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MALIGNANT OSTEOPETROSIS(OP): OBSERVATIONS ON THE DISEASE SPECTRUM. BR Blazar, SL Teitelbaum, MD Fallon, AR Kahn, NKC Ramsay, CC Clawson, and DM Brown

From the Dept. of Ped., Univ. of Minn. Hosp., Mpls., MN and the Dept. of Med., the Jewish Hosp. of St. Louis, St. Louis, MO.

7 patients (pts) with OP (4 infants ages 0.3-0.6 yrs and 3 children ages 2.0-3.8 yrs) were studied biochemically and by bone biopsy to correlate laboratory parameters with disease outcome. All pts presented in the first 6 mo of life with optic atrophy, cranial n. dysfunction, respiratory abnormalities, and pallor. Distinguishing features are summarized below:

Clinical:	Infants (N=4)	Children (N=3)
hepatosplenomegaly	massive	mild-moderate
Biochemical:		
serum Ca; Phos.	low (4); low (3)	normal; normal
acid phos. (>30 IU/L)	3 pts	0 pts
Bone Pathology:		
osteoclast number	mod-marked +	normal
osteoid amount	increased	normal
fibrosis	advanced(2); mild(2)	mild

Two infants (with advanced fibrosis) received massive doses (24 ug/d) of 1,25-(OH)₂D₃ for 3 weeks without bone biopsy improvement despite hydroxyprolinuria. Three infants and 1 child underwent bone marrow transplantation. Bony remodeling occurred in 1 infant and 1 child. Of the 2 infants with advanced fibrosis, 1 was evaluable and had engraftment in the nonfibrotic, membranous bone but not in the fibrotic endochondral bone. We conclude that the above parameters may correlate with bone biopsies and that advanced fibrosis may be predictive of resistance to therapies.

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GLYCOGEN SYNTHASE DEFICIENCY: METABOLIC AND TISSUE STUDIES. Rosalind S. Brown, Jean-Pierre Flatt, Thomas B. Miller, Jr., Univ. of Mass. Med. School, Depts. of Pediatrics and Biochemistry, Worcester, MA (Spon. by Philip L. Townes)

Glycogen synthase deficiency is a rare cause of hypoglycemia in childhood. We studied a 17 mo. old male infant whose AM blood glucose (BG) was 18 mg/dl during an evaluation for seizures. Family hx, BW(7 lbs), psychomotor devt. and growth rate were normal (nl). On exam he was 78 cm in length (10%ile) and weighed 10.2 kg (10-25%). Phallus was normal. Liver was not palpable. After an 8 hr. fast BG fell to 28 mg%, cortisol was 43.1 ug/dl, insulin 2 uU/ml, gr. hormone 6.9 ng/ml. Plasma ketones were elevated (80Hbutyrate 1.5mM, acetate .62mM), alanine low (.14mM), lactate nl (1.45mM). Glucagon 1 mg IM did not evoke a rise in BG in the fasted state nor at 5 hrs pc. Two hrs pc, BG rose from 75 to 116mg% and lactate fell from 3.91mM to 1.6mM. Feeding was associated with 1/2 to 3% glycosuria. Liver biopsy performed during constant glucose infusion revealed moderate fatty change and minimal glycogen on EM. Total (T) and active (A) glycogen synthase (nM/min/mg prot were:

	LIVER		GRANULOCYTE		FIBROBLAST
	A	T	A	T	T
Control (n)	.32	2.81(1)	.52±.10	6.50±.3(5)	1.91-3.12(2)
Patient	.06	.11	.63±.19	7.10±1.1	1.43

Phosphorylase was nl. CONCLUSIONS: 1) The metabolic profile is strikingly similar to "ketotic hypoglycemia". Lactic acidemia pc but not fasting and glucose intolerance are important differential features. 2) The defect resides in the enzyme itself rather than in its activating system. 3) Granulocytes and probably fibroblasts do not express the defect.

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INFANTILE PHYTANIC ACID STORAGE DISEASE: A DEFECT IN PHYTANIC ACID OXIDATION. N. Buist, S. Budden, R. Weleber, N. Kennaway, Oregon Health Sci. Univ., Portland, OR; A. Poulos, Adelaide Children's Hosp., Australia.

Refsum's disease is caused by deficient activity of phytanic acid α oxidase; phytanic acid may account for 30% of plasma fatty acids. Four cases of infantile phytanic acid storage disease have been reported. We describe 2 other unrelated infants. Both had very similar Downs-like facies with epicanthal folds, low set ears, large mandible, severe sensorineural deafness, developmental delay, retinopathy with abnormal ERG, hypotonia and hepatomegaly; serum cholesterol was usually low. Case 1 had a subdural hemorrhage at 8 weeks due to vit K deficiency from malabsorption which persisted. Gut biopsy showed villous atrophy without infiltrates. X-rays showed old fractures of 2 metatarsals. In Case 2, liver biopsy showed neutral lipid deposits within hepatocytes; on EM there were scanty crystals adjacent to the lipid deposits. Serum phytanic acid was 1.1-2.4 mg/dl (0.5-1.5% total fatty acid) in Case 1 and 1.2-1.6 mg/dl (1.0-1.5% total fatty acid) in Case 2 (normal: <0.2 mg/dl; <0.5% total fatty acids). Phytanic acid oxidation in cultured skin fibroblasts was 2.3 and 4.5 p mol/h/mg protein in Case 1; 6.7 and 10 p mol/h/mg protein in Case 2 (normal: 23-87 p mol/h/mg protein). The striking physical findings and hypocholesterolemia should suggest this diagnosis. The severity of the disease and minor elevation of phytanic acid compared with classic Refsum's implies that the molecular basis of the two conditions are probably distinct.

