ELSEVIER
SAUNDERS

Crit Care Clin 21 (2005) S1 S8

CRITICAL
CARE
CLINICS

Unmasked Adult-Onset Urea Cycle Disorders in the Critical Care Setting

Marshall L. Summar, MD[a,*], Frederick Barr, MD, MS[b,c], Sheila Dawling, PhD[d], Wendy Smith, MD[e,f], Brendan Lee, MD, PhD[g], Rani H. Singh, PhD, RD[h], William J. Rhead, MD, PhD[i], Lisa Sniderman King, MSc[j], Brian W. Christman, MD[h,k]

[a]*Center for Human Genetic Research, Division of Medical Genetics, Department of Pediatrics, Vanderbilt University Medical Center, Nashville, TN, USA*
[b]*Department of Pediatrics, Division of Pediatric Critical Care Medicine, Vanderbilt Children's Hospital, Nashville, TN, USA*
[c]*Department of Pediatrics, Vanderbilt University Medical Center, Nashville, TN, USA*
[d]*Associate Professor of Pathology, Department of Pathology, Vanderbilt University Medical Center, Nashville, TN, USA*
[e]*Division of Genetics, The Barbara Bush Children's Hospital, Maine Medical Center, Portland, ME, USA*
[f]*Department of Pediatrics, Division of Genetics, Maine Pediatric Specialty Group, Portland, ME, USA*
[g]*Department of Molecular and Human Genetics, Baylor College of Medicine, Houston, TX, USA*
[h]*Division of Human Genetics, Emory University School of Medicine, Atlanta, GA, USA*
[i]*Medical College of Wisconsin Genetics Center, Madison, WI, USA*
[j]*University of Washington, Seattle, WA, USA*
[k]*Division of Pulmonary and Critical Care Medicine, Department of Medicine, Vanderbilt University Medical Center, Nashville, TN, USA*

Urea cycle disorders (UCD) are caused by a defect in the waste nitrogen disposal system that converts ammonia to urea (Fig. 1) [1–4]. A defect in or absence of one of the five enzymes, two substrate transporters, or cofactor producer of the cycle impedes the conversion of nitrogen and its elimination as urea, often resulting in hyperammonemia.

The classic presentation of UCD has been critically high blood levels of ammonia in the newborn period [4–8]. This pattern constitutes most of the literature on the subject; however, there is a growing body of knowledge concerning urea cycle disorders that have manifested or only been recognized in adulthood. A partial or milder enzyme deficiency can permit an individual to function relatively normally, sometimes for decades, until confronted by an environmental stressor that triggers a hyperammonemic crisis. Box 1 lists some of the conditions described in the literature that can result in hyperammonemia in older patients. These conditions typically either increase the need for nitrogen clearance or interfere with the enzymes of the urea cycle. The underlying urea cycle disorder can be difficult to recognize, because the patient is frequently ill for other reasons. Nevertheless, prompt recognition is critical for treatment to be effective. Without early diagnosis and aggressive intervention, the prognosis for these patients is poor.

This article presents three cases of adult onset urea cycle disease precipitated by stressful medical situations in the intensive care environment. These cases have similarities in presentation and history that should provide clues for recognizing patients in similar situations. The report also outlines an approach to the diagnosis and management of adult patients who have hyperammonemia, which is different to some degree from suggested practice in hyperammonemia and suspected urea cycle disease in childhood.

Case 1

A white male in his early 30s presented following a four-wheeler accident. He had a right clavicular fracture and a right tibial plateau fracture requiring open reduction and internal fixation.

On the night following the orthopedic surgical procedure, he became confused and combative. He had tachycardia, hypertension with a diastolic pressure of 140 mmHg, and hyperthermia reaching a maximum of 106°. Additionally,

Dr. Summar acknowledges the support of NIH grants MOI-RR-0095 and U54-RR-019453.

Complete financial disclosure information for each author is provided in the frontmatter of this supplement on page iii.

* Corresponding author. Department of Pediatrics, Vanderbilt University Medical Center, 525D Light Hall, Nashville, TN 37232–0165.
E-mail address: marshall.summar@vanderbilt.edu (M.L. Summar).

