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R. KAULI, A. SCHOENFELD*, Y. OVADIA*, S. MATZ*, S. ASSA* & Z. LARON, Inst. of Pediat. & Adolesc. Endocrinol., Dept. of Obstet. & Gynecol., Div. of Ultrasound & Neuroradiol. Unit, Beilinson Medical Center, Tel Aviv University, Israel.

Delayed puberty and hypoplastic uterus associated with hyperprolactinemia and successfully treated with bromocriptine.

A 15 year-old-girl referred because of primary amenorrhea was found to have a hypoplastic uterus and persistent hyperprolactinemia (72-110 ng/ml). Pubertal development was retarded: breasts Tanner stage 3, pubic hair - Tanner stage 4, bone age was 13 yrs. Endocrinological examinations revealed: LH- basal 0.85, peak after LRH- 5.04 mIU/ml; FSH- basal 4.27, peak 12.88 mIU/ml; PRL response to TRH- basal 79.2, peak 101.6 ng/ml, and no suppression after Nomifensine (125 mg orally). CT of the brain was suggestive for a pituitary microadenoma. Following therapy with bromocriptine (2.5 mg/day) PRL levels dropped to 5-6.8 ng/ml with accompanying pubertal development and a marked growth of the uterus, as documented by repeated ultrasound examinations. Menarche occurred 5 months after the initiation of therapy followed by regular mensis thereafter. During the 4 yrs of therapy she grew 9.1 cm. Repeated CT of brain showed a decrease in the density and size of the lesion, which however persisted. This patient demonstrates that hyperprolactinemia can cause delayed puberty with a particular inhibitory effect on uterine growth and development.

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W.v.PETRYKOWSKI, H.REINWEIN*, C.OSTERTAG*, and R.FÜRMAIER*. Childrens' Hospital, Dept. of Diagnostic Radiology, Neurosurgical Clinic of Freiburg University and Institute Fürmaier-Schmidt, Freiburg, West Germany

Asymptomatic primary empty sella syndrome in a 14 yrs. old girl. Comparison of CT and NMR imaging.

Primary empty sella syndrome is well characterized in adults, but extremely rare in children and adolescents. It is caused by a combination of intra-or suprasellar factors and a defect in the sellar diaphragm, allowing the subarachnoid space to extend into the sella. Despite compression of the pituitary to the sellar floor its function usually is maintained. The enlarged sella however requires exclusion of a pituitary tumour. Unequivocal documentation of the syndrome so far depended on positive cisternography with computerized tomography. By this technique the pituitary and its stalk could be visualized well in a 14 yrs. old girl with an enlarged sella and normal endocrine function. The procedure however is unpleasant and involves x-irradiation. Nuclear magnetic resonance technique avoids these disadvantages and promises even better resolution of anatomic details. This could be confirmed in the patient and is evident from comparative images of the flattened pituitary and its stalk within the empty sella.

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R.RAPPAPORT, R.BRAUNER*, P.CZERNICHOW. Unit of Pediatric Endocrinology and Diabetes. Hôpital des Enfants Malades, Paris. France.

Precocious puberty secondary to cranial irradiation for tumors distant from the hypothalamo-pituitary area.

The effect of cranial irradiation on pubertal development so far reported is the unfrequent occurrence of partial or complete gonadotropin deficiency (10 to 20 % of the cases in our experience). It is generally associated with GH deficiency. The present study shows that precocious puberty can also be observed after irradiation.

Out of 29 children, who had been irradiated before 7 yr and had reached pubertal age at time of this study, 6 patients had presented signs of true sexual precocity (5 girls and 1 boy). They had received 2400 to 5000 rads for medulloblastoma (3), leukemia (1), cerebellar astrocytoma (1) and facial tumor (1) at a mean age of 5 2/12 yr (2 to 6 8/12 yr). First sign of puberty appeared at a mean age of 7 5/12 yr (6 10/12 to 7 10/12 yr) in the 5 girls, and at 9 yr in the boy. Clinical signs of puberty procceded at a normal rate. Plasma prolactin, E2 or T, LH and FSH response to LRF were normal for pubertal stages.

In 5 children with GH deficiency, growth spurt was blunted and 3 of them ended up with short stature. Only 1 patient has been treated with GH with a poor result.

In conclusion, it appears that cranial irradiation can impair gonadotropin secretion by producing precocious puberty as well as pituitary deficiency by a still unknown mechanism.

