UREA CYCLE DEFECTS (UCD)

What are Urea Cycle Defects?

The urea cycle is the main pathway of the body to dispose of excess nitrogen. It allows for the conversion of ammonia into urea that can be excreted into the urine. Citrullinemia and Argininosuccinic Aciduria are inherited in an autosomal recessive manner. Citrullinemia occurs as a result of argininosuccinic synthase deficiency while argininosuccinic aciduria is due to a deficiency of argininosuccinic lyase. Both conditions may manifest with tachypnea, lethargy, vomiting, irritability, seizures, coma and ultimately death if left untreated. The increased levels of ammonia may cause brain damage.

Due to blocks in the urea cycle owing to the enzyme deficiency, patients with UCD have low levels of arginine. This makes arginine an essential amino acid among patients with UCD.

Urea Cycle Defects include:

- Citrullinemia (CIT)
- Argininosuccinic Aciduria (ASA)

Urea Cycle Defects	Confirmatory Testing
Citrullinemia (CIT)	Plasma amino acids and urine organic acids
Argininosuccinic Aciduria (ASA)	Plasma amino acids and urine organic acids

Further confirmatory testing may be required after referral to a metabolic specialist.

Treatment of Urea Cycle Defects

Treatment is through the dietary restriction of protein and the supplementation of a protein free formula. Sodium benzoate, an ammonia scavenger, is given as well as arginine supplementation.

Preliminary / Initial Management During Metabolic Crisis

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

UREA CYCLE DEFECTS (UCD)

Argininosuccinic aciduria (ASA)

What is Argininosuccinic aciduria (ASA)?

Argininosuccinic aciduria is an inborn error of metabolism resulting from the deficiency of the enzyme argininosuccinic lyase.[1]

CLINICAL MANIFESTATIONS

The classic presentation of argininosuccinic aciduria is an overwhelming illness in the newborn period presenting with vomiting, lethargy progressing rapidly to deep coma, apnea, seizures and death. Patients may also have hair abnormalities (trichorrhexis nodosa).[1-2]

PATHOPHYSIOLOGY

Argininosuccinate lyase is an enzyme that converts argininosuccinic acid to arginine, the absence of which causes an increase in argininosuccinic acid, citrulline and ammonia.[2]

Inheritance: autosomal recessive

CONFIRMATORY TESTING

Plasma acylcarnitine and urine amino acid (high-voltage electrophoresis). Further confirmatory testing may be required after referral to a metabolic specialist.

Overview of Disease Management

Long-term management, as with other urea cycle disorders, consists of a low protein diet supplemented with special milk formula, provision of 250 mg/kg/day in divided doses of arginine and 250 mg/kg/day in divided doses of sodium benzoate. Initiation of management should be done in consultation with an attending physician/ metabolic specialist.

Prognosis

Prognosis for intellectual development probably depends on the nature of the initial hyperammoniemia, especially in duration or the nature of recurrent episodes.[2]

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.

UREA CYCLE DEFECTS (UCD)

Argininosuccinic aciduria (ASA)

WHAT TO DO

If unwell and cannot tolerate oral intake:

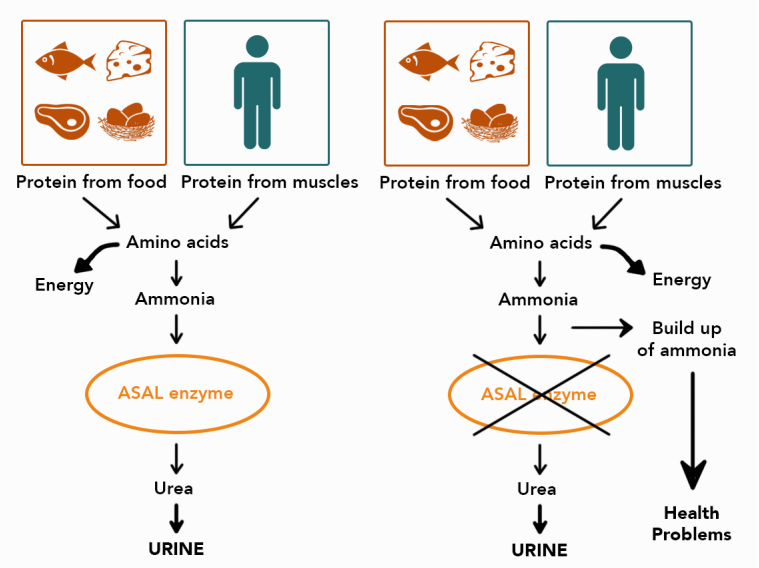
- Nothing per orem
- Ensure patient's airway is secure
- Insert IV access. Collect sample for serum ammonia. May request for investigations (i.e. CBC, etc.) as needed.
- May give fluid boluses if the patient requires it.
- Start D12.5% 0.3NaCl at full maintenance. Assess the patient and clinically, if there is need to increase fluid, may do so up to 1.2 or 1.5x the maintenance.
- Start IV sodium benzoate loading dose (250mg/kg) to run for 1-2 hours.
- Start IV arginine loading dose (250mg/kg) to run for 1-2 hours.
- Monitor input and output strictly (q6 hours)

If unwell and can tolerate oral intake:

- Insert oro- or nasogatric tube and start continuous feeding with protein free formula at maintenance rate
- Insert IV access. Collect sample for serum ammonia. May request for investigations (i.e. CBC, etc.) as needed.
- Start D12.5% 0.3NaCl at 5-10 cc/hr.
- Start IV sodium benzoate loading dose (250mg/kg) to run for 1-2 hours.
- Start IV arginine loading dose (250mg/kg) to run for 1-2 hours.
- 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 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 breakdown of protein vs Arginiosuccinic Aciduria patient's breakdown of protein



[1] *Zchocke J and Hoffmann GF, Vademecum Metabolicu, 3rd ed., Germany:Milupa Metabolics, 2011*
[2] *Nyhan WL, Barshop BA and Al-Aqeel A. Chapter 27: Argininosuccinic aciduria. Atlas of Inherited Metabolic Diseases 3rd ed. Great Britain:Oxford University Press, 2012 pp216-222*