

# **EMERGENCY PROTOCOL UREA CYCLE DISORDERS ARGINASE DEFICIENCY**

## **INTRODUCTION**

This protocol is for patients with Arginase deficiency presenting to the emergency department with illness or hyperammonemia. Arginase is one of the five enzymes of the urea cycle associated with a known clinical disorder (collectively known as the Urea Cycle disorders (UCDs)).

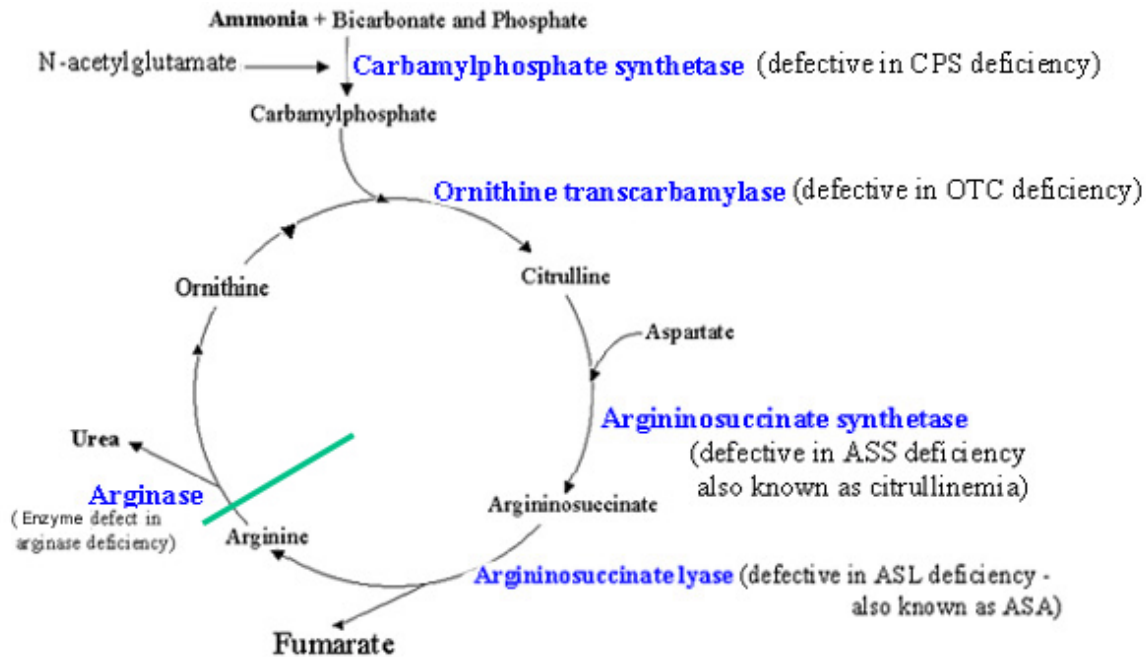
Though hyperammonemic crises is less common in arginase deficiency than the other urea cycle defects it does occur in patients ranging from infancy to adulthood and may be secondary to an intercurrent illness, possibly subclinical in presentation. Incipient or frank hyperammonemia may present with anorexia, nausea or vomiting. Lethargy often suggests progressive accumulation of ammonia. Arginase deficiency has also been reported in the newborn and can be devastating despite a less severe degree of hyperammonemia than seen in other neonatal urea cycle defects.

## **PATHOPHYSIOLOGY**

Arginase deficiency usually presents with developmental delay and progressive neurologic features in later childhood. The Arginase isoenzyme associated with the arginase deficiency phenotype, Arginase A1, is cytosolic in location and is found primarily in hepatocytes (the site of activity) as well as red blood cells (utilized for diagnostic assay)

Unlike fats and carbohydrates, the body does not store protein. An excess of protein leads to an excess of liberated nitrogen from the amino acids of protein with a consequent excess of ammonia ( $\text{NH}_3$ ). This additional  $\text{NH}_3$  cannot be metabolized by a defective urea cycle, so the ammonia accumulates. In general, protein overload comes from two sources –

1. Dietary protein intake beyond what is needed for tissue formation and replacement.
2. Any catabolic process, e.g. stresses of the newborn period, infection, dehydration etc...