0749-0704/05/S – see front matter
doi:10.1016/j.ccc.2005.05.002

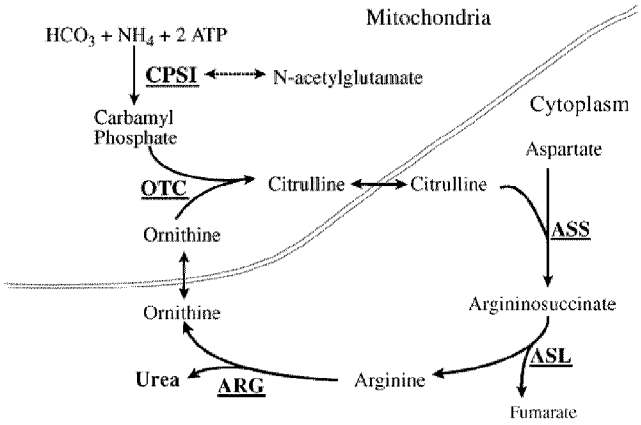

Fig. 1. Urea cycle pathway. ARG, arginase; ASL, argininosuccinic acid lyase; ASS, argininosuccinic acid synthetase; CPS1, carbamyl phosphate synthetase 1, OTC, ornithine transcarbamylase.

the patient exhibited generalized tonic-clonic seizures that the local hospital was unable to control.

Past medical history

Following a closed head injury at 5 years of age, the patient developed a seizure disorder that was well-controlled on carbamazepine and primidone. He had chronic hypertension, for which he was prescribed quinapril, amlodipine, and hydrochlorothiazide, although his compliance was questionable. His gastroesophageal reflux was being treated with pantoprazole, and he had a history of persistent anemia, with a hemoglobin of 9 and hematocrit of 27. Discussions with the patient's family revealed that he was an "auto-selective" vegetarian; he systematically picked out and rejected the meat in any dish served him. He also had a history of nonspecific psychiatric problems.

Box 1. Published reports of triggers of urinary cycle disorders in adulthood

Valproic acid [9–20]
Postpartum stress [21]
Heart-lung transplant
Short bowel and kidney disease [22]
Parenteral nutrition with high nitrogen intake [23,24]
Gastrointestinal bleeding [25]

Note that hyperammonemia, although not necessarily UCD, has also been reported in patients on high-dose chemotherapy, particularly during bone marrow transplantation, and in severe hepatic disease [26–28].

The patient had only an eighth-grade education and was described as "slow." He had one daughter, who was healthy.

Clinical course

CT evaluation at the local hospital showed what appeared to be a lacunar infarct of the left caudate. MRI indicated increased signal in the left frontal periventricular region; it was uncertain whether this was attributable to an old infarct or previous trauma. The patient's electroencephalograph EEG showed severe brain dysfunction in the setting of a seizure disorder. In fact, he remained in status epilepticus for 12 hours despite the administration of antiepileptics, and required intubation before transportation to our center.

Laboratory work at the outside hospital revealed a low blood urea nitrogen and an ammonia level of 553 μmol/L at approximately 24 hours into the course of coma.

Upon arrival at our tertiary care center, the patient was dialyzed to remove excess ammonia, and the level dropped quickly to 250 μmol/L. Despite this improvement, he remained in a deep coma and unresponsive to all stimuli. His pupils were fixed and dilated, and remained so during his entire hospitalization. He displayed evidence for generalized cerebral edema. He was dialyzed further and placed on continuous veno-venous hemodialysis. He was begun on the nitrogen scavengers sodium benzoate and sodium phenylbutyrate, the latter solubilized and placed in the gastrointestinal tube. The patient also received arginine hydrochloride and was started on a glucose insulin drip in an effort to prevent further catabolism.

Despite aggressive therapy, the patient's ammonia level never fell below 200 μmol/L. A plasma amino acid profile showed very high glutamine and high alanine levels, as well as very low citrulline and low arginine concentrations. On

the second hospital day, the patient developed hypotension, requiring norephinephrine, and progressive hypoxia, despite being on a ventilator and receiving aggressive ventilatory management. He subsequently developed pulmonary edema and failed an apnea test. After extensive discussion with his family, support was withdrawn, resulting in rapid asystole and death.

