Maple Syrup Urine Disease (Branched-Chain Ketoaciduria)

Maple syrup urine disease (MSUD) (OMIM database No. 248600),[108] also known as branched-chain ketoaciduria, is caused by a deficiency in activity of the branched-chain α-keto acid dehydrogenase (BCKD) complex. Deficiency of the BCKD complex results in accumulation of the branched-chain amino acids (BCAAs) leucine, isoleucine, and valine and the corresponding branched-chain α-keto acids (BCKAs).[109] A pathognomonic finding in individuals with MSUD is the presence of alloisoleucine, a compound that is not present in other individuals. There are 5 phenotypes observed in patients with MSUD: classic, intermediate, intermittent, thiamine-responsive, and dihydrolipoyl dehydrogenase (E3)-deficient. Although enzyme activities overlap to some degree in these phenotypes, in general, lower enzyme activity is associated with a more severe disorder.

Incidence

The worldwide frequency of MSUD (including classic and some variant forms), which is based on routine screening data from 26.8 million newborn infants, is approximately 1 in 185000.[109,110] Newborn screening of 756163 newborn infants over an 8-year period in Georgia revealed a much higher frequency of 1 in 84000.[111] In the population of Mennonites living in Lancaster and Lebanon counties in Pennsylvania, the incidence is 1 in 176 newborn infants, most likely attributable to a founder effect.[112,113]

Clinical Manifestations

Classic MSUD (residual enzyme activity ≤2%) is the most severe and most common form. Affected infants are normal at birth, with symptoms usually developing between 4 and 7 days of age; however, lower intake of protein, as in breastfeeding, can delay the onset of symptoms until the second week of life. Initial symptoms are lethargy and poor sucking with little interest in feeding. Weight loss follows with abnormal neurologic signs (alternating hypertonia and hypotonia; dystonic posturing of the arms) becoming more and more apparent. The characteristic odor of the urine, described as smelling like maple syrup, burnt sugar, or curry, is then noted. Finally, seizures and coma, leading to death (in untreated cases), occurs.[109] Laboratory findings include increased concentrations of BCAAs, ketosis, acidosis, and occasionally hypoglycemia.[114] Patients with intermittent MSUD (enzyme activity 5%–20%) exhibit normal growth and intelligence. These children do not go into metabolic crisis unless the body is in a stressful situation, such as an infection (ie, otitis media) or after surgery.[115] Although patients with intermittent MSUD generally present between 5 months and 2 years of age secondary to a minor infection, some individuals have not shown symptoms until the fifth decade. Concentrations of BCAAs are normal between episodes.

In contrast, patients with intermediate MSUD (enzyme activity 3%–30%) do not present with catastrophic illness during the neonatal period but have gradual neurologic problems, eventually resulting in mental retardation. In one study, most were diagnosed between 5 months and 7 years of age while undergoing evaluation for developmental delay or seizures.[116,117] Several patients have had episodes of ketoacidosis, but acute encephalopathy is rare.[118] Increased concentrations of BCAAs and BCKAs in serum and urine are present. Patients with thiamine-responsive MSUD (enzyme activity 2%–40%) have a clinical course similar to those with intermediate MSUD. These patients have decreased concentrations of BCKAs and/or BCAAs with thiamine therapy in varying dosages ranging from 10 to 1000 mg/day.[119,120] In some instances, the patient does not show the full response to thiamine until therapy has commenced for 3 weeks.[121] In all documented cases, patients required dietary intervention in conjunction with thiamine to achieve metabolic control.[109]

E3-deficient MSUD (E3 deficiency) is rare, with fewer than 20 patients having been described.[109,122,123] Clinically, newborn infants with E3 deficiency are similar to patients with intermediate MSUD, but severe lactic acidosis is also present. The infants develop a persistent lactic acidosis between 8 weeks and 6 months of age followed by progressive neurologic deterioration with hypotonia, developmental delay, and movement disorder. Laboratory findings include mild to moderately increased concentrations of BCAAs and increased lactate, pyruvate, α-ketoglutarate, α-hydroxyisovalerate, and α-hydroxyglutarate concentrations. The patients have a combined deficiency of BCKD, pyruvate, and α-ketoglutarate dehydrogenase complexes, leading to the more complex phenotype. Various combinations of dietary therapy, vitamin therapy (thiamine and biotin), and lipoic acid have been tried without success.[122]

Pathophysiology

The BCKD complex is a macromolecule composed of 3 catalytic components: a thiamine pyrophosphate–dependent decarboxylase (E1) with α and ß subunits, a transacylase (E2), and a dehydrogenase (E3). In addition, the BCKD complex contains 2 regulatory enzymes, a kinase and a phosphatase, that control activity of the complex.[109] The genes encoding E1α, E1ß, E2, E3, and the specific kinase are cloned. Mutations with genotype/phenotype correlations have been described (see "Inheritance" below).

