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Sex-specific sensitivity of the hypothalamic pituitary axis to estradiol benzoate in normal children.

The influence of i.m. estradiol benz. (EB)(10-15 mcg/kg) on basal plasma E_2, LH and FSH and their response to LRH (50 mcg/m^2 i. v.) in normal children was studied. In all pubertal (n=10), early (n=15) and late pubertal (n=6) boys the single EB inj. suppressed basal LH and FSH and their response to LRH. Pre- (n=5) and early pubertal (n=6) girls had suppression of basal LH and FSH but in late puberty (n=14) the basal LH rose from 1.2±0.5 to 3.0±1.6 mIU/ml ($p < 0.05$) whereas FSH remained suppressed. The mean peak response of LH to LRH following EB (single inj.) was increased in all pubertal stages (to 1.7±0.4, 17.0±14.8 & 27.3±23.6 mIU/ml respectively). FSH response was increased only in early and late puberty (to 13.4±6.0 and 10.5±1.8 mIU/ml respectively). Following 4 daily EB inj. basal plasma LH and FSH levels and their response to LRH in boys (n=22) and girls (n=17) were inconsistently variable in all stages. In conclusion EB modulates the hypothalamic pituitary regulation of gonadotropin secretion, particularly the pituitary response to LRH, which was found to differ at various pubertal stages in normal boys and girls. The sex-specific sensitivity to physiological plasma estrogen levels may be of importance in the maturation of the hypothalamic pituitary axis during puberty.

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The effect of Phenytoin (DPH) on the Conversion of Testosterone(T) to Dihydrotestosterone (DHT) in vitro.

Diminished or absent virilization of male external genitalia is an occasional feature of the fetal hydantoin syndrome. We have studied the effect of DPH on the conversion of ^{14}C-testosterone to its 5α reduced metabolites in skin of male infants. Neonatal foreskins obtained at circumcision were incubated for two hours with ^{14}C-testosterone in buffer, with glucose, penicillin, and supra-pharmacological concentrations of DPH. Using thin layer chromatography, the incubation mixture was assayed for T and androstenedione plus the 5α reduced metabolites, DHT, androstanedione, androstanediol, and androsterone. Testosterone metabolites formed were expressed as nanomoles/100 mg tissue/hour with and without DPH. There was a significant nonlinear decrease in the amount of both DHT and total 5α reduced metabolites formed with increasing amounts of DPH, with minimal production at 4,400 nanomoles of DPH. This result was comparable to that obtained under identical experimental conditions following addition of progesterone, a known 5α reductase inhibitor. These in vitro results may explain the mechanism of abnormal phenotypic sexual differentiation of the male fetus exposed to DPH in utero.

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Abnormal osmoreceptors in Kallman's syndrome (KS).

We have previously described high set osmotic threshold (OT) for vasopressin release and deficient thirst in a patient with KS (ESPE-meeting 1980). In the present study the OT was evaluated by an isovolemic infusion of 5% NaCl in 7 patients with KS. The OT was defined at the plasma osmolality (Posm) at which the free water clearance (CH_2O) abruptly fell. The OT was abnormally high in 5 patients, 291-296mOsm/kg. It was normal in one, 287mOsm/kg, and abnormally low in one patient, 270mOsm/kg. These values are compared to the OT in 73 normal volunteers previously reported (A.M.M & M.M), 287.3 ± 0.9(SD) mOsm/kg. The 5 patients with high set OT denied thirst at Posms as high as 296-316mOsm/kg. Normal response of volume regulation of vasopressin release was demonstrated by an appropriate fall in CH_2O during water deprivation. Normal response of baroreceptors was shown by a fall in CH_2O and a rise in plasma ADH during infusion of the hypotensive agent trimethaphan in 2 patients. It is concluded that the hypothalamic involvement in KS include deficient thirst sensation and abnormal setting of the osmoreceptors, that can be at an abnormal high or low setting.