Diagnosis

The presumptive diagnosis was hyperammonemia secondary to a urea cycle disorder, possibly ornithine transcarbamylase (OTC) or carbamyl phosphate synthetase (CPS1) deficiency. Based on a liver biopsy with enzymatic testing and DNA sequence analysis, the patient had partial N-acetylglutamate synthetase (NAGS) deficiency and was unable to make cofactor for the CPS enzyme (see Fig. 1).

Case 2

A 58-year-old white female who had a history of recurrent episodes of "asthmatic bronchitis" presented to her local hospital having severe wheezing of several days' duration and a productive cough. She was thought to have a viral illness that was exacerbating her asthma. She was treated with an acrosol bronchodilator, but continued to have bronchospasm and dyspnea with wheezes.

The patient was admitted to the outlying hospital and started on intravenous steroids (methylprednisolone), antibiotic therapy (cefotaxime) and intravenous fluids. She was also receiving albuterol and loratadine/pseudoephedrine. Radiographs demonstrated no infiltrates, but the patient was maintained on antibiotics because of her age. Oral intake was minimal during this time. On day 5 of admission she developed acute confusion and an expressive aphasia with focal deficits, progressing to a complete coma within 48 hours. A work-up, including lumbar puncture, EEG, two head CTs, a carotid Doppler test, and a cerebral three-vessel arteriogram, was nondiagnostic. The patient was listed as having steroid psychosis. She was also begun on acyclovir against the possibility of herpes encephalitis, and transferred to the critical care unit at our institution.

The patient was intubated, exhibiting decorticate posturing and sluggish pupils, but no seizures. Her temperature and pulse were normal, blood pressure was 142/80 mmHg, and toes were upgoing in the Babinski reflex.

Past medical history

The patient had recurrent episodes of asthma, along with allergic rhinitis and nasal polyps. She had undergone numerous procedures, including a cholecystectomy, appendectomy, hysterectomy, and a thyroid nodule treated with radiation; however, she had never received intravenous steroids (a critical point in understanding her case). According to her husband, she was on a regular diet, consumed a normal amount of food with a normal protein intake, and had no history of seizures or lethargy. Subsequent history from the patient revealed that she tended to avoid large protein intakes.

Clinical course

The diagnostic and laboratory workup revealed an ammonia level of 120 μmol/L at first measurement, later rising as high as 280; cerebral edema on CT examination; diffuse slowing but no seizure activity on EEG; and very low citrulline and arginine, with a mild elevation of glutamine per her plasma amino acid profile.

The patient was started on dialysis, intravenous sodium phenylacetate/sodium benzoate (after obtaining informed consent), arginine supplementation, and increased intravenous calories as dextrose.

The patient awoke within 8 hours of the initiation of dialysis and drug therapy and was discharged 3 days later. Follow-up over 5 years showed no residual deficits. Despite the earlier cerebral edema, visual field examination has shown no evidence of optic nerve crush injury. Intravenous steroids have been avoided, although this has been difficult in the face of the patient's worsening asthma. Now in her 60s, she has also developed mild pulmonary hypertension. She has not required dietary modification or oral nitrogen scavenging drugs (sodium benzoate, phenylbutyrate).

Diagnosis

Based on family history elicited from the patient's husband, the patient was diagnosed as a symptomatic OTC carrier (ornithine transcarbamylase is on the X chromosome). She had had four male infants who died from OTC deficiency. She has two adult OTC defect-carrier daughters. One (a normal college graduate) lost a son. The other has mild mental retardation and has suffered several mild hyperammonemic episodes in the past.

Case 3

A 34-year-old morbidly obese female was admitted to an outlying hospital 8 months after gastric bypass surgery with a Roux-en-Y procedure. Her presenting symptom was weakness, which progressed rapidly to uncontrolled status epilepticus and neurologic unresponsiveness requiring intubation.

