METABOLIC AND DEGENERATIVE DISORDERS

MOLECULAR BASIS OF METACHROMATIC LEUKODYSTROPHIES

Arylsulfatase A alleles were analyzed in 68 patients with metachromatic leukodystrophy in the Department of Biochemistry II, Georg-August-Universitat Gottingen, Gosslerstr, Gottingen, Germany. Of the 68 patients 50 carried at least one of the two metachromatic leukodystrophy alleles (I or A). Twenty-three patients were homozygous for either allele I or allele A or heterozygous for both alleles. In 18 patients neither allele I nor allele A was found. These two alleles accounted for about half of all arylsulfatase A alleles in this selection of patients. Patients were classified clinically as late infantile, juvenile, or adult forms. All six patients with MCL homozygous for allele I had the late infantile form. Five who were homozygous for allele A had the adult form and three had the juvenile form. Seven with both allele I and allele A had the juvenile onset MCL. The authors conclude that like many lysosomal storage disorders MCL shows clinical heterogeneity that reflects genetic heterogeneity. Allele I is associated with late infantile and more severe disease and allele A occurs with the adult form and juvenile forms of MCL. (Polten A, Gieselmann V et al. Molecular basis of different forms of metachromatic leukodystrophy. N Engl J Med Jan 3, 1991; 324:18-22).

COMMENT. Three forms of metachromatic leukodystrophy are distinguished according to the age of onset: late infantile (1-2 years), juvenile (3-16), and adult (more than 16 years). The incidence is estimated at 1:40,000. These authors describe four genotypes as combinations of two arylsulfatase A alleles that cause MCL and a pseudo deficiency allele. These genotypes are associated with levels of residual arylsulfatase A activity from 0 to 10% and represent the infants and children affected most severely to adults who may be asymptomatic or suffer from a slowly progressive form of MCL. The authors had identified two persons with compound heterozygosity for the pseudo deficiency allele and the MCL allele I. This combination reduces arylsulfatase A to about 10% of normal activity. Both persons were in their third decade of life and were asymptomatic. The most severe type of MCL is associated with homozygosity for allele I. One copy of allele A lessens the severity and produces the juvenile form, and two copies of allele A results in the mildest or adult form of MCL. One copy of arylsulfatase A pseudo deficiency allele permits a normal phenotype. Patients with the juvenile or adult form of MCL were thought to be better candidates for bone marrow transplantation than those with the late infantile form since less enzyme needed to be replaced.

MENKES MAPLE SYRUP URINE DISEASE: TREATMENT

Five patients with maple syrup urine disease were treated intravenously with branched-chain amino acid-free solution of amino acids during nine episodes of acute illness and are reported from the Children's Hospital of Philadelphia, PA. In a regimen of total parenteral

nutrition a 9% branched-chain amino acid-free solution of amino acids reduced plasma leucine levels in acutely ill infants and young children with maple syrup urine disease. The steps in treatment included rapid correction of dehydration or acidosis; recommended dietary allowance of calories; age dependent minimal requirement of amino acids; supplements of isoleucine or valine to prevent deficiency; and treatment of hyperglycemia with insulin. The use of the modified parenteral nutrition was associated with relief from vomiting, improvement in consciousness, and return to the maple syrup urine disease formula. The authors stress the value of this therapy in all acutely ill patients with plasma leucine levels between 1 and 2 mmol per liter who cannot tolerate enteral nutritional therapy. (Berry GT et al. Branched-chain amino acid-free parenteral nutrition in the treatment of acute metabolic decompensation in patients with maple syrup urine disease. N Engl J Med Jan 17, 1991; 324:175-179).

COMMENT. Peritoneal dialysis and hemodialysis have proved effective in the treatment of acute metabolic decompensation in these patients but in those who are not comatose, this form of modified nutritional therapy may be more appropriate. The treatment was thought to lower the plasma leucine levels by favoring the flux of branched-chain amino acids into body protein.

NYSTAGMUS OF PELIZAEUS-MERZBACHER DISEASE

Magnetic search-coil oculography of three brothers, aged 20, 22, and 25, with Pelizaeus-Merzbacher disease (PMD) was used to demonstrate nystagmus not obvious on inspection at the W. K. Kellogg Eye Center, University of Michigan, Ann Arbor, MI. The method disclosed the presence of binocular elliptical pendular nystagmus in two patients and upbeat nystagmus in all three patients. This combination of elliptical pendular and upbeat nystagmus is not described in any other childhood neurodegenerative disease. In conjunction with MRI findings and supportive clinical signs a diagnosis of PMD is strongly indicated. (Trobe JD et al. Nystagmus of Pelizaeus-Merzbacher disease. A magnetic search-coil study. Arch Neurol Jan 1991; 48:87-91).

COMMENT. PMD may be classified by age of onset into a classical infantile type, congenital type, and adult onset type. The classical and congenital forms have X-linked recessive inheritance whereas the adult onset type is autosomal dominant in inheritance. Nystagmus and head tremor are the first signs followed by spasticity, ataxia, choreoathetosis, optic atrophy, and dementia. PMD must be differentiated from congenital nystagmus or spasmus nutans, metachromatic leukodystrophy, adrenoleukodystrophy, Krabbe's disease, and Cockayne's syndrome. The MRI in PMD shows brain atrophy, increased T2 signal in white matter, and decreased signal in basal ganglia and thalami. Pathological correlations of upbeat nystagmus have shown dysmyelination of the pontomedullary tegmentum.