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MULTIPLE HORMONE RESISTANCE IN PSEUDOHYPOPARATHYROIDISM TYPE 1 (PHP-1). D.Colm Costigan, F.John Holland, Michael A.Levine, Sang Whay Kooh, Donald Fraser Univ of Toronto, Hospital for Sick Children, Toronto and Johns Hopkins Hospital, Dept of Medicine, Baltimore.

PHP-1 can be divided into 2 groups, with either diminished(A) or normal (B) G stimulatory regulatory protein activity(Gs) of the hormone receptor-adenylate cyclase system. In 14 PHP-1 patients (pts), aged 9 mos to 22 yrs we measured erythrocyte Gs protein activity and performed detailed endocrine evaluation for evidence of multiple hormonal dysfunction, as previously shown in PHP-1A adults (Am J Med 1983:74,545). Results: 6 pts had PHP-1A (↓Gs) and all had classical clinical features (Albright's Hered. Osteodyst.-AHO). In this group hypothyroidism was diagnosed in 2 neonates by thyroid screening (↑TSH) and 2 others had low/low N T_4 & ↑TSH but neg. thyroid antibodies. All received L-thyroxine. Two girls had an exaggerated LH response to LHRH (Δmax 74 & 93.4 U/L), the first with delayed puberty and delayed menarche (21 yrs) Three pts, 2 with primary enuresis, had elevated AVP/plasma Osm ratios after water deprivation. Eight pts had PHP-1B, and only 1 had clinical features of AHO. Of 6 pts >11 yrs, 4 males had increased LH reserve (ΔLH 54,59,34.5,85 U/L), but normal pubertal development. 4 pts had elevated AVP/plasma Osm ratio, 1 with primary enuresis. Conclusion: (1) AHO is a good clinical marker for PHP-1A in children (2) in PHP-1A, multiple hormone resistance of variable severity is common, with hypothyroidism, pubertal delay and nocturnal enuresis as presenting clinical features (3) In PHP-1B, evidence of mild hormonal resistance is occasionally present, despite normal erythrocyte Gs protein activity.

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ABNORMALITIES IN GROWTH HORMONE (GH) SECRETION IN CHILDREN WITH TURNER'S SYNDROME (TS), NEUROFIBROMATOSIS (NF), CONGENITAL HEART DISEASE (CHD) AND INTRAUTERINE GROWTH RETARDATION (IUGR). G. Costin, F. Kaufman, T.F. Roe and R. Clemons. Univ. of So. Cal. Sch. of Med., Dept. of Peds., Los Angeles.

Fifteen children with short stature and subnormal growth rate had measurements of GH every ½ hr for 24 hrs followed by a GH stimulation test (table).

Pt/ Sex	CA (yrs)	HA (yrs)	BA (yrs)	Dx	Mean 24 hr GH (M± SE)	Peak GH sleep (ng/ml)	Peak GH stimulated (ng/ml)	SmC (U/ml)	Growth Rate (cm/yr)
1/F	13.9	10.9	13	TS	2.3 ± 0.4	13.1	11.3	1.2	4.6
2/F	11.3	8.9	8.9	TS	2.3 ± 0.3	12.7	10.8	0.6	2.8
3/F	9.0	4.9	7.0	TS	1.7 ± 0.3	14.0	7.4	0.2	4.4
4/F	7.9	5.6	6.9	TS	3.8 ± 1.3	40.0	ND	0.4	1.6
5/F	8.3	5.6	5.9	TS	4.9 ± 0.8	25.2	49.5	1.0	4.7
6/F	10.0	8.3	9.0	NF	2.3 ± 0.3	10.7	18.0	0.8	4.7
7/M	10.9	7.3	9.3	NF	2.6 ± 0.4	15.6	14.9	0.2	4.0
8/M	6.9	3.9	4.6	NF	2.5 ± 0.5	13.6	33.2	0.3	3.1
9/F	9.9	8.3	7.9	NF	3.8 ± 0.8	27.9	21.8	0.7	5.0
10/M	13.6	10.0	12.6	NF	6.3 ± 1.5	48.4	10.8	2.0	6.0
11/F	13.3	6.6	10.0	CHD	2.8 ± 0.4	16.3	15.4	0.4	3.0
12/M	10.6	8.6	7.6	CHD	3.0 ± 0.5	21.0	29.2	0.5	3.0
13/M	6.0	5.0	4.6	CHD	2.9 ± 0.6	26.4	18.0	0.2	3.7
14/F	11.9	6.9	10.0	IUGR	5.7 ± 1.0	28.4	29.6	1.1	5.1
15/M	5.9	2.6	4.9	IUGR	6.3 ± 1.3	34.0	15.3	1.1	3.6