Inheritance

MSUD is an autosomal recessively inherited condition.[109] Mutations in the E1α subunit result in the molecular phenotype referred to as MSUD type IA (OMIM database No. 248600). The type IA mutations almost always result in the severe classic form of MSUD. The most prevalent mutation is Y393N, the mutation in the Mennonite community in Pennsylvania. DNA testing has been developed for the Y393N mutation because of its prevalence.[124] Only a few mutations have been

described in the E1ß subunit (type IB mutations; OMIM database No. 248611), all resulting in the classic neonatal MSUD phenotype. Mutations affecting the E2 core of the BCKD complex (type II MSUD mutations; OMIM database No. 248610) characteristically lead to a milder phenotype than types IA or IB. Most patients have the intermediate or intermittent phenotype, and several have been reported to respond to thiamine therapy. All type III mutations (defects in the E3 subunit; OMIM database No. 238331) lead to a distinct severe combined phenotype (MSUD plus primary lactic acidosis).

Benefits of Newborn Screening

Prognosis is poor for the patient with classic MSUD that goes undiagnosed and untreated, with death versus survival with severe neurologic damage as potential outcomes. Patients with classic MSUD who are not treated by 14 days of age generally have a less desirable outcome. In one study, the outcome with treatment was reported in more than 150 patients with classic MSUD and more than 25 patients with the variant forms.[109,125] Most of these cases were detected by newborn screening or because of clinical presentation. In the patients with classic MSUD, one third had IQ scores higher than 90, and one third had scores between 70 and 90. Rapid recognition and treatment (as with newborn screening) is important. When both performance and verbal scores are available, verbal scores are consistently higher than performance scores.[126] The discrepancy between the 2 scores is not surprising, because cerebellar dysfunction is often an early sign of acute metabolic decompensation. Even with newborn screening leading to timely treatment, outcome is not perfect. Short attention span and minor learning disabilities were observed even in patients with normal intellect who were treated soon after birth.[126]

Screening

State-of-the-art screening for MSUD is by MS/MS. The sum of the 3 isomers (leucine, isoleucine, and alloisoleucine) leads to a distinct diagnostic peak.[109] Classic MSUD, the intermediate form, and E3 deficiency can usually be detected by screening in the newborn period. Intermittent MSUD would not be detected, because the patients' concentrations are normal when they are not in crisis. Thiamine-responsive MSUD has been missed by newborn screening.[110]

Follow-up and Diagnostic Testing

A blood leucine concentration greater than 4 mg/dL, or a concentration of 3 to 4 mg/dL (305 mmol) in the first 24 hours of life, requires immediate medical follow-up.[109] Plasma amino acid analysis reveals findings diagnostic for MSUD: increased concentrations of BCAAs, low alanine concentrations, and the presence of alloisoleucine.

Brief Overview of Disease Management

Treatment consists of a carefully regulated diet that provides sufficient BCAAs for normal growth and development without exceeding the patient's degradative enzyme capacity.[109] Because natural protein must be limited, a medical food product (BCAA-free) supplement is necessary. A metabolic team, including not only a physician metabolic specialist but also a metabolic nutritionist, is crucial. A trial of thiamine supplementation (50–300 mg/day for at least 3 weeks) is recommended, because it is therapeutic for some patients and has no adverse effects. There are 2 aspects of treatment: long-term management and treatment during acute metabolic crisis. The goal of long-term dietary management is normalization of blood BCAA concentrations while providing nutrition adequate to sustain growth and development in children. Dietary therapy should be continued for life.[127] Patients with intermediate MSUD may only require protein restriction without supplementation of synthetic formula. Individuals with intermittent MSUD do not require a special diet except during episodes that may lead to metabolic crisis. Treatment during acute illnesses should be aggressive, because the metabolic decompensation can be life-threatening.[109] Toxic metabolites must be removed at the same time that catabolism is minimized and anabolism is promoted. Dialysis (first peritoneal and, more recently, continuous venovenous hemofiltration) has proven useful in BCAA/BCKA clearance.[128] Dietary treatment to break the cycle of catabolism and promote anabolism sometimes requires parenteral nutrition[129] or insulin combined with a large glucose infusion.[130]

Current Controversies

MSUD has been treated since the early 1960s,[131] and consequently, some neurologically intact MSUD-affected women have reached childbearing age and reproduced. As has been reported for other enzyme deficiencies, postpartum metabolic decompensation can be a problem.[132]

REFERENCES

108. National Center for Biotechnology Information. OMIM: Online Mendelian Inheritance in Man [database]. Available at: www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=OMIM. Accessed March 1, 2006

109. Chuang DT, Shih VE. Maple syrup urine disease (branched-chain ketoaciduria). In: Scriver CR, Beaudet AL, Sly WS, Valle D, eds. *The Metabolic and Molecular Bases of Inherited Disease*. 8th ed. New York, NY: McGraw-Hill; 2001: 1971–2006

110. Naylor EW. Newborn screening for maple syrup urine disease (branched-chain ketoaciduria). In: Bickel H, Guthrie R, Hammersen G, eds. *Neonatal Screening for Inborn Errors of Metabolism*. Berlin, Germany: Springer-Verlag; 1980: 19–28

111. Danner DJ, Elsas LJ II. Disorders of branched chain amino acid and keto acid metabolism. In: Scriver CR, Beaudet AL, Sly WS, Valle D, eds. *The Metabolic Basis of Inherited Disease*. 6th ed. New York, NY: McGraw-Hill; 1989: 671–692

