

Urea Cycle Defect: A Case Study

Introduction:

The buildup of ammonia from the degradation of amino acids is a potentially destructive event if the urea cycle is defective. The urea cycle, described by Krebs and Henseleit in 1932, is a series of reactions in the liver and the mucosa of the intestines that breaks down ammonia to urea so that it can be safely excreted in urine. Ammonia has a pH of 11.4 in fluid such as the blood. The buildup of ammonia allows higher concentrations of this toxin, which has drastic effects on the central nervous system, to circulate the body.

The normal breakdown of ammonia to urea by the urea cycle is dependent on five different enzymes: carbamylphosphate synthetase I (CPSI), ornithine transcarbamylase (OTC), argininosuccinate synthetase (ASS), argininosuccinate lyase (ASL), and arginase. The overall cycle is shown in the following figure:

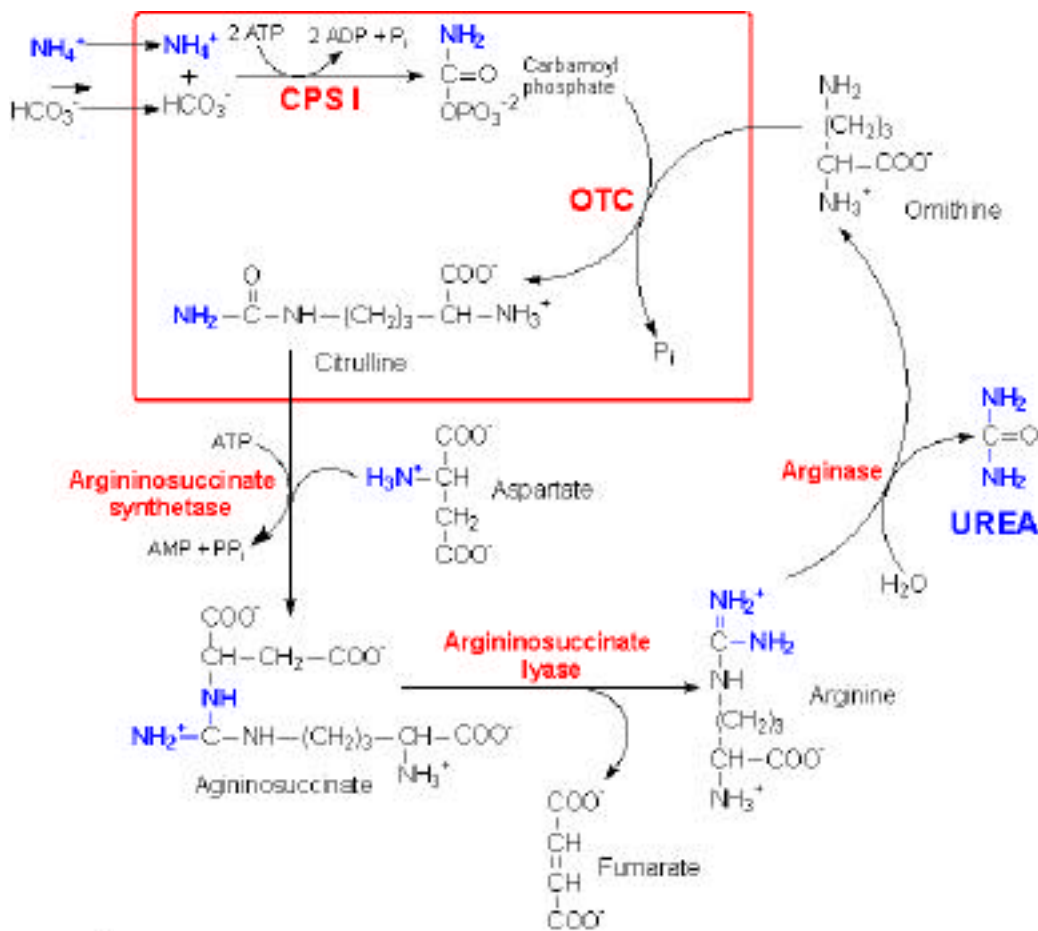


Figure 1: The urea cycle reactions.¹

A defect at any of the steps in the urea cycle can lead to accumulation of intermediate substrates, which in turn can have a range of effects on the body.

The following situation describes a patient that has a defect in one of the urea cycle enzymes. A male baby born after a normal pregnancy appeared to be healthy until the third day after his

¹ <http://domino.peds.swmed.edu/biochem/currdoclib.nsf>

birth. He became lethargic, hypotonic (low muscle function), and his breathing became shallow and eventually led to apnea, which required him to be hooked up to a mechanical respirator. Test results of plasma ammonium gave a concentration of 3044 μ mol/L, which is normally supposed to be 18-54 μ mol/L.

The baby underwent peritoneal dialysis until results from plasma amino acid and urine organic acid tests were available. During this time the ammonium level decreased slightly but the baby fell into a deep coma. The family opted to remove the life support and the baby died on the seventh day of life. Results from the plasma amino acid test and urine organic acid test are shown in the following chart:

Analysis	Patient Value	Normal Value
plasma ammonium	4047 μ mol/L	18-54 μ mol/L
plasma glutamine	2626 μ mol/L	376-709 μ mol/L
plasma alanine	2626 μ mol/L	131-710 μ mol/L
plasma citrulline	normal	
plasma arginine	undetectable	
Urine orotic acid	3328mmol/mol creatinine	0.2-6.0mmol/mol creatinine

Figure 2: Plasma analysis of amino acid and urine analysis of organic acid in a urea cycle defect patient.²

With these values the specific enzyme deficiency in the urea cycle could be pinpointed.