The patient's serum ammonia concentration was 442 μmol/L and her initial aspartate aminotransferase level was elevated, although there was no evidence of transaminitis subsequently. Lumbar puncture and all cultures were negative, except for methicillin-resistant *Staphylococ-*

cus aureus in the sputum. She was placed on broad-spectrum antibiotics without improvement, and transported to our tertiary center.

Past medical history

The patient had been morbidly obese, having previously weighed 400 lbs, which was reduced to 160 lbs during the 8 months after her bariatric surgery. She had a history of respiratory distress syndrome and pneumonia during this period. She had a history of dumping syndrome with hypokalemia and hypernatremia. She also had non insulin-dependent diabetes mellitus and nephrolithiasis. She had been almost chronically hospitalized after her bariatric surgery, but no attempt was made to reverse or modify the procedure. Questioning revealed that she tended to avoid protein, preferring starch and carbohydrate. She had a history of depression.

Clinical course

At our center, the patient's CT examination was normal at first, subsequently exhibiting some cerebral edema. Lumbar puncture showed no culture growth for either viral, fungal, or bacterial organisms. An abdominal CT indicated possible fatty liver, and her chest radiograph revealed an infiltrate in the left lower lung suspicious for pneumonia. At this point she had been in status epilepticus for over 24 hours.

The patient was started on dialysis, phenylbutyrate, and citrulline. Her ammonia levels dropped to less than 100 μmol/L. An organic acid profile showed no orotic acid and an elevated 5-oxoproline and lactic acid.

In spite of the reduction in ammonia, which ultimately decreased to 21 μmol/L, the patient did not regain consciousness, even after 6 days of therapy. Following extensive consultation with her family, the patient was electively extubated and expired within 3 to 4 hours.

Diagnosis

Autopsy and liver biopsy were performed at the time of death. The liver biopsy demonstrated CPS1 deficiency and subsequent mutation analysis uncovered a defect consistent with that finding. In addition, fatty liver infiltrate and a large number of kidney stones were observed at autopsy.

Discussion

These three cases share some common clinical features. They all demonstrated a dramatic and rapid increase in nitrogen load, whether from trauma, rapid weight loss, or increase in protein turnover from intravenous steroid (prednisolones). All three patients presented having altered mental function that progressed to a markedly obtunded state and eventually coma. Their findings were consistent with toxicity from ammonia elevation, and consistent with that seen in patients who have both urea cycle disorders and chronic liver disease. The patient who had multiple orthopedic fractures had to deal with the breakdown and processing of the blood that was lost into the tissues surrounding the breaks. This can often amount to several units of blood, metabolism of which releases a large amount of waste nitrogen. The bariatric surgery patient suffered from malabsorption and nutritional disruption. The rapid weight loss resulted in protein catabolism in her tissues and excess nitrogen. The intravenous steroids used in the asthmatic patient resulted in a generalized increase in protein turnover, which also resulted in excessive nitrogen release [29].

The three patients also exhibited rapid deterioration of neurologic status, with the severity of their encephalopathy masked by their ongoing medical condition. The comorbid conditions led to delays in diagnosis. There was some evidence for cerebral edema by clinical examination or radiograph in all three patients, and seizures occurred in two of the three cases. Because they had all been quite ill and hospitalized, there was a decrease in oral intake leading up to and contributing to the decompensation.

Consistent with the literature regarding unmasked adult cases of UCD, the underlying molecular defects in these patients were at the beginning portion of the urea cycle. These defects tend to be more severe, because blockade in these steps occurs before any nitrogen is pulled into the cycle intermediates (see Fig. 1).

Reaching hyperammonemic threshold

In patients like these who manage to survive to adulthood before reaching a hyperammonemic threshold, the physiologic mechanisms that can tip the nitrogen balance appear to break down into three categories: (1) nitrogen turnover and nitrogen load from catabolism or sudden protein processing, outlined in Box 2; (2) diminished access to processing in the liver, the target organ for most nitrogen clearance, outlined in Box 3; and (3) the genetic capacity of the urea cycle to handle the nitrogen load, outlined in Box 4.

In turn, each of these is affected by a variety of factors.

