

**535** FALSE POSITIVE DIAGNOSIS OF FETAL METHYLMALONIC ACID-EMIA DURING PREGNANCY WITH AN UNAFFECTED FETUS.

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Intrauterine diagnosis of methylmalonic acidemia (MMA-emia) is possible by examining maternal urine for increased levels of methylmalonic acid (MMA) during the third trimester. The possibility of a false positive diagnosis using this method is suggested by the following report.

A clinically normal woman who had previously produced a daughter with B-12 responsive MMA-emia became pregnant by a second husband. Her urinary excretion of MMA during the 36th week of pregnancy was found to be 43.6 mg per 24 hours, comparable to values reported for women carrying 8-month fetuses with MMA-emia. Thus, she was given B-12, 1 mg IM twice weekly. Her urinary MMA excretion just prior to term delivery was 118.1 mg/24 hours. The serum level was 0.24 mg MMA/ml at 8 months of pregnancy and this value decreased to 0.12 mg/ml after parturition. After delivery MMA excretions in the infant were 0.13 and 0.45 mg per 24 hours on B-12 injections and 3.94 mg/24 hours off B-12; corresponding serum levels were 0.19 mg MMA/ml and 0.35 mg/ml, respectively. The infant is not chemically or clinically homozygous for MMA-emia. The increased maternal excretion of methylmalonic acid near parturition may represent a response to the "stress" of pregnancy. The mother has continued to excrete increased amounts of MMA post partum, and the possibility that she is B-12 deficient is being investigated. These observations document the possibility of an erroneous prenatal diagnosis of MMA-emia in an unaffected fetus.

**536** TYROSINOSIS: METABOLISM OF 15N-TYROSINE, John F. Nicholson, Columbia University, College of Physicians & Surgeons, New York, N.Y.

It has been suggested that urinary p-hydroxyphenylpyruvate in Mades-type tyrosinosis may arise from renal deamination of tyrosine.

Two siblings with tyrosinosis were studied. The proband has tyrosinemia (7-10 x normal), and prominent p-hydroxyphenylpyruvic aciduria. His sister has tyrosinemia (18 x normal) but urinary organic acids are less well characterized. Neither child has hepatic or renal disease or Richner-Hanhart Syndrome.

Both children and a control subject received L-15N tyrosine and D-15N tyrosine orally on separate occasions. Of the 15N excreted as ammonia and urea in 5 hrs after D-tyrosine, 43% and 63% were excreted as ammonia by the affected children, and 48% by the control. After L-tyrosine, 14% and 16% were excreted as ammonia by the tyrosinotic children, and 16% by the control. Since D-amino acids are metabolized only through oxidative deamination, these results show that oxidative deamination of amino acids can be expected to yield urinary ammonia. Failure to find increased 15N-NH3 in the urine of the affected children after L-15N-tyrosine indicates that oxidative deamination of L-tyrosine does not play a quantitatively significant role in the metabolism of tyrosine in these children. Furthermore, kinetic analysis of 15N excretion in these studies does not suggest any qualitative abnormality in the metabolism of the amino nitrogen of tyrosine in the affected children, indicating that their physiologic abnormality is failure of catabolism of the carbon skeleton of tyrosine.

**537** GENETIC APPROACHES TO ATHEROSCLEROSIS IN PEDIATRIC PATIENTS. HYPERLIPOPROTEINEMIAS I. James J. Nora and Robin B. Winkler. University of Colorado School of Medicine, Dept. of Pediatrics, Denver, Colorado.

An approach to detecting genetic predisposition in infants and children to early onset coronary heart disease (CHD) in adult life is through lipid screening and lipoprotein analysis. A study of 200 children independently ascertained and 148 children ascertained through one parent having hyperlipoproteinemia has been conducted and discloses that the lipoprotein phenotypes IIa, IIb and IV are detectable in infancy and childhood. Familial data may be subjected to alternate genetic models to seek best fit: multifactorial inheritance, single gene loci for IIa, IIb and IV, bivariate analysis and multiple alleles.

|        | Parent    |           |           |
|--------|-----------|-----------|-----------|
| Child  | IIa       | IIb       | IV        |
| IIa    | 12        | 4         | 0         |
| IIb    | 1         | 11        | 1         |
| IV     | 0         | 2         | 16        |
| normal | 5         | 35        | 45        |
| Total  | 18 (72%+) | 52 (33%+) | 62 (27%+) |

Lipid and lipoprotein levels of a given individual are best interpreted in the context of family studies. Early identification of the infant or child at risk should include family history of early onset CHD with lipid screening. Those individuals or families suspected from screening procedures as being at risk should be evaluated intensively with the goal of immediate medical modification.

**538** A NEW SYNDROME OF HYPERURICEMIA, PULMONARY FIBROSIS, AND RENAL DISEASE IN A KINDRED. Sheldon Orloff,

Bruce McDonald, Michael Becker, Joseph Weinberg, Anil Mukherjee and Joseph D. Schulman. NICHD, NIH, and National Naval Med. Ctr., Bethesda, MD. and U. C.-San Diego, LaJolla, CA.