Questions:

1. According to the information given, which values are abnormal? From these values which enzyme in the urea cycle was the infant deficient in?
2. What is the function of the defective enzyme of this case in the normal process of ammonia breakdown.
3. The defect in this enzyme is caused by a genetic mutation. What kind of inheritance is this defect associated with and what is the mutation?
4. What other symptoms can be associated with this urea cycle defect?
5. What treatments could have prevented the death of this infant?

² Choi, Choong-Gon, and Yoo, Han Wook. "Localized Proton MR Spectroscopy in Infants with Urea Cycle Defect." *American Journal of Neuroradiology* (2001) 22: 834-837.

Commentary:

The abnormal values given in the chart on the previous page are characteristic of a deficiency of the urea cycle enzyme ornithine transcarbamylase (OTC). The primary function of OTC is to catalyze the second reaction seen in the first figure of the urea cycle. In this reaction carbamylphosphate is coupled to the d-amino group of the amino acid ornithine, which together produces the amino acid citrulline. Since the citrulline values in this patient are normal we know that the deficiency in the urea cycle must come from either CPS I or OTC. Plasma arginine levels are undetectable in this patient because this amino acid is normally converted to citrulline by nitric oxide synthase, which is not a part of the urea cycle.

From the increased concentration of orotic acid in the urine of the patient the possibility of the deficiency occurring at CPS I is ruled out. Orotic acid is a substrate of pyrimidine synthesis for which carbamylphosphate can be fed into. If CPS I were deficient increased levels of orotic acid would not be observed. In fact, decreased levels would probably be observed because there would be no carbamylphosphate to feed into the pathway. Therefore, it can be determined that the deficiency is in OTC in this patient.³

Since we get a buildup of carbamylphosphate the function of CPS I is affected. Since the function of CPS I in the urea cycle is to convert ammonia to carbamylphosphate so it can be coupled to ornithine and continue through the urea cycle, we get massive buildup of ammonia. The presence of increased levels of ammonia affects the function of glutamate dehydrogenase, which converts the amino group of glutamate to ammonia. The increase in the plasma glutamine is due to the fact that the presence of glutamate is increased and an enzyme called glutaminase converts excess glutamate to glutamine. This reaction can be seen in Figure 1. Increased alanine levels are also present since the transamination between the increased glutamate and pyruvate yield alanine.⁴

The ornithine transcarbamylase deficiency of the urea cycle is a rare X-linked (from the mother) recessive inborn error of metabolism. It is caused by a structural mutation of the gene coding for normal ornithine transcarbamylase. Its gene mutation has been mapped to Xp21.1. The mutation usually leads to partial deficiency in heterozygous females and complete deficiency in hemizygous males.⁵

The symptoms at the extreme end are coma and eventually death. Other symptoms of OTC deficiency for hemizygous males are apparent within 24-72 hours after birth. These include lethargy leading to coma, hypotonia, seizures, persistent vomiting leading to dehydration, poor appetite, hepatomegaly, hyperventilation and hypothermia. The occurrence of OTC deficiency affect females less since the inheritance is recessive, but 10% of heterozygous females will succumb to OTC deficiency later in childhood. In cases of heterozygote females onset of symptoms in childhood are characterized by lethargy leading to coma, acute ataxia,

³ <http://domino.peds.swmed.edu/biochem/currdoclib.nsf>

⁴ http://www.genome.ad.jp/dbget-bin/www_bget?path:hsa00220

⁵ <http://www3.ncbi.nlm.nih.gov/htbin-post/Omim/dispim?311250>

hyperactivity, migraine-like headaches, persistent vomiting leading to dehydration, and hepatomegaly.⁶

There are many treatments for OTC deficiency but no cures have been found. Experimental gene therapy has been one method that has been gaining popularity for the treatment of OTC deficiency, but it was recently heavily scrutinized upon the death of an 18-year-old treatment volunteer, Jesse Gelsinger, who had OTC deficiency disorder.⁷ Treatments of OTC deficiency include the balancing of dietary protein which decreases the presence of nitrogenous groups and decreases the need to breakdown those groups via ammonia and the urea cycle. Just enough protein, as in supplemental dietary arginine, is given to maintain proper essential amino acids responsible for growth and development. Along with the proper balancing of proteins, the use of medications to provide alternative pathways for ammonia excretion is used. These medications are administered by tube feedings either via a gastrostomy tube (stomach tube) or a nasogastric tube (inserted into nose and fed through to the stomach). These medications include the use of sodium benzoate with conjugates with glycine to be excreted as hippuric acid and sodium phenylacetate, which conjugates with glutamine to be excreted as phenylacetyl-glutamine. Amino acid therapy, vitamins, and calcium supplements often accompany these medications.⁸

⁶ <http://www.icondata.com/health/pedbase/files/ORNITHIN.HTM>

⁷ McCarthy, Michael. "USA Consider National Programs to Oversee Human Research." *Lancet*. April 21, 2001, Vol.357: p. 1272-1273.

⁸ http://www.familyvillage.wisc.edu/lib_urea.htm