

CLINICAL VIGNETTE

A RARE CAUSE OF ALTERED MENTAL STATUS

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A 29-year-old male was brought into the emergency department with an altered level of consciousness that began acutely 6-hours prior to presentation. His family reported he was unable to remember or state his name, perform simple tasks such as video games, use the TV remote and perform simple mathematical calculations. He had been wandering aimlessly at home unable to relax. There was no fever, coughing, nausea, vomiting, head injury or other trauma. Patient's past medical history is significant for carbamoyl phosphate synthetase deficiency (CPSD). Patient's outpatient medications included citrulline and sodium phenylbutyrate.

His presenting vital signs were as follows: 140/103 125 99.2 F 20 99%

His physical exam was essentially benign except for the neurologic exam. He was alert but oriented to name only. His mini-mental status exam was 10/30. There were no motor or sensory deficits. He did have asterixis on exam.

Blood work including CBC, comprehensive metabolic panel and urinalysis were all within normal limits. However, ammonia level was extremely elevated at 320 mcmol/L. Head CT scan was negative for cerebral edema.

After consultation with a Clinical Geneticist, the patient was started on a treatment protocol that included:

1. D10 NS infusion at 100cc/hr
2. Ammonul infusion to deliver 10 grams each of sodium benzoate and sodium phenylacetate over 24 hrs continuously via peripheral line
3. L-arginine infusion to administer 5 grams over 24 hours via peripheral line

The patient was admitted to the intensive care unit and started on an insulin infusion to manage hyperglycemia from the dextrose infusion. Within 36 hours of admission, his ammonia levels normalized and his mental status returned to baseline. He was

discharged with a strict low protein diet of 55 grams per day.

Carbamoyl Phosphate Synthetase Deficiency (CPSD) Discussion

CPSD like other urea-cycle disorders are inborn errors of metabolism that result in high levels of ammonia from complete or partial inactivation of important enzymes needed to remove nitrogenous waste. These disorders have a high mortality rate and survivors frequently have neurologic damage¹. Severe deficiencies can present in the neonatal period with altered mental status and seizures after beginning feeding². Partial CPSD deficiency may present later in life with seizures, episodic confusion and stroke-like symptoms³. Most adults with this disorder develop symptomatic hyperammonemia when precipitated by stressors such high protein load, illness and pregnancy⁴. Metabolism of ammonia to urea occurs in the liver through the urea cycle (figure 1).

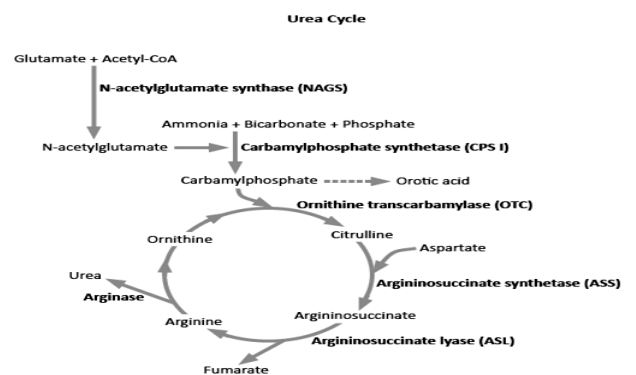


Figure 1

As depicted above, carbamoyl phosphate synthetase is involved with the incorporation of bicarbonate and ammonia into carbamyl phosphate. The nitrogen component of ammonia is then transferred to ornithine catalyzed by ornithine transcarbamylase⁵.

Inactivation of important enzymes, lead to high levels of ammonia leading to a variety of symptoms. Urea cycle disorders have a reported incidence of 1 in 25,000–30,000 cases⁶

The most important course of action in patients presenting with hyperammonemia is removal of excess ammonia to prevent cerebral edema. In the absence of liver metabolism of ammonia, astrocytes rapidly convert ammonia to glutamine, which leads to increased intracellular osmolarity. Cerebral blood flow increases and there is loss of autoregulation resulting in cerebral edema. These changes are seen with arterial ammonia levels > 200 $\mu\text{mol/L}$ ⁷.

Emergent management of this disorder is directed at elimination of hyperammonemia using parenteral infusions of sodium benzoate, sodium phenylacetate and L-arginine. These decrease the total body load of nitrogen by promoting the synthesis of non-urea nitrogen-containing metabolites that can be excreted from the body despite the dysfunctional urea cycle⁸. Dextrose infusions are necessary to enhance anabolism. Insulin infusions may be necessary to control hyperglycemia. Other treatments include exchange transfusion, peritoneal dialysis, and hemodialysis⁹. Once the acute hyperammonemia phase is over, the main stay of treatment is dietary protein restriction. In addition, arginine or citrulline supplements in combination with sodium benzoate and sodium phenylacetate help facilitate the metabolism of ammonia¹⁰.

Orthotopic liver transplant (OLT) has been showed to eliminate dietary restriction and need for alternative pathway medications. This should be considered in patients with progressive liver disease and frequent medical decompensation despite maximal medical management. In one review of 51 patients who underwent OLT for severe urea cycle disorders, 5-year survival rate was 90%¹⁰.

Carbamoyl phosphate synthetase deficiency is a rare disorder manifesting in infancy and children but can sometimes manifest in adulthood. Stressors such as infections and a high-protein diet, lead to hyperammonemia which can be fatal if not recognized and appropriately treated. Our patient has had the diagnosis of CPSD since his teenage years and was therefore treated using established standard protocols. Occasionally, a patient may present for the first time with hyperammonemia in the emergency department and in the presence of normal liver function, a diagnosis of carbamoyl phosphate synthetase deficiency should be considered.

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