A three month old male manifested failure to thrive, neurological dysfunction, moderate renal insufficiency, extreme hyperuricemia (16.5 mg%), and arterial hypoxemia and a radiographic picture compatible with idiopathic pulmonary fibrosis (IPF). A sister had died at age 6 months with IPF proven at autopsy, mild glomerular insufficiency and a disproportionate elevation in serum urate (10.6). There was no parental consanguinity nor positive family history for similar abnormalities. On a purine-free diet and 50 mg allopurinol the proband's serum urate was controlled at 5.5-7 mg%. N-15 uric acid tracer was administered intravenously while continuing allopurinol. Miscible urate pool size was considerably increased (55 mg/kg). Urate turnover was 11 mg/kg/24h; this figure may reflect increased *de novo* purine synthesis but sufficient data on children receiving allopurinol are not available to warrant a firm conclusion. Known enzymatic causes for purine overproduction were excluded since the following activities (nmol/hr/mg prot.) in RBC hemolysates were normal: hypoxanthine-guanine phosphoribosyltransferase, 79-83 (nl. 81±13 S.D.); adenine phosphoribosyltransferase, 18-19 (nl. 21±5); phosphoribosylpyrophosphate synthetase, 84 (nl. 66±18), with normal inhibition by ADP, GDP, and 2,3-diphosphoglycerate. We conclude that the proband and his sister are examples of a previously undescribed disease state, inherited in autosomal recessive manner.

**539** GLUCOSURIA AND UNUSUAL AMINOACIDURIA. Sheldon Orloff, Stephen P. Spielberg, Erlinda Roldan, E. Jean Butler and Joseph D. Schulman. NICHD, NIH, Bethesda, MD.

and Malcolm Grow USAF Med. Center, MD.

The association of glucosuria and aminoaciduria in the absence of other aspects of Fanconi's syndrome is rare. We have studied a kindred in which the proband was an asymptomatic 17 yr. old male referred with glycosuria. He was found to have renal glucosuria, but excretion and tubular reabsorption of phosphate, bicarbonate excretion, concentrating and acidifying ability, GFR, protein excretion, bone radiographs and physical examination were normal. Urinary losses of most neutral and dibasic amino acids were increased 1.5-6 fold generally reflecting an exaggeration of the normal pattern, but of considerable interest are the normal renal clearances and excretions for proline, the dicarboxylic amino acids (glutamate & aspartate), methionine & isoleucine.

|                                    | Mother | Father | Sib. 1 (proband) (age 14) | Sib. 2 (age 9) | Sib. 3 (age 9) |
|------------------------------------|--------|--------|---------------------------|----------------|----------------|
| Aminoaciduria (ion-exchange) Norm. | +++    | ++++   | +++                       | +++            | ++             |
| Glucose, mgm/24h                   | 440    | Norm.  | 4-5000                    | 281            | 162            |

Other proximal tubular functions and GFR were normal in family members. There were fewer abnormally excreted amino acids, and in generally lesser amounts, in father and sibs 2&3 than in the proband. In all siblings, the severity of aminoaciduria correlated with the degree of glucosuria and with age. The association of these abnormalities in this family suggests dominant inheritance of glucosuria from the mother and aminoaciduria from the father.

**540** COEXISTENCE OF  $\beta$ -KETOTHIOLASE DEFICIENCY AND A NEUTRAL AMINO ACID TRANSPORT DEFECT IN TWO SIBLINGS. Elaine F. Otto, James P. Keating and Richard E. Hillman, Washington Univ. Sch. Med., Dept. of Ped., St. Louis Children's Hospital, St. Louis.

A presumptive intrauterine diagnosis of  $\beta$ -ketothiolase deficiency based on decreased ability to oxidize isoleucine by amniotic fluid cells was made in the sib of a known case. The diagnosis has been supported in the infant by studies of his urine metabolites, which show  $\alpha$ -methyl  $\beta$ -OH butyrate,  $\alpha$ -methyl acetoacetate, and tiglic acid. On a low protein diet the child shows few clinical symptoms at six months of age and does not have hyperglycinemia.

We had previously reported that the first sibling's fibroblasts had decreased isoleucine transport and were unable to concentrate isoleucine after several passages in culture. The new infant's cells show a more severe transport defect even in early culture. The transport defect appears to be loss of the high affinity transport system ( $K_m \sim 0.01$  mM) for neutral amino acids seen in normal cell lines. Whether these combined defects represent close linkage of two genes or a secondary transport deficiency due to the biochemical lesion is unclear.

|                        | Isoleucine Uptake (nmoles/mg prot.) |        |
|------------------------|-------------------------------------|--------|
|                        | 1 Min                               | 10 Min |
| Sib #1 (late passage)  | 4.2                                 | 12.8   |
| Sib #2 (early passage) | 2.1                                 | 5.7    |
| Normal                 | 12.2                                | 40.6   |