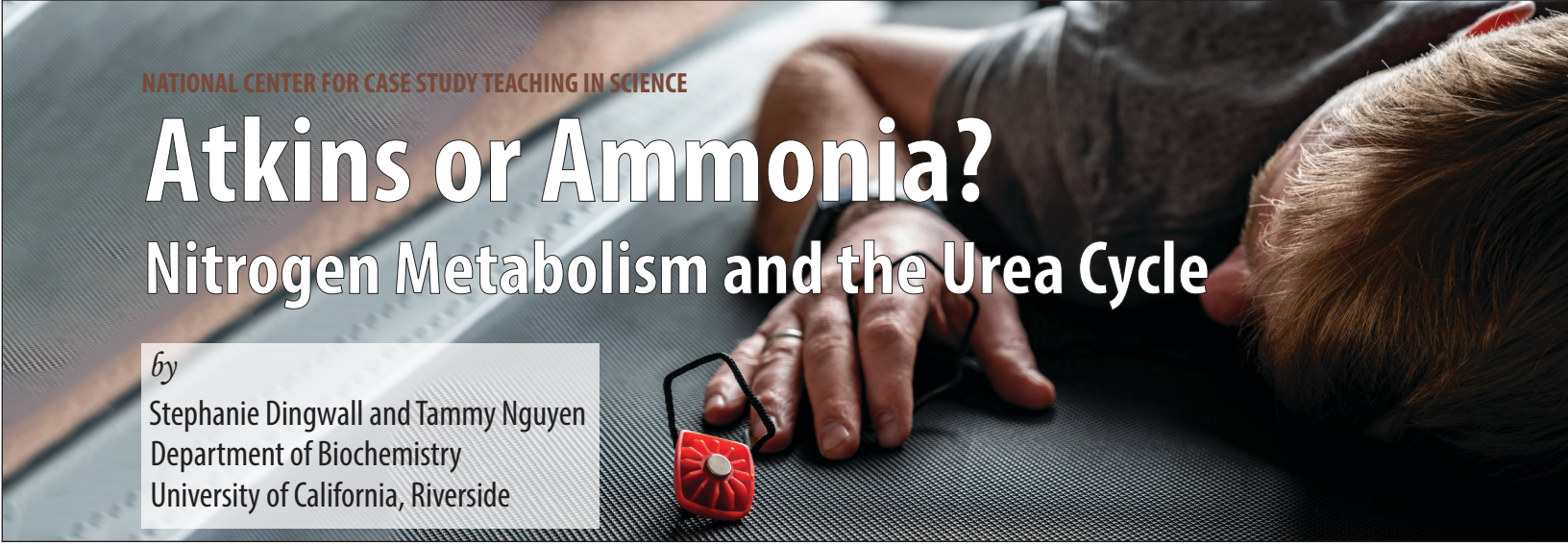
NATIONAL CENTER FOR CASE STUDY TEACHING IN SCIENCE

Atkins or Ammonia?

Nitrogen Metabolism and the Urea Cycle



by
Stephanie Dingwall and Tammy Nguyen
Department of Biochemistry
University of California, Riverside

Part I – The Patient

A previously healthy 21-year-old male is admitted to the emergency room of the local hospital after his mother witnessed his sudden loss of consciousness after returning from a workout at the local fitness gym. He was brought in by ambulance and is now conscious but disoriented with slurred speech. He also complains of "feeling off" and "things creeping on his skin." On arrival to triage, his vital signs are as follows: blood pressure 125/70 mm Hg (normal range: below 120/80 mm Hg), pulse rate 80 beats/min (normal range: 60–100 beats/min), and respiratory rate 16 breaths/min (normal range: 12–16 breaths/min). The patient does not have fever, chills, or sweats. During the examination, the doctor learns that the patient has had intermittent lethargy, nausea, and vomiting over a one-week period. The patient had assumed that his lethargy was due to overexertion from working out since he had recently started a new exercise regimen to gain muscle mass. Over the first 24 hours of admission, the patient becomes increasingly disoriented and aggressive. By the 36th hour, the patient begins having seizures. You are shadowing your local ER physician, who challenges you to determine what might be causing these symptoms.

The physician begins his diagnosis by conducting a medical interview, a physical examination, and ordering laboratory tests for a thorough analysis of the patient's condition.

Medical Interview

The ER physician interviews the patient, asking about any previous diseases or past hospitalizations, current conditions, and overall physical and mental health. The medical history of the patient is found to be unremarkable for any chronic conditions. The patient states that he has never had an episode of altered mental status nor was taking any medication.

The ER physician then interviews the patient's mother, who is in the ER with him. She reports that her son, in an attempt to become more fit, recently started the Atkins diet, which consists of restricting carbohydrates while allowing unlimited amounts of protein and fat. He was also taking a high-protein supplement, and had recently joined a gym and was doing daily strenuous workouts.