GH secretion was reduced (normal 24 hrs mean GH >3.0ng/ml) in 3/5 pts with TS and NF each and in 3/3 with CHD, and normal in IUGR. The data suggests that GH deficiency and dysregulation in GH secretion is common and may not be recognized by stimulated GH and SmC levels.

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SIMULATION OF THE "ADRENAL EXHAUSTION" PHENOMENON BY icv CRF. John Cunningham, Hans H. Bode, Patricia Meara. Shriners Burns Inst., Mass. Gen. Hospital, Harvard Medical School, Boston, MA.

Intracerebroventricular (icv) bolus injection of corticotropin releasing factor (CRF) induces hypermetabolism, catecholamine surge and excess adrenocortical hormone secretion. Chronic icv CRF infusion in rats induces this stress-like picture for 2-3 days. However, corticosterone (B) excretion falls below that of sham rats by day 5. This dampened response to sustained CRF resembles the "adrenal exhaustion" phenomenon described in severe trauma and led to the present study: Jugular catheters were placed prior to icv cannulation and chronic delivery of CRF 20 ug/d or of saline. Hypersecretion of B on day 2 (0.7 ±0.15 ug/d) in CRF rats was suppressed on day 5 (0.3 ±.05, n=8, p<0.01). A 10 ug iv CRF bolus on day 5 caused exaggerated ACTH coupled with elevated plasma B:

	icv Saline (n=3) ACTH (pg/ml	B (ug/dl)	icv CRF (n=3) ACTH (pg/ml	B (ug/dl)
0 min	360±35	16±8	197±77	13±3
+ 5 min	600±50	28±3	>1000	23±2
+ 10 min	810±100	33±3	>1000	26±2

These results suggest: a suppressed adrenal function induced by chronic icv CRF similar to that after severe trauma and 2) a hypothalamic abnormality rather than primary pituitary or adrenal failure.

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THYROID FUNCTION IN YOUNG DOWN SYNDROME CHILDREN(DS) A.T.Cutler, R.Benezra-Obeiter & S.J.Brink, Harvard Med.Schl & Childrens Hospital, Boston (spon.by H.Levy)

A retrospective review of thyroid function tests(TFT) was done to determine prevalence of thyroid disorders in 49 young DS. 24 males & 25 females from 4 mo to 3 yr were compared to age-matched nonDS randomly selected from those screened for hypothyroidism (hypo) because of developmental delay or FTT. T4 & TSH were measured by standard RIA; antithyroid antibodies(Ab) were measured by hemaglutination. 3 DS had congenital hypothyroidism(CH). Of the 3 CH, 1 had Hirschsprung's & 2 had duodenal atresia. 1 of 49 had acquired hypo with +Ab consistent with thyroiditis. His symptoms corrected with Synthroid. Another DS was hyperthyroid with + Ab. She responded well to PTU. 13 of the remaining 44 DS(27%) had mildly increased TSH(6.6-26.8mIU/ml) & normal T4("compensated hypo"). When these 13 were compared to the DS with normal T4 &TSH, there were no differences in sex, growth, maternal age, associated anomalies, development or specific thyroid symptoms. TSH was higher than controls($t=3.9, p<.001$) for the under 1 y/o DS while there was no difference in T4. Of the 31 with normal TFT, 4/19 retested had normal T4 but elevated TSH. Of the 13 with "compensated hypo" 5/7 retested had normal T4 & TSH. A prevalence (3 of 49) of CH in DS this high or the association of CH & GI anomalies in DS has not been reported. While the 2 DS with acquired thyroid disease had +Ab, the relative lack of thyroiditis was unexpected. Transient TSH elevations were common. Routine thyroid screening is important in DS. A prospective study is needed to elucidate the natural history of thyroid disease in Down Syndrome children.

