505

LACK OF SUPPRESSION OF SERUM IGF-I AFTER SEX HORMONE SUPPRESSION IN TRUE AND PSEUDO PRECOCIOUS PUBERTY. A.Belgorosky and M.A.Rivarola.Endocrinología, Hospital de Pediatría Garrahan, Buenos Aires, Argentina

Association of delayed puberty and low serum IGF-I is observed in GH deficiency and chronic malnutrition, while advanced central puberty and high IGF-I is seen in children after long time exposure to high levels of sex hormones(SH). While some workers have reported a decrease of serum IGF-I during therapy of precocious puberty (PP)with GnRHa, others have shown no change. We have studied 7 children with PP, 4 with central PP(2 boys aged 3.5 and 7.5 y, 2 girls aged 6.1 and 5.6 y) and 3 with simple virilizing CAH (mean±SD age 5.7±2.1, bone age 12.9±1.2 y), both before and 2 to 7 months after SH suppression (SHS) with either long acting GnRHa or hydrocortisone. Serum IGF-I, LH, FSH, testosterone (T) and estradiol (E_2) were measured by RIA. A GnRH test was carried out in the 3 patients with CAH. Before SHS, serum IGF-I and T (boys) or E_2 (girls) were 1.52±0.4 U/ml (5 to 11-y-old normal: 0.72±0.4) and 13.7±8.6 nmol/L or 230 pmol/L, respectively (mean±SD or mean of duplicate). After SHS, values were 1.78±0.92 and 0.93±0.14 or 10.5. IGF-I did not decrease in any patient, while SH decreased in all of them. Maximal LH and FSH responses to GnRH in CAH were 1.60±1.1 and 0.88±0.54 before SHS, and 9.27±2.25 and 6.46±2.45 U/L 2 to 12 months after SHS, respectively. Testicular enlargement and clinical evidence of central PP developed in CAH patients after SHS. It is concluded that after SHS to prepubertal values, serum IGF-I remains high in either central PP or CAH, suggesting that SH induce a maturational change in IGF-I values. Since after SHS in CAH, the GnRH test acquires a pubertal pattern of response, IGF-I might be involved in the process of maturation of the gonadostat.

506

EFFECT OF A LONG ACTING LHRH ANALOGUE AND GH ON THE SUPPRESSION OF SECONDARY SEXUAL DEVELOPMENT AND FINAL HEIGHT. M. Ohba, Y. Igarashi, E. Ogawa, I. Fujiwara, A. Asanuma, Y. Hino, Department of Pediatrics, Tohoku University, School of Medicine, Sendai, Japan

LHRH analogue therapy has been estimated as useful for suppressing secondary sexual development in cases of precocious puberty and is expected to improve final height. We studied changes in the pituitary and gonadal functions after cessation of LHRHa in patients exhibiting precocious puberty. Furthermore, we studied the effects of a combination therapy of LHRHa and growth hormone in short patients. *<Patients and method> Group A;* Five girls who had been diagnosed as exhibiting precocious puberty and had been treated with LHRHa(TAP-144-SR) during a period of 1.5 to 3.4years, and who were no longer being treated. *Group B;* Six girls and a boy who underwent pubertal development and exhibited acceleration of bone maturation during a GH supplement for GH deficiency or short stature without GHD, were treated with LHRHa. GH was injected subcutaneously 4-6 times a week at a dosage of 0.5-0.6U/kg/w. *A and B;* LHRHa, 30-60 μg/ml, was administered via a subcutaneous injection every 4 weeks. Changes in secondary sexual characteristics, height velocity, bone age, height SDS for bone age, serum estradiol, serum gonadotropins and IGF-1 were observed in all patients, and serum GH was measured in group A. Height velocity/ΔBA and ΔBA/ΔCA were calculated in group B. *<Results> A;* After cessation of LHRHa treatment, secondary sexual characteristics began to progress within 6 months, and E2 and peak LH were elevated to the pubertal level within one year. Improvement of height SDS for BA and increase of height velocity continued at least 6 months after the off-therapy. *B;* After LHRHa treatment, secondary sexual characteristics were attenuated, acceleration of bone maturation was suppressed and hormonal parameters decreased to the prepubertal range in all cases. Height SDS for BA, growth velocity/ΔBA and ΔBA/ΔCA were all improved by LHRHa treatment. *<Conclusion>* The suppression of pubertal bone maturation by LHRHa was significant. On the other hand, secondary sexual characteristics developed promptly after the cessation of LHRHa treatment. This data suggests the possibility of improving final height without any side effects by a combination therapy consisting of GH and LHRHa.

