MAPLE SYRUP URINE DISEASE
(BRANCHED-CHAIN KETOACIDURIA; BRANCHED-CHAIN ALPHA-KETO ACID DEHYDROGENASE DEFICIENCY; MSUD; KETO ACID DECARBOXYLASE DEFICIENCY)

Classification: Organic aciduria

Inheritance: Autosomal recessive

Population Incidence: Worldwide frequency is 1:185,000 births

Ethnic Incidence: Old Order Mennonite frequency is 1:176 births
Ashkenazi Jews 1:113 births
Increased incidence among the aboriginal tribes in Taiwan.

Gene & Location: E1α– located on 19q13.1-q13.2
E1β– located on 6p21-p22
E2- located on 1p31
E3- located on 7q31-q32

Common Mutation: More than 63 mutations in all four genes
Mennonite population has a common mutation of the Type IA phenotype- Y393N–α
Ashkenazi Jewish common mutation- R183P-E1β
Austronesian tribes with a common E2 gene 4.7kb deletion
Founder mutation among Filipino population- E2 gene deletion

OMIM #: *248600; *248611; *248610; *246900

Symptom Onset: Variable onset, usually by 2 years of age.
Neonatal classic disease onset is most severe and most common.

Symptoms: Infants appear normal at birth and develop symptoms between 4-7 days of life. Lethargy and poor suck are first signs followed by alternating hyper and hypotonia, irritability and dystonia. Progress to severe ketoacidosis, hyperammonemia, with seizures and coma leading to death if untreated. Hypoglycemia is not a prominent feature. Pseudotumor cerebri is occasionally observed. Infants with milder forms may only present with episodic acidosis during intercurrent illnesses or other stressors.

Physical Findings: No particular dysmorphisms do have prominent neurological findings when ill. Cerumen, urine or sweat may smell faintly of maple syrup.
Treatment: Dietary management with decreased leucine in diet and limited isoleucine and valine. Aggressive management of acute metabolic events

Natural History without treatment: The classic form progresses to coma and death if untreated. The intermediate form develops neurological damage and bouts of metabolic decompensation. The intermittent form has normal development with intermittent episodes of metabolic decompensation. Even without metabolic decompensation, chronic high levels of BCAA has been shown to cause demyelination.

Natural History with treatment: Age of diagnosis and metabolic control are the most important determinants of long-term outcome. Patients with classical disease started on treatment after 14 days of life rarely achieve normal intellect. Early treatment has improved outcome, but there can be complications. Even with treatment some have died from brain edema. Depending on severity of metabolic events, neurological outcome varies.

Missing Enzyme & Location: Branched-chain alpha-keto acid dehydrogenase is a multi-enzyme complex loosely associated with the inner membrane of the mitochondria- responsible for the breakdown of the branched chain amino acids.

MS/MS profile: Leucine- elevated
Leucine to alanine ratio – elevated.

Prenatal testing: Prenatal diagnosis is possible by enzyme assay or if mutations known can do molecular diagnosis

Miscellaneous Information: E3 gene deficiency causes a defect in dihydrolipoyl dehydrogenase with resultant defects in branched chain metabolism, pyruvate dehydrogenase and alpha ketoglutarate dehydrogenase and typically a more severe, progressive course and later onset of symptoms.

Prepared for the NW Regional Newborn Screening Program by Sara Copeland MD, Judith Tuerck RN MS and Lorinda Paradise at OHSU in Portland, OR.

References:


38. OMIM- Online Mendelian Inheritance in Man; MAPLE SYRUP URINE DISEASE, TYPE IA-*248600.

39. OMIM- Online Mendelian Inheritance in Man; MAPLE SYRUP URINE DISEASE, TYPE IB-*248611.

40. OMIM- Online Mendelian Inheritance in Man; MAPLE SYRUP URINE DISEASE, TYPE II- *248610.

41. OMIM- Online Mendelian Inheritance in Man; LIPOAMIDE DEHYDROGENASE DEFICIENCY, LACTIC ACIDOSIS DUE TO- *246900.