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RARE ACQUIRED NEUROLOGICAL DISORDERS IN TWO PATIENTS ON LONG-TERM HUMAN GROWTH HORMONE (hGH) THERAPY.

Acquired neurological disorders are not known to occur in association with either GH deficiency or hGH therapy. Two of our group of over 50 patients receiving hGH developed unusual and rare neurological disorders.

A 13 year old boy treated for isolated GH deficiency from the age of 4 years developed the Guillain-Barré syndrome (GBS) while still on therapy, and required assisted ventilation. Recovery was prolonged but complete. A 17 year old boy with anterior hypopituitarism receiving thyroxine and cortisone and on hGH since the age of 4 developed dysphagia and dysarthria. Cranial nerves were affected and there was atrophy and fasciculation of the tongue. After extensive studies the diagnosis of bulbar amyotrophic lateral sclerosis (ALS) was made. The neurological deficit progressed and he required gastrostomy and assisted ventilation.

Both GBS and ALS are rare diseases in children. The cause of neither is known. GBS may follow viral infections or injection of a foreign protein. A slow virus infection and autoimmunity have been postulated for ALS. The occurrence of these rare neurological disorders, possibly having similar etiologies, in two children treated with hGH for years may well be fortuitous. Nevertheless, since hGH is obtained from cadavers, one cannot dismiss the possibility of a causal association.

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Neonatal Diabetes Insipidus Associated with Optic Atrophy,Cerebral Atrophy and Gastroschisis.

Congenital diabetes insipidus has not previously been reported in association with gastroschisis and its' associated anomalies. This is an unusual case of an in utero cerebral vascular accident causing diabetes insipidus, optic atrophy and left cerebral hemisphere atrophy. A 36 week gestation infant with a birthweight of 2.7 Kg. was noted to have herniation of the abdominal wall exposing intestinal contents at birth requiring surgery in the first hours of life. On the 10th post-operative day diabetes insipidus was noted. Serum sodium was 160 mEq/L, serum osmolality was 312, urine osmolality = 83. Aqueous pitressin was administered I.M. resulting in brisk response. The management of a diabetes insipidus in this infant was easier to control with dilute intranasal desmopressin acetate (DDAVP) as compared to pitressin tannate in oil injections. TSH, growth hormone and metyrapone-pituitary adrenal axis studies were normal. CAT-scan of the head revealed left cerebral atrophy resulting from a vascular accident. In conclusion, this case represents an in utero cerebral vascular accident causing diabetes insipidus, optic atrophy and left cerebral atrophy associated with gastroschisis. Recent evidence shows gastroschisis to represent an in utero vascular accident to the abdominal wall musculature.

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A syndrome of periodic ACTH and ADH discharge.

A girl aged 8 yrs had suffered from periodic attacks of vomiting, psychotic depression and hypertension lasting for 5 to 6 days at monthly intervals since 16 months before admission. At the initiation of the attack, serum corticotropin (ACTH) and vasopressin (ADH) levels were prominently increased (610 pg/ml and 41 uU/ml respectively) despite normal plasma osmolality, which consequently produced hypertension (160/110 mmHg), hypercortisolemia and hyponatremia. Serum prolactin was also increased (91 ng/ml). During the attack, urinary excretion of epinephrine (E) and norepinephrine (NE) was elevated while that of dopamine (D) was reduced, resulting in marked rise in E+NE/D ratio (0.8 - 4.5), which decreased to normal level when symptoms disappeared (0.08 - 0.17). Provocation of the attack by hypertonic saline infusion or by metyrapone administration was not successful. Infusion of somatostatin at early stage of the attack suppressed the symptoms and chronic administration of methyl-DOPA with reserpine effectively inhibited the recurrence of the episodes. Her symptoms appear to be induced by periodic discharge of ACTH and ADH. Although the exact cause of this syndrome is unknown, disturbance in catecholaminergic mechanism in hypothalamus is postulated.