112. Marshall L, DiGeorge A. Maple syrup urine disease in the old order Mennonites [abstract]. *Am J Hum Genet.* 1981;33 :139A

113. Love-Gregory LD, Grasela J, Hillman RE, Phillips CL. Evidence of common ancestry for the maple syrup urine disease (MSUD) Y438N allele in non-Mennonite MSUD patients. *Mol Genet Metab.* 2002;75 :79 – 90[CrossRef][ISI][Medline]

114. Treacy E, Clow CL, Reade TR, Chitayat D, Mamer OA, Scriver CR. Maple syrup urine disease: interrelations between branched-chain amino-, oxo- and hydroxyacids; implications for treatment; associations with CNS dysmyelination. *J Inherit Metab Dis.* 1992;15 :121 – 135[CrossRef][ISI][Medline]

115. Dancis J, Hutzler J, Rokkones T. Intermittent branched-chain ketonuria: variant of maple-syrup-urine disease. *N Engl J Med.* 1967;276 :84 – 89[ISI][Medline]

116. Verdu A, Lopez-Herce J, Pascual-Castroviejo I, Martinez-Bermejo A, Ugarte M, Garcia MJ. Maple syrup urine disease variant form: presentation with psychomotor retardation and CT scan abnormalities. *Acta Paediatr Scand.* 1985;74 :815 –818[ISI][Medline]

117. Rittinger O, Bachmann C, Irnberger T, et al. The intermediate form of maple syrup urine disease [in German]. *Klin Padiatr.* 1986;198 :37 –43[ISI][Medline]

118. Gonzalez-Rios MC, Chuang DT, Cox RP, Schmidt K, Knopf K, Packman S. A distinct variant of intermediate maple syrup urine disease. *Clin Genet.* 1985;27 :153 –159[ISI][Medline]

119. Scriver CR, Mackenzie S, Clow CL, Delvin E. Thiamine-responsive maple-syrup-urine disease. *Lancet.* 1971;1(7694) :310 –312

120. Scriver CR, Clow CL, George H. So-called thiamin-responsive maple syrup urine disease: 15-year follow-up of the original patient. *J Pediatr.* 1985;107 :763 –765[CrossRef][ISI][Medline]

121. Elsas LJ II, Danner DJ. The role of thiamin in maple syrup urine disease. *Ann N Y Acad Sci.* 1982;378 :404 –421[ISI][Medline]

122. Robinson BH, Taylor J, Sherwood WG. Deficiency of dihydrolipoyl dehydrogenase (a component of the pyruvate and alpha-ketoglutarate dehydrogenase complexes): a cause of congenital chronic lactic acidosis in infancy. *Pediatr Res.* 1977;11 :1198 –1202[ISI][Medline]

123. Haworth JC, Perry TL, Blass JP, Hansen S, Urquhart N. Lactic acidosis in three sibs due to defects in both pyruvate dehydrogenase and alpha-ketoglutarate dehydrogenase complexes. *Pediatrics.* 1976;58 :564 –572[Abstract]

124. Love-Gregory LD, Dyer JA, Grasela J, Hillman RE, Phillips CL. Carrier detection and rapid newborn diagnostic test for the common Y393N maple syrup urine disease allele by PCR-RFLP: culturally permissible testing in the Mennonite community. *J Inherit Metab Dis.* 2001;24 :393 –403[CrossRef][ISI][Medline]

125. Yoshino M, Aoki K, Akeda H, et al. Management of acute metabolic decompensation in maple syrup urine disease: a multi-center study. *Pediatr Int.* 1999;41 :132 –137[CrossRef][ISI][Medline]

126. Nord A, Van Doorninck WJ, Greene C. Developmental profile of patients with maple syrup urine disease. *J Inherit Metab Dis.* 1991;14 :881 –889[CrossRef][ISI][Medline]

127. Snyderman SE. Treatment outcome of maple syrup urine disease. *Acta Paediatr Jpn.* 1988;30 :417 –424[Medline]

128. Jouvet P, Poggi F, Rabier D. Continuous venovenous haemodiafiltraion in the acute phase of neonatal maple syrup urine disease. *J Inherit Metab Dis.* 1997;20 :463 –472[CrossRef][ISI][Medline]

129. Berry GT, Heidenreich R, Kaplan P, 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.* 1991;324 :175 –179[ISI][Medline]

130. Wendel U, Langenbeck U, Lombeck I, Bremer HJ. Maple syrup urine disease: therapeutic use of insulin in catabolic states. *Eur J Pediatr.* 1982;139 :172 –175[CrossRef][ISI][Medline]

131. Westall RG. Dietary treatment of a child with maple syrup urine disease (branched-chain ketoaciduria). *Arch Dis Child.* 1963;38 :485 –491[ISI][Medline]

132. Grunewald S, Hinrichs F, Wendel U. Pregnancy in a woman with maple syrup urine disease. *J Inherit Metab Dis.* 1998;21 :89 –94[CrossRef][ISI][Medline]