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GROWTH HORMONE (GH) IS NORMAL IN GIRLS WITH PRECOCIOUS PUBERTY DURING SUPPRESSIVE THERAPY WITH LH-RH ANALOGUE (D-TRP-6-LH-RH)

The inhibition of gonadotropin secretion in children with central precocious puberty treated with LH-RH analogues results in suppression of the pubertal development, including growth velocity. In some patients, a marked slowing of growth is observed. To test whether this is related to inhibition of GH secretion, we performed a clonidine test (150 mcg/m^2 p.o.) in 9 girls with central precocious puberty (age range: 4 4/12 to 11 8/12 yrs) treated with D-TRP-6-LH-RH, a superactive LH-RH analogue, 6 by daily s.c. injections of an acqueous preparation, and 3 by monthly i.m. injections of a depot preparation (Decapeptyl - Ferring). The daily dose ranged from 1.5 to 3 mcg/kg/day and the treatment periods were from 10 to 60 months. In all patients a normal GH response was found, by a peak value of 18 ng/ml or higher. In all, gonadotropin suppression was confirmed by a concomitant i.v. LH-RH test. These data show that GH reserve is not affected by the LH-RH analogue therapy and cannot be implicated in the slowing of growth, which is probably due to lack of sex hormones.

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SPERMATOGENESIS IN ADOLESCENT DOGS TREATED FOR ONE YEAR WITH D-TRP-6-LH-RH IN MICROCAPSULES (LRH-M).

Periodic intramuscular injection of LRH-M has been shown to suppress pituitary-gonadal axis in children with precocious puberty (Roger et al. ESPE 1984). In order to assess the effects of LRH-M on spermatogenesis, 50 µg/kg were given to Fox dogs on days 1 and 21, then every 28 days. In the adult dogs treated for 15 weeks spermatogenesis was inhibited during therapy and recovered 90 days after the last injection. A one-year treatment was started in 3 adolescent dogs just before completion of puberty. LH level (ng/ml, $\bar{X}\pm$sem) decreased from 4.6 ± 0.6 to 1.2 ± 0.1 on day 21 ($p<0.05$) and became undetectable beyond the 5th injection. Normal or high levels were recovered 60 days after the last injection. Mean testosterone level (ng/ml) was 1.6 ± 0.2 initially, undetectable beyond the 5th injection and 1.3 ± 0.3 sixty days after the last injection. Histology of the right testis on day 371 showed spermatogonia in all tubes, spermatocytes I in 5 to 57% of tubes and absence of more mature cells. Initially, no spermatozoa were present in ejaculates, but in 2 dogs sperm cells were present from days 56 to 77 and 64 to 105 respectively, disappeared thereafter and reappared 92 days after the last injection. No sperm cells were found in the 3rd dog throughout the study. This work shows that LRH-M induces a regression of spermatogenesis in adolescent dogs and that recovery occurs after treatment.

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URINARY EXCRETION OF BUSERELIN (B) DURING THERAPY OF CENTRAL PRECOCIOUS PUBERTY (PP). A MULTICENTER STUDY.

128 12 hrs urine collections were made in patients presenting with central PP receiving the GnRH agonist B, either subcutaneously (SC) (13 girls and 5 boys) or intranasally (IN) (7 girls and 4 boys). Centers from Belgium, France, Germany, Holland and Switzerland participated in this study. Urinary excretion of immunoreactive B and B metabolites measured after SC administration of 20µg/kg once a day in 14 girls with good control was 88.5± 7.5µg (mean ± SEM) during the first 12hrs and 6.0±1.2µg during the following 12hrs. Mean E_2 levels under therapy was 8.9±0.9pg/ml. 6 girls receiving 20µg/kg t.i.d. has an excretion of 91.5±8.7 and 89.5±9.2µg/12hrs, respectively. Two girls with poor control showed excretion levels similar to those with good control. In the 5 boys treated SC, similar levels to those measured in girls were found. One of them remained resistant (T>3.8ng/ml). In the 5 girls and 4 boys receiving IN 28.7±1.5µg/day of B, urinary excretion was 4.3± 0.9µg/12hrs during daytime and 2.9±0.8µg during nighttime. Clinical control was poor in 2 girls: both had excretion values of 0.004 and 0.093µg, and 0.001 and 0.081µg/12hrs, suggesting a poor compliance or a non-absorption by the nasal mucosa. In a third one with Albright's syndrome, resistance to therapy was observed with B excretion of 1.4 and 1.1µg/12hrs. Measurement of B excretion is of value for the evaluation of control of the therapy, compliance or resistance, particularly when B is administered IN.

