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FAMILIAL PITUITARY DWARFISM(FPD).AN ENTITY OF DIVERSE ETIOLOGY AND MODE OF INHERITANCE.

FPD is quite rare and the available data indicate different modes of inheritance. We present here in eleven cases of FPD, which belong to four family trees. FT1) The affected members are father and son. The father has isolated GH deficiency, while the son has ADH and GH deficiency with no response to GHRH. The pituitary fossa is extremely small. FT2) The known affected members are the index case, a boy, his mother and the mother's brother. All 3 members had low GH values post clonidine or L-DOPA, with a good response to exogenous GHRH. We thus presume that the defect lies in the GHRH synthesis or secretion. FT3) Two females, first cousins, with isolated GH deficiency,whose mothers are sisters and of short stature. The mothers have not been tested as yet. FT4) Four affected members, 2 girls and 2 boys, who belong to four related families, inhabitants of a small village. The low GH values did not rise following exogenous GHRH. Besides GH, other pituitary hormone deficiencies were present in different combinations. DNA analysis of all affected members is in progress. The available data denote that familial pituitary dwarfism has diverse etiology, and extensive studies are needed to determine etiology, pathogenesis and the genetics involved.

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CHARACTERISTICS OF SUBJECTS WITH EARLY ONSET PITUITARY DWARFISM(PD).

Congenital or early onset PD is relatively rare. We present below certain characteristics of 10 cases with very early onset of growth failure and GH deficiency,proven by two provocative tests:

Age of measurement(mos)	Height SDS	Micropenis	M/F ratio	Breech presentation	Birth weight (kg) X±SD
8.5±4.5	-4.7± 1.1	4/6	6/4	0	3.25±0.33

The analysis of the present data, and those of the literature do not support the notion that breech delivery may be an epiphenomenon rather than an etiologic factor in PD. Thus, out of 22 cases (including the present ones), with such information available, only one had breech presentation. The male to female ratio(M/F) in the total group of cases was 19/19, while the M/F ratio in those with pituitary dwarfism, in general, is greater than 2 and close to the M/F ratio encountered in asphyxia neonatorum. Multiple pituitary deficiencies and micropenis predominate. Most interesting is the fact that growth failure is quite evident during the first year of life, an observation, which favors the concept that growth hormone is also needed for normal growth during the first postnatal months.

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N-METHYL-D-ASPARTATE (NMDA) STIMULATES LHRH RELEASE VIA THE NMDA RECEPTOR IN AN LHRH NEURONAL CELL LINE (GT1-1).

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Previous studies demonstrated that an excitatory amino acid analog, NMDA, stimulates LHRH secretion in the ovine fetus, prepubertal primate and rat at the hypothalamic level. It is not known if this stimulatory effect of NMDA is mediated directly on the LHRH neurosecretory neuron. A hypothalamic LHRH neuronal cell line (GT1-1) was used to study the effect of NMDA on LHRH release by both superfusion and static incubation with glycine enriched media. Studies with GT1-1 cells indicate that LHRH neurons exhibit spontaneous autorhythmicity and function intrinsically as a neuronal oscillator for the synchronous discharge of LHRH pulses. Superfusion of GT1- cells after a 90 min control period with a 10 min pulse of NMDA (10^{-4}-10^{-2}M) alternating with 10 min of media alone for 90 min increased LHRH pulse amplitude by 35-50% ($p<0.05$) but had no effect on the interpulse interval (≈18 min by "Cluster"). In static incubations, NMDA (10^{-4}-10^{-2}M) increased LHRH release while $5x10^{-2}$M NMDA had no effect. A competitive NMDA antagonist, AP5 (10^{-3}-10^{-2}M) inhibited the action of NMDA. Hybridization analysis of GT1-1 mRNA with an NMDA receptor cDNA showed this cell line expressed NMDA receptor transcripts. The results demonstrate that NMDA stimulates LHRH neurons directly to secrete LHRH through their NMDA receptors by increasing pulse amplitude without affecting pulse frequency. The role, if any, of endogenous excitatory amino acids acting on the NMDA receptor in the control of the onset of puberty remains to be determined.