Physical Examination

The ER physician conducts a physical examination on the patient, including a careful examination and palpation of the abdomen. The patient does not report any feelings of pain or tenderness in his abdomen. All palpated organs, including the liver, appear to be normal in size.

Laboratory Results

Blood samples were taken from the patient upon ER admission. No common poisons were found in a toxicology test.

When the reults of the patient's bloodwork come back from the laboratory, the ER physician allows you to look at the printout (Table 1).

Table 1. Results of patient's blood work.

Test	*Patient' Results*	*Normal Range*
White Blood Cell (WBC) Count (10^9/L)	12.7	4.5–11.0
Hemoglobin (g/dL)	16.0	13.8–17.2
Platelets (10^9/L)	239	150–400
Glucose (mg/dL)	96	60–100
Blood Urea Nitrogen (BUN) (mg/dL)	5	6–20
Lactate (mg/dL)	16.0	4.5–19.8
Aspartate Aminotransferase (U/L)	80	8–33
Alanine Aminotransferase (U/L)	58	4–36
Bilirubin (mg/dL)	1.02	0.1–1.2
Ammonia (µg/dL)	541	15.0–45.0

Now that you have viewed the results of the physician's interview with the patient and the patient's family, observed the physical examination, and examined the blood results, the physician asks what you think might be going on with the patient.

Questions

1. What did you learn from the patient and family interviews that might be important for treating this patient?

2. Which test results were irregular?

3. With which organ are aspartate aminotransferase and alanine aminotransferase typically associated?

4. The physician then provides you a website to reference:

   > Healthgrades Editorial Staff. (2022). Elevated blood ammonia level: what it means and what to do [webpage]. *Healthgrades*. <https://www.healthgrades.com/right-care/kidneys-and-the-urinary-system/elevated-blood-ammonia-level>

   Based on the reference provided and the information you have about the patient so far, list all possible causes for his elevated blood ammonia level.

Part II – Diagnosing the Patient

You review with the physician your thoughts about the results of the patient's blood work. Elevated WBC count may indicate an infection or inflammation. Elevated levels of AST, ALT, and ammonia indicate excess nitrogen processing by the liver. However, the low BUN level indicates that ammonia is not being released as urea but instead into the blood, causing hyperammonemia.

The ER physician nods in approval and tells you that excess ammonia in the brain can cause neurological damage by inducing changes in the transport of the excitatory amino acid neurotransmitter glutamate, altering brain energy metabolism, and changing the neuronal electric activity by inhibiting the generation of synaptic potentials.

He orders the nurse to collect more blood and urine samples for additional testing. He also orders hemodialysis for the patient to reduce the amount of ammonia in the blood and prevent further neurological damage. (Hemodialysis is a treatment that removes toxins from the blood through a dialyzer, a device that acts as an artificial kidney.)

The blood and urine tests come back, and the physician allows you to examine the results (Tables 2 and 3).

Table 2. Concentrations of specific amino acids in blood plasma.

Amino Acid	*Patient's Result*	*Normal Range*
Arginine (μmol/L)	53	68–104
Citrulline (μmol /L)	10	20–60
Glutamine (μmol/L)	1300	420–700
Glutamate (μmol /L)	140	10–50
Ornithine (μmol /L)	26	20–70

Table 3. Concentrations of specific amino acids in urine.

Amino Acid	*Patient's Result*	*Normal Range*
Glutamine (mmol/mol creatinine)	170	<100
Orotic Acid (mmol/mol creatinine)	120	<5

Now that you have had a chance to see the test results, answer the following questions.

Questions

5. Citrulline is one metabolite whose levels are "out of range." The unusual levels of citrulline could be explained by the loss of function of which enzyme? Draw the reaction catalyzed by this enzyme.

6. Name the specific cellular compartment where the above reaction occurs.

7. The above reaction occurs in what metabolic pathway? What is the purpose of this pathway? In what organ does this pathway take place? Briefly diagram this pathway, including all molecules and enzymes.

8. Which of the amino acids from the blood and urine tests (Tables 2 and 3) are the key nitrogen carriers in the body for the metabolic pathway?

9. Orotic acid is an intermediate in pyrimidine biosynthesis. Why would there be an increase in the amount of orotic acid excreted in relation to this disorder? (*Hint:* Pyrimidine biosynthesis involves a reaction with aspartate and carbamoyl phosphate.)

10. Brain damage can be caused by hyperammonemia because under high ammonia conditions, alpha-ketoglutarate in the brain is turned into glutamate. What other metabolic pathway could be affected by this reaction (i.e., in what other pathway is alpha-ketoglutarate found)? What is the overall bioenergetic effect of this other metabolic pathway being compromised?

11. The ER physician gives you a flowchart with possible disorder diagnoses and the associated plasma amino acids abnormalities. Based on the information you have, what urea cycle disorder (UCD) does the patient most likely have?