Alterations in nitrogen turnover and load can be triggered by poor nutritional intake and rapid weight loss, such as that associated with gastric bypass surgery, chronic starvation, or self-starvation disorders such as anorexia and bulimia. They might also be precipitated by internal bleeding or damage, whether resulting from a large bone fracture or surgical trauma, or by viral illnesses and other chronic diseases that cause total body stress. Even the postpartum period has been implicated as a trigger mechanism [21].

A dramatic increase or decrease in habitual protein intake may also contribute to nitrogen imbalance. Consider high protein diet strategies, change in food access or preparation,

Box 2. Urea cycle defect triggers from nitrogen turnover and load

Rapid weight loss and poor nutritional intake
Gastric bypass surgery
Internal bleeding or damage
Fracture
Surgical damage
Viral illness or other generalized stress
Postpartum period
Dramatic increase/decrease in habitual protein intake
High protein diet strategies
Change in food access or preparation
Malabsorption conditions
Medications affecting protein catabolism
Intravenous or high-dose glucocorticoids
Chemotherapy

malabsorptive conditions, or medications that affect protein catabolism. Medications influencing protein turnover include high-dose or intravenous glucocorticoids, as well as chemotherapy. Most chemotherapy patients decrease their oral intake because of nausea or esophageal ulceration. Chemotherapy may also destroy some of the villi cells in the gut, thus compromising protein absorption. Elevations in ammonia and even a few deaths have been reported as a result of hyperammonemia from chemotherapy [26].

If access to functional hepatocytes is blocked, a physical urea cycle defect is created. This could occur following portacaval shunt (for severe cirrhosis), or varicocele shunting from a cirrhotic liver. Even a partial shunt could unmask a partial urea cycle disorder. So too could a decrease in the available hepatocyte pool. The most common cause of this decrement in liver function and resultant hyperammonemia is chronic cirrhosis, although acute chemical or viral damage could also be the underlying cause.

Box 3. Urea cycle defects triggered by decreased access to processing in liver

Vascular shunting of blood from liver

Portacaval shunt
Varicocele shunting from cirrhotic liver

Decrease in available hepatocyte pool

Chronic cirrhosis
Acute chemical or viral damage to the liver

Box 4. Genetic predisposing conditions affecting capacity of the urea cycle

Genetic defects in enzyme/transporter function of the urea cycle components or decreased function polymorphisms
Chemical or toxic affect on enzyme function
5-pentanoic acid (Jamaican vomiting sickness)
Valproic acid
Chemotherapeutic agents (cyclophosphamide)
Comorbid metabolic conditions
Organic acidemias
Fatty acid oxidation defects

Abnormalities in the urea cycle can stem from either genetic defects in the enzymes or transporters, or chemical/toxic effects on enzyme function. The classic toxicity affecting enzyme performance was 5-pentanoic acid (Jamaican vomiting sickness), although this is rarely seen anymore. Today the most widely recognized agent in this regard is valproic acid, which has a direct inhibitory affect on enzyme function [10,11,30,31]. There is some anecdotal evidence that zonisamide can also cause ammonia elevation. There is evidence of direct effects exerted on urea cycle function by chemotherapeutic agents, most notably cyclophosphamide [32,33]. Finally, metabolic comorbidities such as organic acidemias and fatty acid oxidation defects generate metabolites that can disrupt the urea cycle and potentially unmask a partial defect.

Diagnostic clues

There are clues suggestive of a possible UCD—illustrated to one degree or another in these cases—that can help the clinician recognize a urea cycle disorder. Although a family history of metabolic disease is a strong indicator, most families may not be aware of the existence of metabolic abnormalities, and the recessive inheritance pattern of most of these diseases may make the patient the only case. In older patients who had childhood symptomatology, the relatives familiar with the history may no longer be available, and the adult patient may not remember the childhood stories. A directed history is very useful. Specific questions should be asked about infant mortality, consanguinity, and other family characteristics. A dietary history of autoselective vegetarianism (ie, elective decreased protein intake), as well as high carbohydrate intake and obesity are other suggestive clues. A history of behavioral and psychiatric illness (possibly resulting from chronic low-grade hyperammonemia) or a history of prolonged clinical courses with seemingly routine illnesses should also prompt suspicion. For

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.