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AUTOIMMUNITY IN HYPOPITUITARISM

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45 hypopituitary patients (29 M, 16 F) aged 3-22 years were studied for autoimmunity. Serum non-organ-specific antibodies (NOSA-Ab) such as nuclear, DNA, mitochondrial (MA), smooth muscle (SMA), liver/kidney microsomal (LKM), reticulum (RA), ribosomal and organ-specific antibodies (OSA) against pituitary gland, testis, adrenal cortex, ovary, thyroid (thyroglobulin and microsomal), pancreas islet cells, gastric parietal cells (PCA) and intestinal epithelial cells were evaluated. Thyroid antibodies were detected by passive haemagglutination test while indirect immunofluorescence was used for the others. 98 healthy age-sex-matched subjects were used as controls. Magnetic resonance imaging revealed:anterior pituitary hypoplasia, stalk agenesis and ectopic posterior pituitary lobe in 22 patients, 9 with isolated GH deficiency (IGHD) and 13 with multiple pituitary hormone deficiencies; isolated anterior pituitary hypoplasia in 12 IGHD; apparently normal pituitary gland in 11 IGHD.
The frequency of autoantibodies was not significantly different in controls as they were present in 7 patients (15.5%): MA in 1 case, SMA in 2, MA and LKM in 1 and RA in 1; PCA in 1 case and pituitary-Ab in 1 case with normal pituitary gland. Only one female without thyroid-ab developed Graves hyperthyroidism at puberty.
Pituitary insufficiency in our patients seems unlikely to be secondary to an autoimmune process as observed in adults; this suggests that pituitary hypoplasia has a different etiology. Patients with hypopituitarism have not a higher risk of developing autoimmune disease than normal subjects at least during the first two decades; this indicates the presence of normal immune surveillance. The autoimmune involvement of hypothalamus remains to be determined.

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URINARY PROLACTIN: A NEW MARKER FOR THE RENAL PROXIMAL TUBULAR FUNCTION IN CHILDHOOD.

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The role of the kidney in the metabolism of prolactin (PRL) in humans has not yet been established, though previous rat model studies showed a 67 % contribution of kidney to PRL metabolic clearance rate. To investigate whether urinary PRL (u-PRL) represents an index of renal proximal tubular function, a time-resolved fluoro-immuno assay was developed. After dialyzation/concentration of urine samples, recovery rate of added PRL was (M ± SD) 97.0 ± 14.4 %, while intra- and inter-assay variations (CV %) were 4.2 ± 3.4 and 6.1 ± 4.3 %. Lower limit of the assay was 0.25 ng/ml. Immuno cross-reactivity to GH was 0.0032 % at a maximal concentration of 300 ng/ml. Urine samples of 30 normo-prolactinemic subjects (M:9, F:21, age 14.6 ± 5.4 y) with renal disease and associated proteinuria were tested. u-PRL concentration range was 4.2 to 12,824 pg/ml (2.2-17,330 ng/g CR). u-PRL concentrations were significantly correlated with urinary beta-2 microglobulin ($r=0.86$, $p<0.001$), and with serum BUN ($r=0.46$, $p<0.001$). Thus, u-PRL is proved to be an additional index of renal proximal tubular function.

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WHOLE BODY ENERGY EXPENDITURE AND PLASMA CATECHOLAMINE CONCENTRATIONS IN CHILDREN FOLLOWING SEVERE HEAD INJURY.

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Head injury is the most common cause of death and long term morbidity in children over one year of age. Elevated plasma catecholamines (CAs) and subnormal energy expenditures (EE) are associated with poor outcome in critically ill adults but these relationships have not been described in children. 102 measurements of EE and CAs were made serially in 17 severely head injured children aged 2-15 years receiving intensive care. EE was measured using indirect calorimetry and arterial CAs analysed by double-isotope radioenzymatic assay. EE was lower than anticipated for such stressed subjects when compared to normal resting children and varied markedly between and within children (range -40%-+47%, mean -1%). However, CA levels were considerably higher than normal adult reference values. Within each child there was a significant positive correlation between EE and plasma CA concentration ($p<0.01$) but, surprisingly, between children there was a significant negative correlation ($p<0.05$). 2 children who died acutely had subnormal EE and elevated CA levels. CA levels were significantly correlated with Glasgow Coma Score, the most severely injured children having the highest CA levels. Although CAs are major hormonal mediators of EE, we conclude that their effects are reduced in critically injured children. The mechanism and relationship to prognosis require further study.