INTELLIGENCE AND RESPONSE TO PHENYLALANINE TOLERANCE TESTS AMONG PARENT CARRIERS OF PHENYLKTONURIC AND HYPERPHENYLALANINEMIC CHILDREN

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Parents of 115 phenylktonuric and hyperphenylalaninemic children were administered a phenylalanine tolerance test, as well as individual intelligence (WAIS) and the Wide Range Achievement test. Canonical correlation and multiple regression analyses indicate that adult carriers' reactions to phenylalanine are significantly associated with mental ability on several verbal and visual motor tasks (R=.732, p=<.025). Parent Full Scale I.Q. scores (as well as scores on certain WAIS subtests such as Arithmetic, Picture Arrangement and Block Design) were inversely related, in general, to the extent to which they had high phenylalanine values during the tolerance test, although all parents were functioning within the normal range of intelligence. Similar statistical analyses with their carrier offspring suggested a similar outcome, although sample size limited the generalizability of these results (N=62). These findings suggest that those biochemical mechanisms associated with phenylalanine metabolism are related to intellectual strengths and weaknesses, even within the normal range of intelligence.

GLUTARIC ACIDEMIA: A NEW DISORDER OF AMINO ACID METABOLISM. Stephen I. Goodman, Paul Moe, and Sanford P. Markey (Intr. by Donough O'Brien). University of Colorado Medical Center, Dept. of Pediatrics, Denver.

Glutaric acid was elevated in plasma (0.1-0.6 mg %;normal=undetected), urine (5 gm/gm creatinine;normal=undetected),and CSF (0.25 mg %;normal=undetected) of two siblings, a 1½ year old girl and a 7½ year old boy. Both have a neurodegenerative disorder characterized by initial normalcy followed by progressive deterioration to opisthotonus and posturing. Recurrent metabolic acidemia was present in the male. One sibling has neither glutaric acidemia nor neurologic dysfunction, and the parents deny consanguinity.

Glutaryl-CoA is an intermediate in the metabolism of L-lysine, L-tryptophan, and hydroxy-L-lysine, being further metabolized through glutaconyl-CoA to crotonyl-CoA. Oral administration of L-lysine augmented the glutaric aciduria;L-valine did not. Decreasing protein intake from 4.1 to 1.6 gm/kg/day decreased glutaric acid excretion from 5 to 2 gm/gm creat. The metabolism of glutaric acid-1,5-^{14}C in peripheral leucocytes and cultured fibroblasts was normal.

If inherited, transmission may be as an autosomal recessive trait; carriers cannot be differentiated easily from controls by lysine loading. It is speculated that (1) the disorder is due to a block at the level of glutaryl-CoA dehydrogenase, and (2) that CNS dysfunction may relate to inhibition by glutaric acid of transport or metabolism of glutamic acid.

INTRAHEPATIC FOCAL BILE STASIS IN 45,X TURNER'S SYNDROME: NEW SYNDROME COMPLEX? Lytt I. Gardner, State University of New York, Upstate Medical Center, Dept. of Ped., Syracuse, N.Y.

Two cases are presented of 45,X Turner's syndrome who also had liver disease characterized by hepatomegaly and intrahepatic focal bile stasis with plugging of bile canaliculi. In one case a diagnosis was made of "neonatal hepatitis", and the infant had a rapid downhill course with death at 10 1/2 months. The other patient is alive at age 18 with chronic hepatomegaly. Liver biopsy in the infant showed portal fibrosis with round cell infiltration. Lobular bile ducts were decreased in number, and many bile canaliculi were plugged with bile. Parenchymal giant cells were seen. In the older child there was hepatic focal bile stasis with bile plugs. Many nuclei showed glycogen vacuolization. Both children had anomalies of the great vessels: the infant an A-V malformation at the bifurcation of the iliacs, and the older girl aortic stenosis and anomalous pulmonary venous return. The hepatic syndrome could be due to a mutant allele on the pairing segment of the X chromosome, thus requiring monosomy X for its expression. Alternate hypotheses are that the hepatic disease is due to a rare X-linked trait, with expression only in monosomy X or XY individuals, or that aneuploidy in general may predispose to the hepatic syndrome (cf. Alpert et al., N.E.J.Med. 280:16, 1969).