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ALTERED GLUCAGON AND PHOSPHOENOLPYRUVATE CARBOXY-KINASE ACTIVITY (PEPCK) IN THE HYPOGLYCEMIC GROWTH RETARDED NEWBORN RAT. Mary Bussey, Sandra Finley, Andrew LaBarbera, Edward Ogata, Northwestern University Medical School, Depts of Pediatrics, OB/Gyn, and Physiology, Chicago.

The role of insulin and glucagon in causing hypoglycemia in the growth retarded neonate is not well-understood. These hormones not only directly regulate glucose availability but also affect enzyme induction. Glucagon induces PEPCK, a key gluconeogenic enzyme, while insulin inhibits its induction. We studied newborn rat pups whose mothers had undergone bilateral uterine artery ligation (L), sham (S), or no surgery (N). L pups were significantly smaller than S and N pups and were hypoglycemic at birth, 20, and 240 minutes but had values comparable to S and N pups at 60 and 120 minutes. L pups had significantly reduced hepatic glycogen concentrations. Plasma insulin was low and did not differ at any time between groups. Glucagon in L pups significantly exceeded S and N values at 20 and 60 minutes (60 min: L 641±106; S 217±31; N 318±28 pg/ml; p <.01). PEPCK increased significantly in S and N but not L pups by 240 minutes (L .14±.03; S .26±.05; N .24±.03 μ moles PEP/g liver/min; p <.01). Glucagon administered to L pups at birth significantly increased PEPCK by 240 minutes. In L pups, hypoglycemia does not exaggerate the normal decrease in insulin. Deficient glycogen is responsible for the initial hypoglycemia while diminished gluconeogenesis due to limited glucagon induction of PEPCK is responsible for the later hypoglycemia. Diminished sensitivity to glucagon may be responsible for delayed PEPCK induction in L pups.

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VITAMIN D DEPENDENT RICKETS TYPE II (DDII) WITH ALOPECIA. TREATMENT WITH MEGA DOSES OF 1,25(OH)₂D₃ OVERCOMES AFFINITY DEFECT IN RECEPTOR FOR 1,25(OH)₂D₃. S. Castells, F. Greig, M. Fusi, L. Finberg, S. Yasumura, U.A. Liberman, C. Ell, and S. Marx, SUNY, Downstate Med. Ctr. Depts. of Ped., Brooklyn, N.Y., N.I.H., Bethesda, Md.

A 1 1/2 yr old hispanic male with alopecia, muscle weakness, inability to stand, severe growth retardation, skeletal deformities and radiological rickets was found to have serum 25(OH)D 26ng/ml (N 8-55), 1,25(OH)₂D 319 pg/ml (N 26-70) and in cultured skin fibroblasts a cytosol binding of 1,25(OH)₂D₃ with a kd of 2.7 nM (N 0.13±0.02) and a binding capacity of 19fmole/mg protein (N 32±2). The abnormal affinity is more significant than the abnormal capacity unlike previous studies of cultured cells of DDII. The *in vitro* data suggest a defect that might be overcome by high levels of calciferols; he was started with a high concentration of 1,25(OH)₂D₃ at 10mcg P.O. twice daily, (5mcg/ml RO-21-5535, Roche Lab.). After 4 m of treat. he was able to walk, to catch up in growth, radiological improvement was apparent, and serum analyses changed from pre to post periods Ca 7.2mg/dl to 8.9, P. 2.2mg/dl to 4.0, Alk. Phosph. 1646 to 961, PTH 122fmole/ml to 27 (N 2-50). Ucamp 4.8nmole/dl of glomerular filtrate to 4.8 (N 3.2±0.82), osteocalcin 18.1ng/ml to 42.0 (N 16-30), 24 hr urinary a.a. were increased before treatment and there was no significant decrease during therapy. Serum 1,25(OH)₂D was >500-pg/ml measured 12 hr after a dose. The results suggest that extremely high doses of 1,25(OH)₂D₃ in this type of DDII produce a satisfactory clinical and biochemical improvement and can be maintained over a prolonged period without evidence of toxicity.

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INSULIN IS A GROWTH-PROMOTING PEPTIDE IN THE RAT BRAIN. DW Clarke, F. Boyd, MS Kappy, MK Raizada, University of Florida College of Medicine, Departments of Pediatrics and Physiology, Gainesville, Florida.

Previous work in this laboratory documented specific insulin binding (IB) in various areas of the developing rat brain (J Neurochem, Jan. 1984, in press). IB was correlated with brain growth and increments in protein content in these areas during the first 21 days of postnatal life, supporting our hypothesis that insulin stimulates brain growth directly.

We recently studied the effect of insulin on protein and nucleic acid synthesis in newborn rat brain glial cells in culture to further substantiate the role of insulin as a growth factor for the brain.

IB to glial cells is rapid, reversible and specific (particularly with respect to insulin-like growth factors which competed only 3% as well as insulin for binding). Insulin stimulated the incorporation of valine into glial cell protein beginning at a concentration of 0.8nM. The stimulation was dose-dependent and became significant at 3.5nM, which was well below the empty site dissociation constant for IB by glial cells. A dose-dependent stimulation of thymidine incorporation into DNA nucleoprotein was also seen, but at higher concentrations of insulin.

The studies document that glial cells have specific receptors for IB. In addition, and of particular importance, glial cells in culture are target cells for insulin with respect to those metabolic processes (i.e. protein and nucleic acid synthesis) which mediate brain growth.