Characteristically, the amino acid glutamine (containing two nitrogenous moieties and therefore a temporary “repository” for ammonia) accumulates in excessive quantities in affected, untreated individuals. Alanine is also elevated in plasma sampling. Amino acid abnormalities usually precede hyperammonemia and the onset of symptoms.

### Acute management of arginase deficiency

**Plasma ammonia** levels (direct index of toxicity, important for acute management).  
1.5 ml blood in sodium-heparin tube (green top tube).

**Plasma amino acids** (glutamine, as an ammonia buffer, reflects direction of control of hyperammonemia, should be checked daily). Require 2 ml blood in green or red top tube.

**Urinalysis**, assessing ketonuria.

**Liver function tests** (specifically transaminases, bilirubin, albumin, PT and PTT)

**Blood gases, lytes+CO<sub>2</sub>**: Alkalosis (associated with respiratory stimulation by the hyperammonemia). Alkalosis is more common than acidosis (as opposed to organic acidemias) but, acidosis can occur, anion gap typically < 20 (but again not always), normal glucose, low ketones more indicative of UCD.

**BUN**: often low but not always, is neither sensitive nor specific for UCDs.

**Newborn screening blood sample**. In neonate carry out at 24 hours of age and call screening lab to track and report results as soon as possible. Though extremely rare arginase deficiency will be picked up in the neonatal variant of arginase deficiency.

### RISING BLOOD AMMONIA

Specimens must be placed immediately on ice and walked to the laboratory. The most common reason for a (mild) elevation in blood ammonia is a delay in this process, necessitating the (unfortunate) drawing of another sample.

### **THE DEFINITIVE DIAGNOSIS**

If there is uncertainty about the diagnosis, **arginase** can be assayed via red blood cell assay (through the laboratory of Dr. Vivian Shih at the MGH; tel. 617-726 3884/5.)

Differential diagnosis of other metabolic disorders will be assisted by carrying out the **above** tests **PLUS**, assays in the ACUTELY ill child for

- Urinary organic acids/orotic acid/amino acids/acylglycines
- Plasma citrulline/carnitine/acyl carnitines/lactate/pyruvate and where indicated
- CSF Amino acids/lytes/glucose/lactate/pyruvate

The results of these tests will help to direct the differential diagnosis

### **THERAPY**

A child with arginase deficiency, either at high risk for metabolically decompensating (acutely ill), or currently hyperammonemic should be treated aggressively. The rationale of treatment includes –

1. Minimize protein intake.
2. Reverse or minimize catabolism.
3. Promote waste nitrogen excretion.

#### **1. MINIMIZE PROTEIN INTAKE**

The caloric intake on day 1 is provided by intravenous dextrose and supplemented with Intralipid to provide 120-130 kcal/kg/day. Protein intake commences after 24 hours at 0.6 grams/kg/day, administered as essential amino acids. On day 2, 1.2 grams/kg/day should be supplied, half in the form of essential amino acids, the other half in the form of a natural protein source (avoid elemental formulas in infants as they are high in nitrogen content). Supplemental calories are added from a non-nitrogenous formula with vitamins and minerals (Mead-Johnson 80056 formula, Ross formula Prophee or equivalent). Water is then added to dilute to the proper concentration. Thereafter, the protein intake is increased gradually in 0.25 – 0.5 gram/kg increments per day to a maximum of 2 grams /kg/day.

Enteral feeds should be started as soon as practical, and may even occur concomitant with IV via NG or NJ tube if necessary. Essential amino acids should not be withheld > 24 hours, to avoid catabolic breakdown of endogenous proteins. To avoid excess amino acid load aim for 1.0 - 1.5g protein/kg body weight (50% as essential amino acids). Contact the metabolic nutritionist (and discuss with the parent) before starting oral diet such as Mead Johnson 80056 or Ross ProPhree.

Once patient stabilized, feedings established and the ammonia not fluctuating may switch to oral UCD medications.