THE EFFECT OF PROLONGED INTRAVENOUS THERAPY ON COPPER METABOLISM IN TRICHOPOLIODYSTROPHY. Grover, W.D.* and Scrutton, M.C.*(Intr. by Baird, H.W.) Temple Univ. Sch. of Med. and St. Christopher's Hosp. for Children., Dept. of Ped., Neurol.,and Biochem., Philadelphia,Pennsylvania

Recognition of trichopoliodystrophy (TPD, Menkes Disease, Kinky Hair Syndrome) in two patients (3days,2½mos) permitted the study of the kinetics of Cu metabolism in this disease. I.V. administration of cupric salts in a dosage of 150 mg/kg daily for five days was necessary to achieve normal serum levels. These values were maintained for 5 to 8 days after cessation of therapy. Hepatic Cu levels increased from 14 to 38 ug/g dry wt. and 7 to 45 ug/g dry wt. in the two patients when higher serum levels were obtained. In both patients,the hepatic Cu content remained in the same range with continued therapy. Defective absorption from the gastrointestinal tract was demonstrated by a progressive fall in serum Cu levels from normal values when the older patient received oral Cu acetate 3 mg. per day. Before adequate therapy mitochondria isolated from muscle showed low levels of $C^{14}O_2$ production from C^{14} pyruvate. After serum values increased to normal levels, improved oxidation was demonstrated by muscle homogenate. CSF Cu levels were within normal range and increased 2 to 3 fold after I.V. Cu administration. At 7 months of age the younger infant functions at a 5 month level; the older infant has not improved after therapy for 8 months. Our data suggest that neurologic and biochemical dysfunctions of TPD can be altered by early I.V. administration of cupric salts.

X-LINKED HYPOPHOSPHATEMIA IN Hyp/Y MOUSE. A MODEL OF THE HUMAN DISEASE. F.H.Glorieux,C.R.Scriver,E.M. Eicher,J.L.Southard,R.Travers. MRC Genetics Group, Montreal Children's Hosp. & Shriners Hosp., McGill Univ.,Montreal,Canada;Jackson Lab.,Bar Harbor,Maine.

C57BL/6J Hyp/Y male mice, and X-linked hypophosphatemic human males are dwarfed and have rickets responsive to orthophosphate (Pi). Serum Pi in mature Hyp/Y mice is low (4.6±0.9mg/dl) vs normal +/Y male littermates (7.6±1.0mg/dl, p<0.001). Serum calcium is low normal in Hyp/Y. The renal "excretion index" (mg Pi in urine/mg creat.)/(mg Pi/ml serum) is 103±25 vs 65±16 in +/Y mice (p<0.01). Endogenous kidney cortex Pi is 314µg/g wet wt. in Hyp/Y despite hypophosphatemia, & 307µg/g in +/Y mice. Concentration-dependent uptake of ^{32}Pi into organic and inorganic pools in renal cortex slices is normal in Hyp/Y kidney, under initial-rate and steady-state conditions. The mutant gene product in Hyp/Y is apparently limited to the luminal surface in the kidney tubule since net reabsorption in vivo (luminal membrane) is depressed, while in vitro uptake by slices (basilar membrane) is normal. Preliminary evidence for a luminal membrane defect is also present in Hyp/Y intestine. These findings offer the first in vitro evidence to support the hypothesis that the XLH gene affects Pi luminal back-flux during transepithelial absorption.

NEW VARIANT OF GALACTOSEMIA. Gerhard Hammersen and Harvey L. Levy. State Lab. Inst., Mass. Dept. Public Health, Harvard Med. Sch., and Mass. Gen. Hosp., Dept. of Neuro., Boston.

Several variants of galactose-1-phosphate uridyltransferase (G-1-P UT) are known. We have studied an infant with what is probably a new biochemical variant of galactosemia. He was identified by routine newborn screening at the age of 3 days when he was found to have a slightly increased blood galactose concentration. Unlike "classical" galactosemics, blood galactose in this infant varied from <4 mg/100 ml. to >50 mg/100 ml. on a normal diet. Activity of erythrocyte G-1-P UT was measured at 0.6 U/gm Hgb by UDPG consumption assay at 3 hour incubation. This is within the range of activity found in "classical" galactosemia and is less than corresponding activity in any "Duarte" variant state. However, in contrast to "classical" galactosemia and the "Negro" variant, there was repeatedly moderate activity by the fluorescent spot technique after 16 hours incubation. Additional studies ruled out presence of the "Indiana" variant. By a "milk loading test", this infant accumulated galactose in blood to a peak of >50 mg/100 ml. at 90 minutes but completely cleared galactose from the blood by 180 minutes, in contrast to a "classical" patient who did not clear by 4 hours, to a "Negro" variant patient who "peaked" only to 4 mg/100 ml., and to "Duarte" variant patients who did not accumulate any detectable blood galactose. Galactosemic variants such as this have considerable significance in terms of therapy and subsequent evaluation.