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THE EFFICACY AND SAFETY OF 1α-ANALOGS OF VITAMIN D IN PSEUDOHYPOPARATHYROIDISM(PHP). Shermine Dabbagh, Russell W. Chesney, Hector F DeLuca and Jacob Lemann Jr., University of Wisconsin, University Hospitals, Madison, WI. and Medical College of Wisconsin, Milwaukee, WI.

PHP is characterized by end-organ resistance to parathyroid hormone (PTH). Of 10 children(5 F:6 M) with PHP and 1 with pseudo-PHP(PPHP). Two had PHP with bone responsive, renal nonresponsive variant (BR,RNR). Age of onset was 5.52±1.67(SE) yr. The disorder was familial in 73%. 82% have Albrights hereditary osteodystrophy (AHO). The 2 with BR,RNR-PHP had elevated alkaline phosphatase levels and hyperparathyroid bony changes on X-ray. PTH was elevated in all 3 pts. hypothyroidism. Calcitriol levels were measured: PPHP (N=1) 34.0 mg/ml vs Classical PHP (N=2) 17.5±1.5 vs PHP-BR,RNR (N=2) 36.0±3.01 ($P<0.05$). Treatment included Vit D_2-3 pts; DHT-4 pts. or calcitriol-4 pts.

	D_2	DHT	Calcitriol
Growth(cm/pt-yr)	6.27±0.36	6.31±0.58	4.79±2.15
Serum Ca at last F/U (mg/dl)	9.02±0.05	8.83±0.26	9.12±0.28
Dose per day	50,000U/d	450 mcg±50	0.55 mcg±0.15
Ca supplementation	-	100%	100%
PO_4 binders	-	67%	40%

Hypercalcemia occurred using D_2 at 1 episode/121 Pt. months. Hypocalcemia occurred at a rate of 1 episode/66 pt.-months with D_2, 1 episode/20 pt.-months with DHT and 1 per 4.5 pt.-months with calcitriol, the latter occurring because of documented non-compliance. The 1α vitamin D metabolites appear to be safe and efficacious in long term therapy.

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EFFECT OF T4 OR T3 ON MATERNAL (M)-FETAL (F) GLUCOSE (GLU)-GLYCOGEN (GLY) METABOLISM. U. Devaskar, J. Church, V. Chechani, F. Sadiq & S. Devaskar. (Spon. by W.J. Keenan). St. Louis Univ. School of Medicine, Cardinal Glennon Children's Hospital, St. Louis, MO.

A potential for T4 or T3 therapy in prevention of IRDS of the newborn has been recently proposed (J.C.I.74,898,1984). We explored the dose-responsiveness of F/M GLU-GLY metabolism to M administration of T4 or T3. T4 (150 or 250μg/kg), T3 (75,125,175 or 225μg/kg) or vehicle were administered IM on d 25 & 26 of pregnancy to rabbit doe. F & M plasma GLU, insulin (I), free T4 (FT4) & T3 concentration, cardiac (Ca) & hepatic (H) GLY content were quantitated on d 27. All data X±SEM (P*<0.05 vs control (c)). n = No. of litters. UD = undetectable.

(n)	FGLU (mg/dl)	FT4 (ng/dl) M	FT4 (ng/dl) F	T3 (ng/ml) M	T3 (ng/ml) F	μmol-GLY-U/gm Ca M	Ca F	H M	H F
C-16	68±5	.7±.2	.1±.05	1.9±.3	.9±.1	3±1	16±2	45±8	28±3
T4150-3	110±8	4±1	1.4±.5	14±2	2±.8	4±.4	3±2	43±5	3±1
T4250-5	120±5	7±1	1.7±.2	17±1	3±.5	3±.4	4±1	45±6	4±1
T375-4	110±3	UD	UD	11±1	2±.2	3±.5	4±1	46±6	9±3
T3125-4	110±9	UD	UD	17±2	3±.4	-	2±.3	30±9	20±2
T3175-6	148±9	UD	UD	30±4	4±.1	3±1	4±.5	13±4	7±1
T3225-3	106±9	UD	UD	58±9	4±.1	5±1	3±2	30±13	11±4

M GLU, M & F I were similar in all groups. Conclusions: 1) T4 or T3 crosses the rabbit placenta from M→F in a dose dependent manner. 2) M T4 or T3 Rx causes F but not M hyperglycemia without change in I 3) T4 or T3 deplete F Ca & H GLY. 4) M H but not Ca GLY is depleted with higher dose of T3.