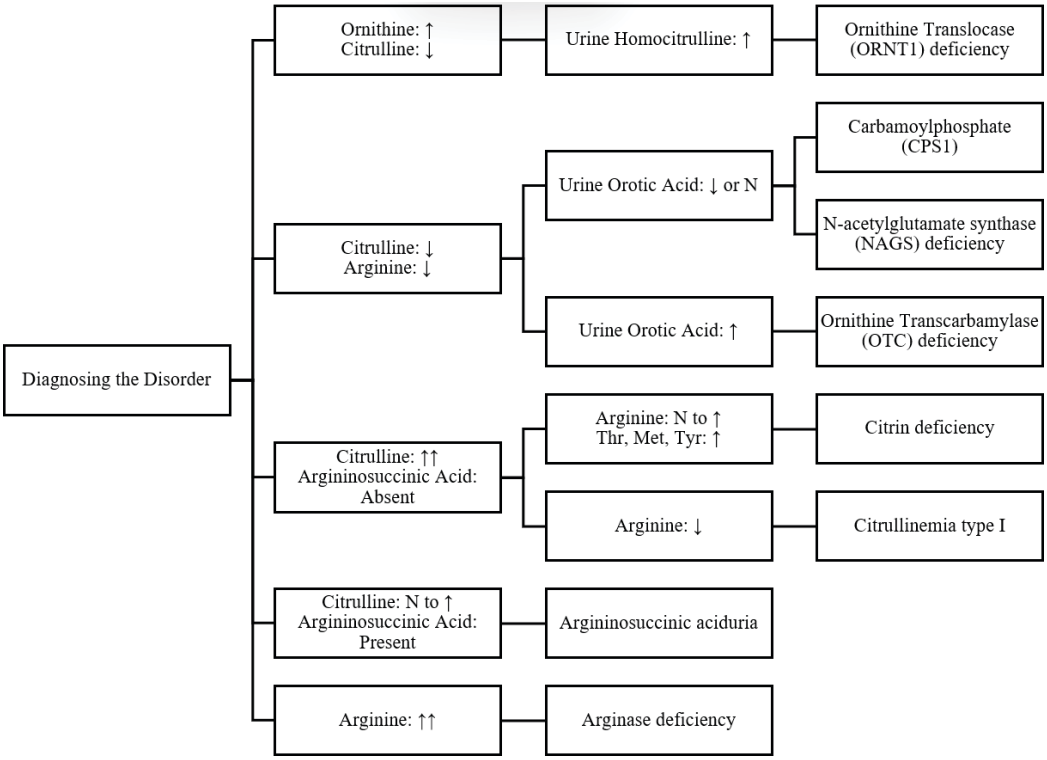


Figure 1. Diagnostic flowchart.

12. Considering patient history, what could have possibly triggered the disorder to become unmasked in this patient?

Part III – Treatment

High glutamate and glutamine levels indicate a high level of protein degradation into amino acids. However, the low levels of arginine and citrulline (both urea cycle intermediates) indicate that the excess ammonia is not entering the urea cycle but being released into the blood, causing hyperammonia. This seems to indicate a disconnect between the entry of ammonia into, and processing by, the urea cycle.

The ER physician agrees with you that the patient's results are consistent with the urea cycle disorder ornithine transcarbamylase (OTC) deficiency. The physician refers the patient to a specialist in metabolic diseases, who has the patient's DNA sequenced for analysis. The physician, pleased with your answers so far, concludes by asking you some final questions.

Questions

13. A DNA analysis of the affected gene showed a missense mutation that led to an isoleucine to methionine substitution in exon 5. Why would this amino acid change be significant in the function of the enzyme?

14. Supplementation with arginine is often used as a treatment for urea cycle disorders. Why would this be an effective treatment?

15. Sodium benzoate is another suggested treatment for urea cycle disorders. In a series of metabolic steps, benzoate is converted to benzoyl-CoA and conjugates with glycine to form hippurate. Hippurate can then be rapidly excreted by the kidneys into urine. The reversible oxidation of glycine is catalyzed by a multienzyme complex, the glycine-cleavage system, to yield carbon dioxide, ammonia, 5,10-methylenetetrahydrofolate, and a reduced pyridine nucleotide. Suggest a reason why sodium benzoate would be an effective treatment for hyperammonemia.

Conclusion

Following the diagnosis of OTC deficiency, the patient was treated with arginine and sodium benzoate and placed on a low-protein diet. His serum ammonia level normalized and the patient's mental status returned to normal. The patient was discharged home after two weeks with instructions to continue taking the prescribed medication. He was also referred to a nutritionist to help create a healthy diet plan and prevent future attacks of hyperammonemia. Because OTC deficiency is an inherited X-linked urea cycle defect, the patient and his family were also advised to seek genetic counseling to evaluate risk for other relatives to be affected by the OTC gene variant.