507

PRECOCIOUS PUBERTY IN NEUROFIBROMATOSIS TYPE 1 (NF-1). R. Habiby, B.L. Silverman, R. Listernick, J. Charrow. Department of Pediatrics, Northwestern University, Chicago, IL 60614, USA.

Precocious puberty (PP) has been reported in children with NF-1, primarily in the presence of optic pathway tumors (OPT). We evaluated 201 children with NF-1, 157 of whom had CNS imaging; 31 had OPT. Of these, 19 were 2-10 yrs old. Four of these children had PP, while no child without an OPT had clinical PP. We conducted a prospective case control study to investigate the effect of OPT on the maturation of the hypothalamic-pituitary-gonadal axis in children with NF-1, and the association between NF-1 and PP in the absence of OPT. We enrolled 24 prepubertal children, 2-10 yrs old, with NF-1, 12 with OPT and 12 without OPT, matched for sex and age. We measured height, weight, parental heights, bone age, and the LH and FSH response to LHRH. A 6 cm difference in height was found between the group with OPT 117.4±3.9 (MEAN±SE) and without OPT 111.5±4.0, (p=0.15). Height Z-scores were higher in children with OPT (0.12±0.39 vs -1.07±0.35,p=0.02). Bone age minus chronological age was also higher in the glioma group (0.08±0.37 yrs vs -0.65±0.35, p=0.08). In response to injected LHRH 100μg, there was a greater rise in LH in the group with OPT (p=0.06). FSH responses were identical. All 4 pubertal responses (peak LH>15mIU/ml) occurred in children with OPT (p<0.05). Three of these children had lesions confined to the intraorbital portion of the optic nerve. We conclude: 1) PP occurred in NF-1 only in the presence of OPT, 2) accelerated growth was present in the children with OPT, consistent with early puberty, 3) contrary to expectations, a pubertal response to LHRH was evident in children with tumors remote from the hypothalamus, and 4) we have identified a subpopulation who provide a unique opportunity to prospectively investigate the pathogenesis of PP.

508

FINAL HEIGHTS FOLLOWING GnRHa-INDUCED PITUITARY-GONADAL SUPPRESSION IN GIRLS WITH CENTRAL PRECOCIOUS PUBERTY (CPP). PA Boepple, MJ Mansfield, JD Crawford, JF Crigler, RM Blizzard, WF Crowley. Massachusetts General Hospital, Children's Hospital, Boston, MA, USA; Univ. of Virginia, Charlottesville, VA, USA

In our ongoing studies, 60 girls with CPP have been evaluated at 6-12m intervals for ≥ 12 months following the discontinuation of GnRHa. All received daily sc injections of either deslorelin or histrelin for 3.8 ± 0.2 years (range 2.0-7.7). Of these 60 girls, 36 have attained their final height (at FHT; GV < 2 cm/year, TW BA = 16 years), while the remainder have some residual growth potential (near FHT). In both subsets, the latest measured HT, while remaining 7.1 ± 1.0 cm below the genetic target HT, significantly exceeded the Bayley-Pinneau prediction prior to GnRHa administration (*, p = 0.0001). A single girl with a pre-GnRHa BA < 10 yrs has reached her FHT, while such patients comprise 34% of our total CPP female population. Since changes in predicted HT during GnRHa administration correlate significantly with pretherapy CA and BA, we must still await the FHT outcomes in young patients enrolled early in puberty to judge comprehensively the impact of gonadal sex steroid suppression on FHT in patients with CPP.

	n	Pre-GnRHa CA	Pre-GnRHa BA	D/C GnRHa CA	D/C GnRHa BA	Pre-GnRHa BP PredHT	LATEST Height
At FHT	36	7.9	12.6	11.2	13.9	148.7	152.5 *
Near FHT	24	6.3	10.3	10.8	13.3	151.9	156.3 *

509

LH AND FSH TO GnRH ASSESED BY TWO HIGHLY SENSITIVE ASSAYS IN NORMAL PUBERTY, DELAYED PUBERTY (DP) AND HYPOGONADOTROPIC HYPOGONADISM (HH). M. Stivel, G. García Arias, S.B. Campeni, C. Zylbersztein, H. Scaglia, A. Oneto and C. Aranda. Ceusa Lab. Estudios Hormonales y Div. Endocrinología. Hosp. Durand. Bs. As. Argentina.

