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ABSENCE OF MUTATION IN THE G PROTEIN α_S SUBUNIT GENE IN PATIENTS WITH Mc CUNE ALBRIGHT SYNDROME (MAS)

It has been recently reported that MAS results from an activating somatic mutation of the α subunit of the G protein ($G_S\alpha$) occurring early in development. Arg201 mutations in Cys or His have been previously described in several patients with MAS. We report molecular analysis of the $G_S\alpha$ gene in DNA extracted from various tissues in 4 patients with MAS.

Patients. Patient 1 is a girl who associated precocious puberty with advanced growth and bone maturation and ovarian cysts, polyostotic fibrous dysplasia, *café-au-lait* spot, and GH-secreting pituitary adenoma. The patient was resistant to LH-RH analog treatment. The 3 other patients presented with various forms of MAS.

Methods. In patient 1 DNA was extracted from peripheral blood leucocytes (PBL), ovarian kystectomy tissue and the *café-au-lait* lesion. For patients 2, 3 and 4 only DNA extracted from PBL was only available. Exons 8 and 9, and intron 8, of the $G_S\alpha$ subunit gene were amplified by PCR and directly sequenced. These exons contain the known hot-spot sites of activating mutations of the G protein : Arg201 and Gln227. Results. In the 4 patients, sequences of the two exons from the DNA from PBL were normal. In the DNA extracted from the skin lesion and ovarian tissue of patient 1 there was no mutation within the two studied exons.

Discussion. It was recently reported that majority of MAS patients have a mutation within the $G_S\alpha$ gene : Arg201→Cys or His. The absence of mutation within the *café-au-lait* lesion and PBL from the studied patients confirms previous reports which indicated that mutation is rarely detected in these tissues. The absence of any alteration in the ovary may be due to the mosaic distribution of the mutation. Absence of thyroid and adrenal dysfunction in patient 1 may account for a mutation occurring relatively late in development which could explain a low percentage of mutated cells even in the affected tissues. The presence of mutation within other exons of the $G_S\alpha$ gene cannot, however, be ruled out.

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FINAL HEIGHT AFTER SPONTANEOUS GROWTH IN GIRLS WITH SLOW EVOLUTIVE FORM OF CENTRAL PRECOCIOUS PUBERTY (CPP).

The indications and the effect on final height (FH) of luteinizing hormone releasing hormone agonist (LHRHa) therapy in girls with CPP remain difficult to evaluate because of 1) the variability on the level and on the evolution of estrogenic activity before therapy, and 2) the limited number of patients having reached their FH after LHRHa. We have shown that LHRHa is more likely to improve FH prognosis in girls who initially have a markedly advanced bone age and a great difference between their target and predicted heights (Eur J Pediatr 1992, p728). Eleven girls with slow evolutive form (prepubertal estradiol and gonadotropin response to LHRH, bone age advance < 2 yrs at the 1st evaluation) of idiopathic CPP (breast, pubic hair development and growth acceleration <8 yrs, 7.1 ±0.2yrs, m±SE) receiving no therapy were followed until their FH. The age at 1st menstruation was 10.2 ±0.2 yrs (8.9 to 11.4yrs). It did not correlate with that of their mothers (12.3 ±0.5yrs). The total height gain between breast development and FH was 32.4±1.5cm (22.1 to 40) ; which correlated with the age at breast development ($r=-0.86$, $p<0.005$). The FH was 160.3±1.7cm, which was not different from the predicted height (162.7±2cm by Bayley-Pinneau method, difference -7.7 to 4.6cm) at the first evaluation (7.8±0.2yrs) nor with the target height (161.3±1.2cm). However the FH was significantly lower than the height level at 4 yrs (1.4 ±0.3 vs 0±0.3SD, $p<0.05$).

Conclusion. Precocious and persistant low secretion of estradiol in girls did not decrease the final height. This development may be explained by an early growth acceleration preceeding the breast development and by an increased pubertal height gain.

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PUBERTAL DELAY IN BOYS AS A MODEL OF THE ROLE OF GH, IGFI AND TESTOSTERONE IN THE PUBERTAL GROWTH.

The respective role of the sex steroids, GH and IGFI increase in the pubertal growth acceleration is not clear. Clinical data suggest that sex steroids have a direct and preponderant effect. Girls with central precocious puberty have an early growth acceleration which is independent of plasma IGFI level (Horm Res, 1991, p116). 72 boys were evaluated for short stature (<-2SD) and pubertal delay (P1 stage >14 yr) . All had GH peak after arginine insulin stimulation >8 ng/ml. They were classified in 2 groups according to their plasma testosterone (T, ng/ml) : Group I 0-1 (0.5 ± 0.1, n=54) and II 1-2 (1.5± 0.2, n=18). The mean age and height level were similar 15 ±0.1/15± 0.2 yr and -3.0±0.1/-3.4 ± 0.2 SD in I/II respectively. m±SE, $p<0.05$, $^{***}0.001$

	GH, ng/ml	IGFI, u/ml	cm/yr	bone age advance, yr
I	13±1	1.0±0.1	3.7±0.2	2.3±0.1
II	20±2	1.8±0.3	4.3±0.2	2.7±0.2
I vs II	***	***	*	NS

T correlated with plasma IGFI ($r=0.42$, $p<0.001$) but not with GH peak. Height gain during the preceding year did not correlate with GH peak, IGFI or T.

Conclusion. The initial increase in testosterone secretion in boys is accompanied by a significant and important increase in GH peak and in plasma IGFI. In spite of this increase, growth velocity remains in the prepubertal level. This is at variance with which occurs in girls ; a small increase in estradiol secretion induces growth acceleration before incrasing plasma IGFI. These data suggest that the increase in GH/IGFI is not critical for the pubertal growth acceleration in boys and that plasma testosterone levels >2 ng/ml are required to induce growth acceleration and bone age progression.

