541 INCREASED HEPARIN BINDING IN CYSTIC FIBROSIS: A REFLECTION OF ALTERED GLYCOPROTEIN BIOSYNTHESIS?" Ronald D. Pearson, A. Harold Lubin (Spon. by Stella B. Kontras) Ohio State University, College of Medicine, Children's Hospital, Department of Pediatrics, Columbus Ohio.

Difference between the ability of serum proteins to bind with heparin (heparin binding capacity) in children with cystic fibrosis and in normal individuals was studied in an in vitro system. Results indicate the 'heparin binding capacity' of serum proteins in individuals with cystic fibrosis is significantly increased compared with normal subjects and quantitatively increases with progressing severity of the disease. By weight the combining ratio of protein to heparin is twenty-five per cent (25%) lower in cystic fibrosis affected individuals and is independent of the severity of the disease process. Some of the proteins which bind to heparin were characterized as glycoproteins; those from cystic fibrosis serum were twenty-seven per cent (27%) higher in fucose (methylpentose) content, twenty-seven per cent (27%) lower in sialic acid content, and thirty-one per cent (31%) lower in hexose content when compared to heparin precipitated serum glycoproteins from control subjects. Hexosamine content of the heparin precipitated serum glycoproteins was not altered. The results of the investigation suggest that glycoprotein biosynthesis is altered in cystic fibrosis.

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542 NEURAMINIDASE (NEU) DEFICIENCY IN MUCOLIPIDOSIS II (I-CELL DISEASE; ICD) ESTABLISHED USING 4-METHYLUMBELLIFERYL-α-D-N-ACETYLNEURAMINIC ACID (MU-NAN) AS SUBSTRATE. M. Potier, L. Mameli, L. Dallaire and S.B. Melançon. U. of Montreal, Ste-Justine Hosp.,Sect. of Med. Genet.,Montreal.

ICD is characterized by deficiency of several lysosomal hydrolases in cultured fibroblasts and by higher than normal activities of these enzymes in culture medium and physiological fluids. Deficiency of neuraminidase activity in ICD was suggested by reports of higher than normal amounts of N-acetylneuraminic acid in glycosphingolipids and oligosaccharides excreted in urine or extracted from tissues. We developped a sensitive and simple fluorometric assay of NEU using MU-NAN as substrate and report NEU deficiency in ICD. With MU-NAN, cultured fibroblast NEU showed optimum pH at 4.2-4.4 and apparent Km of 0.13 mM. The NEU activity in cultured fibroblasts from 4 patients with ICD was less than 3% normal (0.35 ± 0.06(S.D.) U/g of protein). In one obligate heterozygote enzyme activity was about 50% of normal (0.21). NEU activity was not detectable in both normal and ICD culture medium although the assay method could detect as little as 0.01 mU of enzyme activity. Other hydrolases did not show such a profound deficiency in both ICD fibroblasts and culture medium and therefore neuraminidase assay was the method of choice for diagnosis of ICD. Preliminary studies indicate that the fluorometric method could also be used for NEU assay in white blood cells and cultured amniotic fluid cells.

543 THIAMINE RESPONSIVE INTERMITTENT BRANCHED-CHAIN KETOACIDURIA. Siegfried M. Pueschel, Michael J. Bresnan, Harvey L. Levy. (Spon. by Robert Schwartz) Brown University, Rhode Island Hospital, Department of Pediatrics Providence; Harvard University, Children's Hospital Medical Center, Department of Neurology and Massachusetts General Hospital, Department of Neurology, Boston.

A 2 1/2-year-old white boy with normal psychomotor development was noted to have intermittent episodes of ataxia, lethargy and vomiting associated with intercurrent illnesses. Initial urine amino acid chromatographic screening revealed a marked increase of leucine, isoleucine and valine suggesting a disturbance in the branched-chain amino acid metabolism.

During subsequent investigations challenge studies with L-leucine (50 mg/kg), once with additional thiamine hydrochloride (10 mg) and once without thiamine hydrochloride indicated that the latter compound enhances the oxidative decarboxylation of the keto acids.

In order to find the most suitable diet for the patient he was given a protein intake that was low (1.5 gm/kg/day), medium (3.0 gm/kg/day) and high (4.5 gm/kg/day) at three separate time periods. Biochemical and clinical parameters revealed that the diets with low and medium protein content were fairly well tolerated; however, while on a high protein diet the patient became symptomatic and a marked increase in branched-chain amino acid was observed.

