AMINO ACID DISORDERS

Maple Syrup Urine Disease (MSUD)

What is Maple syrup urine disease (MSUD)?

Maple syrup urine disease (MSUD) is due to a defect or deficiency of the branched chain keto acid dehydrogenase complex in which elevated quantities of leucine, isoleucine, valine, and their corresponding oxoacids accumulate in body fluids.[1]

CLINICAL MANIFESTATIONS

Infants with MSUD appear normal at birth.[2] There are different classifications of MSUD based on the enzyme activity and these include: classical, intermediate, intermittent, thiamine response, and E-3 deficient MSUD. Classical MSUD (residual enzyme <2%) is the most severe and common form with symptoms of poor suck, lethargy, hypo and hypertonia, opisthotonic posturing, seizures, and coma developing 4-7 days after birth.[3] The characteristic odor of maple syrup may be detected as soon as neurological symptoms develop.[2] Intermediate MSUD (residual enzyme 3-30%) have gradual neurologic problems resulting in mental retardation.[3] Intermittent form of MSUD go into metabolic crisis when there is a stressful situation such as an infection or after surgery.[2,3] Thiamine-responsive MSUD's clinical symptomatology and metabolic disturbance is ameliorated once pharmacologic dose of thiamine has been given.[3] E-3 deficient MSUD present with symptoms similar to those with intermediate MSUD but also have lactic acidosis.[2,3]

PATHOPHYSIOLOGY

Due to a mutation of the branched chain keto acid dehydrogenase enzyme, the levels of leucine, valine, and isoleucine increase in blood. The increase in leucine may cause competitive inhibition with other precursors of neurotransmitters causing the neurologic manifestations.[2]

Inheritance: autosomal recessive[2,3]

CONFIRMATORY TESTING

Plasma amino acids (leucine, isoleucine, valine, allo-isoleucine) and urine organic acids (alpha-ketoacids). Further confirmatory testing may be required after referral to a metabolic specialist.

Overview of Disease Management

Long term treatment of MSUD is based on dietary restriction of branched-chain amino acids and supplementation of thiamine if proven beneficial; valine and isoleucine supplementation is also recommended.[1,2,3] Frequent determination of leucine levels are likewise encouraged so that proper dietary adjustments be done for effective management of the condition.[5] Initiation of management should be done in consultation with an attending physician/ metabolic specialist.

Prognosis

Children with the classical form of MSUD have only a satisfactory prognosis if they are diagnosed and treated early.[3]

Preliminary / Initial Management During Metabolic Crisis

Metabolic crises may be caused by illness, prolonged fasting or stressful situations such as surgery and severe infection. The goal of treatment is to reverse the catabolic state, correct the acidosis, and prevent essential amino acid deficiency.

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WHAT TO DO

If unwell and cannot tolerate oral intake:

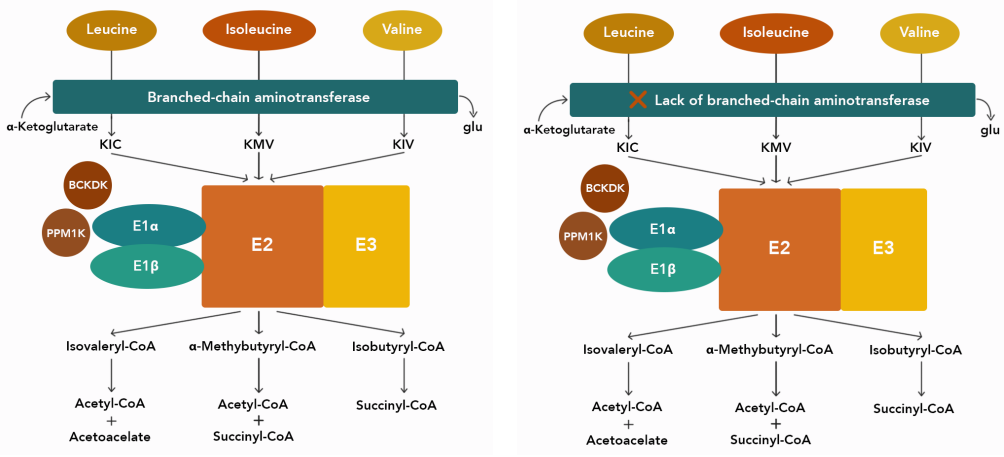
- Nothing per orem except medications
- Ensure patient's airway is secure
- Insert IV access. Collect samples for plasma amino acids, dried blood spot (for leucine levels), blood glucose and urine ketones. May request for investigations (i.e. CBC, blood gas, etc.) as needed.
- May give fluid boluses if the patient requires it.
- Start D12.5% 0.3NaCl at full maintenance. Assess the patient and clinically, if there is need to increase fluid, may do so up to 1.2 or 1.5x the maintenance.
- Start intralipid at 1g/kg/24 hours.
- Give valine (30-50mg/kg/day) in 6 divided doses
- Give isoleucine (20mg/kg/day) in 6 divided doses
- Monitor input and output strictly (q6 hours).

If unwell and can tolerate oral intake:

- Insert oro- or nasogatric tube and start continuous feeding with BCAD milk formula or protein free formula at maintenance rate
- Give valine (30-50mg/kg/day) in 6 divided doses
- Give isoleucine (20mg/kg/day) in 6 divided doses
- Insert IV access. Collect samples for plasma amino acids, dried blood spot (for leucine levels), blood glucose and urine ketones. May request for investigations (i.e. CBC, blood gas, etc.) as needed.
- Start D12.5% 0.3NaCl at 5-10 cc/hr
- Monitor input and output strictly (q6 hours)

**Children should not be protein restricted for longer than necessary (24-48 hours)*
**If the patient does not improve with the initial management (within 12 hours), hemodialysis may be indicated. Monitor the patient clinically, the necessity of hemodialysis will depend on the patient's clinical status.*
**Inform the metabolic doctor on call for further guidance regarding on-going management*
**If the patient is well, coordinate with a metabolic specialist regarding further management.*

Normal break-down of protein vs MSUD patient's breakdown of protein



[1] *Nyhan WL, Barshop BA and Ozand P. Chapter 24 Maple syrup urine disease. Atlas of Metabolic Diseases 2nd ed. Great Britain:Oxford University Press, 2005 pp 159-164.*
[2] *Schulze A, Matern D, Hoffmann GF. Chapter 2: Newborn screening in Sarafoglou K, Hoffman GF and Roth KS (eds). Pediatric Endocrinology and Inborn Errors of Metabolism. New York:McGraw Hill, 2009 pp 17-32.*
[3] *Hoffman GF and Schulze A. Chapter 7: Organic Acidurias in Sarafoglou K, Hoffman GF and Roth KS (eds). Pediatric Endocrinology and Inborn Errors of Metabolism. New York:McGraw Hill, 2009 pp 93-94.*