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UNSUSTAINED CENTRAL SEXUAL PRECOCITY IN GIRLS

It is assumed that idiopathic central precocious puberty in girls is progressive and leads to sexual maturity. Its natural course, however, is not well defined. Four girls presented with breast enlargement (B3) at age 4.0-6.0 yrs and have been followed for up to 3.5 yrs. All had normal CT brain scans. Stimulation of LH and FSH by LHRH was excessive for age in all. Estradiol (E2) was 62-122 pmol/L. Bone age was advanced by 1.8 and 2.8 yrs in 2 girls and progressed rapidly in all. Ultrasound visualized follicular ovarian cysts in 3/4. In 2 girls, E2 fell slowly to levels around 40 pmol/L and breast enlargement decreased 1.0 to 1.5 yr after the initial work-up. The other 2 girls showed a regression of clinical signs with normalization of E2 levels after 6 and 10 months, respectively. Another 6 months later, puberty was progressing clinically and biochemically in both. As illustrated, central precocious puberty can be transient and regressing, or fluctuating in its course. This has to be considered when new drugs to control precocious puberty are evaluated for their effectiveness.

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THREATENED ABORTION AND/OR PROGESTINS THERAPY IN PREGNANCY AS CAUSE OF PRECOCIOUS PUBERTY.

To detect an early hypothalamic impairement in 33 children with idiopathic precocious puberty we reviewed their fetal and maternal gravidic history. Forthy-eight per cent of the mothers had threatened abortion in the 1st trimester (16 cases) or gestosis (3 cases). Most of the women (13/19) were treated with progestins alone or in combination with estrogens; and in one additional mother progesterone was given prophylactically for a history of habitual abortion. The hormonal therapy was given at different doses and for different periods of time. The association of maternal gravidic pathology - mainly threatened abortion - and idiopathic precocious puberty seems not to be fortuitous, since the incidence of threatened abortion in our population is 4-5% of the pregnancies carried out. We therefore indicate the possible role of hormonal therapy, more than gravidic pathology itself, in determining the early awakening of the hypothalamic centers. Finally it is interesting to note the different mean age of the onset of puberty in girls with and without gravidic pathology or treatment: 6.9±0.4 yrs vs. 5.3±2.4 yrs ($p < 0.02$). This difference could depend on a real hypothalamic dysfunction in the latter and on an early hormonal stimulation in the former.

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PRECOCIOUS PUBERTY AND PITUITARY TUMOUR IN PRIMARY HYPOTHYROIDISM. EFFECT OF THYROXINE AND IMPLICATIONS FOR THE PATHOGENESIS

The association between precocious puberty (PP) and primary hypothyroidism (PH) is known, but although an enlarged sella may be seen, a pituitary tumour has not been reported in this syndrome. A 5 year old girl presented with vaginal bleeding, and multicystic ovaries were detected by sonography. PH was found with markedly elevated TSH (1500 IU/l), decreased T_4 (22 nmol/l) and T_3 (0.85 nmol/l), in spite of few clinical signs of hypothyroidism. Serum FSH (5.5 IE/l), LH(0.4 IE/l), and prolactin (PRL) (150 µg/l) were compatible with central PP. The response to LHRH (50 µg/m^2 i.v.) showed no significant increases. A cerebral CT scan revealed a large intra- and suprasellar tumour without signs of raised intracranial pressure. Two months of thyroxine therapy was followed by normalization of thyroid hormones, TSH, PRL, FSH and the ovarian sex steroids, and the pituitary tumour was markedly regressed. A repeated LHRH test showed now a significant increase in FSH and LH.

Increased endogenous TRH or the hyperprolactinemia itself may have caused PP in this patient whereas LHRH does not seem to be involved. The tumour may be an adenoma consisting of TSH, PRL and FSH secreting cells. A remarkable feature was the advanced stage of estrogenization at debut without overt clinical hypothyroidism.