Enzyme studies revealed 10% of normal branched-chain decarboxylase activity.

544 ARGININOSUCCINIC ACIDURIA: A SURVIVOR OF THE NEONATAL VARIANT. Mary A. Rathbun, Michael F. Bryson, Gary J. Myers & Vivian Shih (Spon. by Gilbert Forbes). Univ. of Rochester Sch. of Med. & Dent., Strong Memorial Hosp., Dept. of Ped., Rochester, N.Y.; Harvard Med. Sch., Mass. Gen. Hosp., Neurol. Service, Boston.

The neonatal form of argininosuccinic aciduria (ASA) is usually fulminating and lethal. J.V. presented at two days of age with this variant and is developmentally normal at four months.

At two days of age, following milk feedings, J.V. became hypothermic and lethargic. He had respiratory alkalosis (ph=7.57), hyperammonemia (771 μg/dl) and ASA. EEG was diffusely abnormal. Family history was negative. Therapy included mechanical ventilation, peritoneal dialysis and gut sterilization. An initial protein free formula was followed by a 1.6 gm protein/kg/d formula at 16 days of age, after his blood ammonia had fallen below 200 μg/dl. Urine quantitation had 328 mg/d of ASA (normal = trace). Skin culture assay for argininosuccinase activity showed J.V. had 0.006 μmoles urea/ mg protein/hr, his parents 0.044 and 0.049, with the control of 0.073.

At four months J.V. has normal blood ammonia (38 μg/dl) on a 1.6 gm protein/kg/d diet. Growth parameters are all at the third percentile. Denver Developmental, neurological, and EEG are all currently normal. ASA should be considered in neonates presenting with signs of sepsis because even the " fulminant " form of the disease may be amenable to aggressive medical therapy.

545 THE CAT AS A MODEL FOR ENZYME THERAPY IN GM_2 GANGLIOSIDOSIS. Mario C. Rattazzi, Children's Hospital of Buffalo, Dept. of Pediatrics, SUNYAB, Buffalo, N.Y.

A genetic neurodegenerative disorder with lysosomal storage of Gm_2 ganglioside, its asialo derivative, and globoside, and β-hexosaminidase deficiency has been described in domestic cats (Cork et al, Science, 1977, in press). To strengthen the apparent analogy with human Gm_2 gangliosidosis type II, feline β-hexosaminidase has been studied. Two major forms of this lysosomal enzyme, Hex A and Hex B, are present in organs and body fluids from normal animals, with biochemical and kinetic properties remarkably similar to those of the corresponding human enzymes. These data, and the deficiency of both components in affected cats, support the analogy between feline and human diseases. Thus it is possible to utilize this animal model for enzyme therapy experiments. Structural differences between human and feline β-hexosaminidase, however, may result in different cellular uptake, endocellular activity and stability, limiting the relevance of replacement experiments with feline enzyme. Thus, plasma clearance and organ disposition of human placental Hex A and Hex B has been studied in normal cats, utilizing the apparent absence of interspecific immunologic cross-reactivity. The results so far indicate a rapid, preferential hepatic uptake, possibly via a saturable receptor mechanism, with recovery of the exogenous enzymes in a lysosomal fraction. Further studies using human enzymes should result in enzyme replacement strategies, to be tested in diseased cats, relevant to therapeutic attempts in human Gm_2 gangliosidosis.

546 A NEWLY DEFINED HYPEROSTOTIC DWARFING SYNDROME. Meinhard Robinow, Ann J. Johanson, Thomas H. Smith. University of Virginia School of Medicine, University Hospital, Departments of Pediatrics and Radiology, Charlottesville, Va.

A distinct dysmorphic dwarfing syndrome has been delineated from studies of a patient observed by the authors and from description of three other cases, previously published under different diagnostic labels. The syndrome combines characteristic congenital malformations, a distinct facies, cutis laxa and mental retardation with failure to thrive, severe growth retardation and a progressive skeletal hyperostosis. Marked elevation of alkaline phosphatase has been the only abnormal laboratory finding. Chromosome studies have been normal. Advanced paternal age suggests an autosomal dominant mutation as the cause.

In the author's case the evolution of the skeletal disorder has been documented by repeated radiographic surveys from soon after birth to age 5 years. The diagnosis of this syndrome can now be made in the neonatal period.