=0.002, 0.03 and 0.001 respectively). Fourier transformation and autocorrelation revealed dominant LH periodicity in group 2 at 12 months and group 3 at 6 months but not in group 1 at any time. Inhibin levels decreased at 3 months in group 2 and 3, and testosterone levels decreased at 3 months in group 2 but both inhibin and testosterone levels gradually increased throughout the 12 months in group 1. CONCLUSION Both oxandrolone and testosterone in low dosage may affect the pituitary-testicular axis but this effect appears transient.

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CRANIAL IRRADIATION AND EARLY PUBERTY

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Low doses of cranial irradiation (1800-2400 cGy) employed in the management of acute lymphoblastic leukaemia may cause early or precocious puberty in girls but not boys. To determine if this sexual dichotomy exists at higher irradiation doses (2500-4700 cGy) the onset of puberty was identified in 46 children (30 male), previously irradiated for a brain tumour not involving the hypothalamic-pituitary axis, and compared with the normal pubertal standards of Tanner. Regression analysis was employed to assess whether tumour diagnosis, sex, age at irradiation, chemotherapy, use of GH before puberty and radiotherapy protocol influenced age at pubertal onset. The onset of puberty occurred at an early age in both sexes (mean 8.51 years in girls and 9.21 years in boys plus 0.29 years for every year of age at irradiation). In the context of GH deficiency which is usually associated with a delay in the onset of puberty this is abnormal. There was a significant linear association between age at irradiation and age at onset of puberty in both sexes. At each age of irradiation the estimated age at the onset of puberty was approximately 0.7 years earlier in girls than boys. A similar trend was seen for bone age, which was abnormally early at the time of pubertal onset (mean 7.39 years in girls and 8.66 years in boys plus 0.25 years for every year of age at the time of irradiation). Radiation induced early puberty is not restricted to females at the doses of irradiation employed in the treatment of brain tumours. The clinical consequence of early puberty in the management of poor growth associated with radiation induced GH deficiency is to foreshorten the time available for treatment with GH.

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TREATMENT OF ADOLESCENT MALES WITH CONSTITUTIONAL DELAY OF GROWTH AND PUBERTY (CDGP) WITH SUBLINGUAL TESTOSTERONE (SL-T) COMPLEXED WITH HYDROXYPROPYL-ß-CYCLODEXTRIN (HPBCD).

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We investigated the pharmacokinetics and the effects on sexual maturation and growth of HPBCD complexed SL-T in five prepubertal males aged 14-17 years with CDGP. Patients were treated with 2.5 mg SL testosterone TID for 12 weeks. Patients revealed no evidence of side effects and had greater than 95% compliance with the drug regimen. SL-T raised serum testosterone (T) levels from a baseline of 20±10 to a peak of 1400±120 ng/dl within 20 minutes with a half life of 25±5 minutes. Serum estradiol and gonadotropin levels were not acutely affected by SL-T. SL-T kinetics were not significantly changed after 12 weeks of therapy. In three patients followed over 6-18 months after the SL-T course, sexual maturation stage progressed from stage I to stage II-IV, testicular volume increased from 2±1 to 11±4 ml, growth velocity increased from 4±1 to 11±2 cm/year, and height SDS rode from -2.5±0.2 to -1.8±0.5. Serum testosterone levels increased from 20±10 to 250±100 ng/dl, and serum IGF-I levels rose from 150±30 to 300±60 ng/ml. Bone age advanced from 11±1 to 13±0.5 years over 1.2±0.3 years while predicted adult height remained unchanged. Our preliminary data suggest that a 12 week course of SL-T is a safe, effective, and well accepted treatment for the induction of puberty and the concurrent promotion of growth in male adolescents with CDGP.

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USEFULNESS OF SEQUENTIAL URINE FSH AND LH MEASUREMENTS IN THE DIAGNOSIS OF ADOLESCENT-AGED HYPOGONADOTROPISM.

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Urine concentrates assessed by RIA provide as sensitive a methodology for gonadotropin measurements as newly available immunofluorometric techniques. The ease of obtaining repeated, short-term (3-6hr), timed urine specimens and allowing the kidney to integrate for pulsatile secretion lends itself to distinguishing patients with gonadotropin deficiency from those with constitutional delay in adolescence. We have compared the rate of gonadotropin rise in males between the ages of 12-18 yrs. in 48 normal boys, 96 patients with constitutional delay, 19 patients with isolated gonadotropin deficiency, and 10 patients with multiple tropic hormone deficiency. A total of 511 specimens were analyzed by a longitudinal model that allowed for separate intercepts and linear slopes on log transformed data for each of the four diagnostic categories. For LH, the linear equation describing the constitutional group was log LH=0.6 + 0.32 x age (p<0.0001 for slope of line) but for the isolated hypogonadotropic patients was log LH=4.14 + 0.03 x age (p=0.74). Using a Bonferroni correction, the rate of hormone increase was markedly different for the constitutional delayed boys as compared to the hypogonadotropic patients (p=0.02). Similar findings existed for FSH. The model utilized provides a guide for determining the appropriate diagnosis for a patient with delayed adolescence who is followed for a year or more with sequential gonadotropin determinations. In conclusion, a separation of adolescent boys with hypogonadotropism from those who have constitutional delay can be made by following sequential urine gonadotropin determinations over a year or more.