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N.STAHNKE, P.HAUPT*, R.P.WILLIG, G.SINNECKER*, K.WINKLER* Dept. of Pediatrics, Univ.-Clinic, Hamburg, FRG.

Endocrine Function after Cranial Irradiation (CI).

3 groups were studied. Group I: 2o patients who had been off treatment for acute lymphatic leukemia for at least 2 years. All patients had received prophylactic CI of 18oo-24oo rads. Group II: 11 patients studied at least 2 yrs. after CI (dose 4ooo-5ooo rads) for brain tumors not involving hypothalamic-pituitary area. - Oestradiol and testosterone (T) levels and T/SHBG ratio were in the normal range in group I, II. Basal and peak FSH levels after LH-RH were reduced in pubertal girls and prepubertal boys of group I and in pubertal girls of group II. Basal LH levels were lower in pubertal boys and LH peak was blunted in pubertal girls of group II. There was no significant difference in basal and TRH-stimulated prolactin, TBG, $T_4$, $T_3$ levels and $T_4$/TBG ratios between group I, II and normal controls. Basal TSH was impaired in group II. Group I and II patients showed decreased basal and peak GH levels following insulin-hypoglycemia (IH). After arginine infusion (AI) lower peak GH values were found in group II. A decrement in basal and peak ACTH levels after IH, lysinevasopressin (LVP) and in circadian cortisols levels was found in group I, II. Following IH peak cortisol levels were reduced in group I and II, basal and LVP-induced peak cortisol values were decreased in group I. An increase in basal and peak insulin levels after AI was found in group I and in peak insulin values in group II. Group III: 4.9 yrs. after treatment for acute leukemia adult height was measured in 37 patients: height SDS was + o.68 ± 1.2.

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F.WALDHAUSER+, H.J.LIEBERMAN+, H.FRISCH, K.HERCKNER+, W.F.CROWLEY+, R.J.WURTMAN+. Mass.Inst.Tech., Cambridge; Mass.Gen.Hosp., Boston, USA; Ped.Dept., Univ.Vienna; L.Boltzmann Inst., Vienna, AUSTRIA.

Melatonin does not alter human serum gonadotropin and testosterone levels, but it increases prolactin levels.

Administration of the pineal hormone melatonin (MEL) lowers serum gonadotropin (GN) levels, delays sexual maturation and elicits gonadal atrophy in rodents. In humans an antigonadotropic effect of the pineal has been sought for many years. Recently we reported higher nocturnal serum MEL levels in prepubertal children than in young adults. Now we have examined the immediate effects of exogenous MEL on basal levels of various hormones. After giving informed consent 5 healthy, male adolescents received 80 mg oral MEL at 11:00; 3 volunteers received the same dosis at 11:00,12:00 and 13:00. Serum concentrations of MEL, GN, testosterone (T) and prolactin (PRL) were determined at 30-min. intervals several hours prior to, during, and after MEL administration. Though serum MEL concentrations increased at least 1000 times above basal levels GN and T were not altered. PRL rose from 4.6±0.7 (x±SEM) to 7.6±0.9 ng/ml ($p<0.005$) after MEL application. To examine the effect of the pineal hormone on the pulsatile secretion patterns of GN and PRL, in 2 adolescents sera were taken at 10-min. intervals for 6 hours before and after MEL treatment. The pulstile secretion pattern of GN was not altered by MEL; again, PRL levels were higher after MEL than before. Thus, a single dosis of MEL does not affect serum GN levels in humans, but it increases PRL serum concentrations.

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P.S.WARD*, M.G.MOTT*, D.C.L.SAVAGE. Bristol Children's Hospital, Bristol, U.K.

The growth of children following cranial irradiation.

Children who have required cranial irradiation for malignant disease may become growth hormone (GH) deficient. We have reviewed the records of 37 children to determine whether their height velocity in the first 2 years following radiotherapy predicts those who would become GH deficient. Heights and pubertal stage were noted at presentation and annually until 5 years after diagnosis. Height and height velocity standard deviation scores (SDS) were calculated for each patient year of follow up. The results were analysed separately for those with a peak serum GH >15mU/L and those with a peak <15mU/L. Mean height SDS at 2 years fell to -0.7 and -1.06 in the GH normal and GH deficient groups respectively. Mean height velocity SDS for years 1 and 2 were -4.07 and -2.69 in the GH deficient patients compared with -1.68 and -1.12 in the GH normal patients. We conclude that the effects of cranial irradiation on height velocity are apparent within the first 12 months of treatment in those patients who become GH deficient.