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EVIDENCE THAT NEUROPEPTIDE Y (NPY) COULD REPRESENT A NEUROENDOCRINE INHIBITOR OF SEXUAL MATURATION IN UNFAVORABLE METABOLIC CONDITIONS IN THE RAT. N.M. Gruaz, D.D. Pierroz, F. Rohner-Jeanrenaud, P.C. Sizonenko, and M.L. Aubert, Biology of Growth and Reproduction, Dept of Pediatrics, and Laboratory of Metabolic Research, University of Geneva School of Medicine, 1211 Geneva 14, Switzerland.

NPY is known to be involved in the central regulation of appetite, metabolic processes, and reproductive functions. We have demonstrated that central administration of NPY results in an inhibition of the gonadotropic axis in the rat. In the female rat, sexual maturation can be delayed by severe diet restriction and in this situation, NPY is increased in the paraventricular nucleus (PVN). In order to evaluate a potential role of NPY for this delay, we attempted to prolong this period of sexual immaturity by infusing NPY centrally after restauration of normal feeding condition. Sexual maturation was prevented by maintaining food allowance at 5.5 g/day. At 50 days of life (d), a cannula was placed in the lateral ventricle and at 60 d, the animals were implanted with Alzet pumps delivering 18 µg NPY daily to the cannula, or vehicle. One day later, food restriction was discontinued. The switch to *ad libitum* feeding produced a rapid acceleration of growth rate and, in the animals receiving vehicle, the expected full sexual maturation after 2 to 5 days. Animals receiving NPY exhibited an even more important increase in weight gain, but only one out of 9 rats studied had experienced vaginal opening after 6 days, at the end of pump capacity. In another series, sexual immaturity could be prolonged for 13 days. Thus, since NPY is increased in the PVN of food-restricted rats and that administration of NPY could prolong the situation of sexual immaturity observed during food restriction, it is tempting to speculate that NPY is instrumental for inhibiting GnRH release and sexual maturation in unfavorable metabolic conditions.

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EFFECT OF LONGTERM GnRH AGONISTS (GnRHa) ON FINAL HEIGHT IN CHILDREN WITH TRUE PRECOCIOUS PUBERTY (TPP). D. Paul, M.M. Grumbach and S.L. Kaplan, Department of Pediatrics, University of California San Francisco, San Francisco, CA 94143, USA

We have compared the final height of GnRHa treated patients to untreated patients with TPP. 45 children received deslorelin (4-8 ug/kg/d s.c.) or nafarelin acetate (800ug IN bid). 26 of the 45 (20F/6M) are at final height or near final height (F BA>12 y; M BA >14 y). The median CA at onset of puberty was 3.2 y (R=1.0 to 7.3) in girls and 4.0 y (R=3.9 to 9.1) in boys. The mean BA/CA at start of therapy was 1.7±.4 SD and the mean Ht SD was +3.0±1.3 SD and the mean Ht SD for BA was -1.4±1.0 SD. Therapy was stopped in girls at a median age of 11.4 y and in boys at 12.2 y. The mean duration of therapy was 5.7±2.3 years. At termination of therapy, the change in mean BA/CA was 0.7±0.3, in mean Ht SD/BA +1.1±1.0 and in mean predicted Ht SD +1.4±1.6. The mean current height for the 20 girls is 157.7 cm (R=145.5 to 172.1) and for the boys is 166.1 cm (R=150.1 to 179.7), which already exceeds the mean height of the untreated group by 5.0cm for girls and 10.5cm for boys. 7 of the 26 children are taller than target Ht and 18 are within 2 SD of target Ht. The latest mean predicted Ht for girls is 164.6±9.7 and for boys 172.8±11.3. The mean predicted Ht SD for all 26 children is 0.0±1.7 (R= -3.9 to +3.9), whereas the mean final Ht SD of 116 untreated TPP children (literature review) is --2.1. The mean predicted target HT SD in the GnRHa treated group is +0.2±1.9 compared to -2.7 for the untreated group. These data provide strong evidence that sustained suppression of puberty by GnRHa improves final height prognosis.

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GONADOTROPIN-INDEPENDENT PRECOCIOUS PUBERTY: CLINICAL AND HORMONAL EVALUATION. TV Semicheva, VA Peterkova, EB Koledova, AD Dobracheva, MI Bronshtein, AA Znamensky, OV Fofanova. Endocrinological Center, Moscow, Russia.

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In some children premature sexual maturation occurs in the absence of pubertal levels of gonadotropins and gonadal hormone producing tumors. Clinical and hormonal evaluation of 7 children (3 girls and 4 boys) was performed. In all girls the onset of sexual development was seen before 3 years of age. The clinical picture was characterised with features of McCune-Albright syndrome, including Cushing syndrome (1 case), euthyroid goitre (1 case). All girls demonstrated the absence of pubertal gonadotropin fluctuations (1,5±0,5 U/l). BioLH was decreased (3,5±1,5 U/l) compared to girls with central precocious puberty (28,6±4,2 U/l). Cushing syndrome was ACTH independent. All boys developed precocious puberty before 2 years of age without family history. On testicular biopsies diffrent stages of testicular maturation was found: from the incipient puberty to the normal adult testes. Compared to data seen in central precocious puberty all boys demonstrated high level of T (15,8±4,2 nmol/l) low LH (2,3±1,2 U/l), FSH (0,5±0,3 U/l), absence of gonadotropin pulsation, lack of LH response to LHRH, low bioLH (4,3±2,1 U/l). We conclude that gonadotropin independent puberty is a distinct syndrome with intragonadal mechanism of development.