The Basal (B) on GnRH (P) stimulated levels of LH and FSH were measured by ultrasensitive (0.4 and 0.3 mUI/ml) IRMA (CIS International) assay in 54 normal children: pre pubertal (PP n=24 (M 11, F 13); Early Pubertal (EP) n=17 (M9, F8); Advanced Pubertal (AP) n=13 (M8, F5). 10 patients (M8, F2) with DP (Tanner I, test vol.< 3, CA: n + SD: 13.84 + 1.14 y, BA: 11.94 + 0.47 y) and 9 patients with HH (Tanner I, test vol < 3, CA: 17.21 + 3.23 y, BA: 13.87 + 0.97 y) were also investigated. Ultrasensitive LH and FSH (0.04 and 0.04 mUI/ml) IFMA (Delfia) were assayed in a subgroup of 29 of the normal children. Across the entire range of pubertal sample LH and FSH, and also in the range PP,FSH values derived from the IRMA and IFMA were highly correlated (r = 0.97). In the B PP range LH not correlated (R = 0.27). In PP, B LH was undetectable by IRMA in 19 of the 24 and in 4 of the 11 by IFMA. B LH rose significantly with the onset of puberty. However, was in the range of PP in 7 of 17 by IRMA and 2 of 7 by IFMA. By AP every child had > 2 mUI/ml values. B FSH levels was detectable in all the groups and was significantly (p< 0.03) greater in F than in M in PP. Upon GnRH test, the distinction between the groups was better. P LH $\bar{x}$ + DS PP: 2.93 + 0.94 vs EP: 10.34 + 4.93 (P< 0.0001) vs AP: 21.8 + 8.98 mUI/ml (p <0.0001). No statically difference was found between IRMA or IFMA. All of the PP, F and M, had a ratio P LH to P FSH which was less than 1 and increased significantly with pubertal onset. In DP, before the appearance of pubertal signs, at BA 11.94 + 0.47 y, the LH response to the Gn RH was 10.40 + 4.60 vs 2.61 + 2.14 mUI/ml (p <0.0001) in HH. LH responses did not overlap in either group. We conclude, that the test of Gn RH using gonadotropin ultrasensitive assay is useful in identifying the onset of puberty, and in the discrimination of DP from HH.

510

THE MELATONIN EXCRETION IS INVERSELY CORRELATED WITH THE GONADAL DEVELOPMENT DURING CHILDHOOD. J.C.Commentz, H.Uhlig and A.Henke, Children's Hospital, University of Hamburg, Martinistraße 52, 2000 Hamburg 20, F.R.G.

To test the hypothesis, that the Pineal hormone Melatonin is involved in the control of the onset of puberty, we determined the Melatonin (MLT) and the Melatoninsulfate (MLTS) excretion in childhood from prematurity to adolescence. The urine of 216 children from the 26. week of gestation to adolescence was collected in two portions and MLT, MLTS and creatinine was mea-sured in the day and night time urine samples. Results: MLT/MLTS excretion decreased with advancing gestational age with lowest values at term. The values remained low during the first 6 months of life and increased thereafter. Highest excretion values for total amounts as well as for day/night differences were reached at 4-7 years of age. The excretion remained fairly constant thereafter resulting in a decrease of MLT/MLTS to creatinine or bodysurface area ratio at the beginning of puberty. A significant day/night difference was not detectable before the sixth month of life. Conclusion: The MLT/MLTS to bodysurface area ratio, reflecting the MLT/ MLTS bloodconcentrations, is inversely correlated to the activity of the hypothalamic-pituitary-gonadal axis. With respect to the proven antigonadal activity of Melatonin in other species, an involvement of Melatonin in the control of the timing of puberty in man is likely.