## 2. REVERSE OR MINIMIZE CATABOLISM

The caloric intake for these infants should run at least 120-130 kcal/g/day. Accurate records of intake and output should be kept to monitor hydration. Infection as a potential but severe catabolic stressor should be considered early (when clinical signs are apparent) and managed vigorously. Avoid valproic acid, as it decreases urea cycle function and accentuates hyperammonemia.

## 3. PROMOTE WASTE NITROGEN EXCRETION

To help facilitate the excretion of waste nitrogen, the following medications are employed.

- (i) Sodium benzoate – conjugates with glycine to form hippuric acid, which bypasses the urea cycle and is excreted in urine.
- (ii) Sodium phenylacetate – conjugates with glutamine to form phenylacetylglutamine, which bypasses the urea cycle and is excreted in the urine.

Avoid carnitine, not shown to be helpful. Although UCD infants are often low in carnitine, it is known to conjugate with sodium benzoate

If an IV is required, that solution should NOT contain sodium

## **MANAGEMENT OF PROGRESSIVE HYPERAMMONEMIA**

If the blood ammonia is > 100 – 125 ug/dl, repeat the level. If confirmed:

- discontinue oral feedings and oral medications
- administer a 10% (or higher) glucose solution and Intralipid.
- administer the urea cycle medications as an IV bolus.
- in neonate insert umbilical lines for potential dialysis (7Fr or larger)

Sodium benzoate (250 mg/kg/day)

Sodium phenylacetate (250 mg/kg/day)

Mix this in 35 cc/kg of 10% dextrose (no sodium) and run as a bolus over 90 minutes. This is then followed by the same solution administered as a 24 hour infusion.

These infusions should begin regardless of the amount of medication already provided. Monitor ammonia levels every 4 hours, amino acids daily. Electrolytes, acid-base status

and the anion gap should be monitored regularly. If another IV is required, that solution should not contain sodium.

It is helpful when giving the bolus to also provide an antiemetic such as ondansetron (0.15mg/kg, up to 8 hourly PRN)

Glucose levels should be kept between 120-170 mg/dl. If necessary for control of hyperglycemia can use insulin (remains controversial) bearing in mind that wide swings in glucose levels affect brain osmolarity.

Cerebral edema; Oncotic agents such as albumin will increase the overall nitrogen load but may in selected cases be considered. Mannitol has not been found to be helpful for edema secondary to hyperammonemia and steroids should not be used. Hyperventilation, under close control by the neonatologist, is recommended.

### **Potential side effects of sodium benzoate/phenylacetate regime**

Increased incidence of nausea and vomiting with bolus.

Overdoses (3-5x recommended dose) can lead to symptoms reminiscent of hyperammonemia, specifically agitation, confusion and hyperventilation. Death has occurred (associated with cerebral edema, hypotension and cardiovascular collapse).

#### If the ammonia continues to rise >200-250 µg/dl

Suggest transfer to PICU with metabolic and hemodialysis facilities and alert pediatric nephrology team.

If dialysis is not immediately available, give a loading dose of sodium benzoate/phenylacetate, to slightly retard ammonia rise and in anticipation of dialysis ASAP.

#### If the ammonia continues to rise >300 µg/dl

#### CONSIDER DIALYSIS

Dialysis will clear ammonia at :-

170-200ml/min for ECMO based dialysis. Osmotic shifts have NOT been observed with this rapid rate of clearance. Additionally a hemofilter in the circuit will continue to remove ammonia between dialysis cycles.

10-30 ml/min hemodialysis

3-5 ml/min peritoneal dialysis (this rate will however take several days to significantly reduce the ammonia load, at a time when brain damage is related to duration of hyperammonemia toxicity)

Adapted from

Proceedings of a consensus conference for the management of patients with Urea Cycle disorders. J Peds. Suppl. Vol. 138 (1), 2001

Any questions about the patient or this protocol, please call or have paged the Genetics/Metabolism Fellow-on-call or, failing this, the Metabolic attending on call at your hospital or nearest pediatric tertiary care center.