

## NEUROLOGICAL BULLETIN

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**A Case of Suspected Urea Cycle Dysfunction in a Patient with Unexplained Hyperammonemia**

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Urea cycle disorders are inherited deficiencies of the enzymes involved in the cellular excretion of excess ammonia produced during protein metabolism. Hyperammonemia associated with these disorders is usually manifested by decreased level of consciousness, irritability, seizures, vomiting, and poor feeding. Although the majority of recognized patients are children, a delayed presentation is seen in patients with partial enzyme deficiency, including heterozygotes. These patients become symptomatic in later childhood or adulthood. Diagnoses of urea cycle defects (UCD) in the adult population have been reported.<sup>1-3</sup> Often, the diagnosis only becomes apparent during times of increased metabolic stress, such as with acute or chronic illness. Prompt recognition and treatment are essential in determining the outcome of these patients. We present a case of hyperammonemic encephalopathy from a presumed urea cycle defect.

**Case Report**

We report a case of a 48-year-old woman with a history of bulimia and bipolar disorder

who presented with a four week history of confusion and lethargy in the setting of a twenty-pound weight loss. Per family, the patient began to exhibit poor recall and personality changes over the course of a year and had begun to lose weight over the previous 6 months. In the week prior to admission, she had been speaking very little and was consuming only fluids. In the ER, she was minimally responsive and appeared poorly groomed. She had an initial lumbar puncture that was normal. Her head CT showed scattered, patchy, ill-defined hypodensities in the white matter of both cerebral hemispheres, more than expected for the patient's age. Initial laboratory studies demonstrated a low bicarbonate level, consistent with a non-anion gap metabolic acidosis, for which she was placed on bicarbonate drip. Her B12, folate, thiamine, TSH, and toxicology screen were unremarkable with the exception of an ammonia level of 371  $\mu\text{mol/L}$  (10-50  $\mu\text{mol/L}$ ). There was no other evidence of liver failure.

Shortly after the patient's arrival, the patient experienced three episodes of non-sustained ventricular tachycardia and became obtunded. She was noted to have roving eye move-

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Table 1: Quantitative amino acid panels. Abnormal values in red, HD = Hospital Day.

Test	Reference	HD#3	HD#5	HD#7
Taurine	25-80	18 $\mu\text{mol/L}$ (L)	9 $\mu\text{mol/L}$ (L)	7 $\mu\text{mol/L}$ (L)
Aspartic Acid	0-20	10 $\mu\text{mol/L}$	9 $\mu\text{mol/L}$	11 $\mu\text{mol/L}$
Hydroxyproline	6-50	46 $\mu\text{mol/L}$	25 $\mu\text{mol/L}$	16 $\mu\text{mol/L}$
Threonine	60-220	100 $\mu\text{mol/L}$	37 $\mu\text{mol/L}$ (L)	71 $\mu\text{mol/L}$
Serine	60-200	56 $\mu\text{mol/L}$ (L)	21 $\mu\text{mol/L}$ (L)	34 $\mu\text{mol/L}$ (L)
Allo-isoleucine	0	0 $\mu\text{mol/L}$	0 $\mu\text{mol/L}$	0 $\mu\text{mol/L}$
Homocystine QBAA	0	0 $\mu\text{mol/L}$	0 $\mu\text{mol/L}$	0 $\mu\text{mol/L}$
Glutamic Acid	10-120	46 $\mu\text{mol/L}$	44 $\mu\text{mol/L}$	36 $\mu\text{mol/L}$
Glutamate	410-700	1054 $\mu\text{mol/L}$ (H)	328 $\mu\text{mol/L}$ (L)	376 $\mu\text{mol/L}$ (L)
Proline	110-500	521 $\mu\text{mol/L}$ (H)	238 $\mu\text{mol/L}$	143 $\mu\text{mol/L}$
Glycine	140-490	224 $\mu\text{mol/L}$	92 $\mu\text{mol/L}$ (L)	152 $\mu\text{mol/L}$
Alanine	240-600	283 $\mu\text{mol/L}$	160 $\mu\text{mol/L}$ (L)	222 $\mu\text{mol/L}$ (L)
Citrulline	10-60	20 $\mu\text{mol/L}$	8 $\mu\text{mol/L}$ (L)	3 $\mu\text{mol/L}$ (L)
Valine	140-350	88 $\mu\text{mol/L}$ (L)	26 $\mu\text{mol/L}$ (L)	55 $\mu\text{mol/L}$ (L)
Cystine	7-70	12 $\mu\text{mol/L}$	4 $\mu\text{mol/L}$ (L)	5 $\mu\text{mol/L}$ (L)
Methionine	17-53	10 $\mu\text{mol/L}$ (L)	3 $\mu\text{mol/L}$ (L)	9 $\mu\text{mol/L}$ (L)
Isoleucine QBAA	30-130	13 $\mu\text{mol/L}$ (L)	0 $\mu\text{mol/L}$ (L)	13 $\mu\text{mol/L}$ (L)
Leucine	60-230	35 $\mu\text{mol/L}$ (L)	21 $\mu\text{mol/L}$ (L)	27 $\mu\text{mol/L}$ (L)
Tyrosine	30-120	17 $\mu\text{mol/L}$ (L)	10 $\mu\text{mol/L}$ (L)	13 $\mu\text{mol/L}$ (L)
Phenylalanine	30-80	23 $\mu\text{mol/L}$ (L)	19 $\mu\text{mol/L}$ (L)	24 $\mu\text{mol/L}$ (L)
Ornithine QBAA	20-135	82 $\mu\text{mol/L}$	22 $\mu\text{mol/L}$	69 $\mu\text{mol/L}$
Lysine	80-250	234 $\mu\text{mol/L}$	91 $\mu\text{mol/L}$	155 $\mu\text{mol/L}$
Histidine	50-130	96 $\mu\text{mol/L}$	64 $\mu\text{mol/L}$	69 $\mu\text{mol/L}$
Arginine	40-160	27 $\mu\text{mol/L}$ (L)	8 $\mu\text{mol/L}$ (L)	21 $\mu\text{mol/L}$ (L)

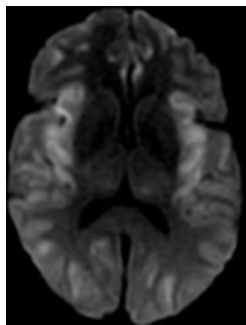
ments and posturing of all four limbs. The patient received heavy sedation and anticonvulsants for presumed status epilepticus, which was later confirmed by EEG. Her neurological exam was compromised by heavy sedation. She did have a minimal gag reflex, but no other brainstem reflexes, no elicitable response to pain, and no response to plantar stimulation bilaterally. Initial MRI brain revealed widespread restricted diffusion in the insula and cerebral cortex, suggestive of hypoxic-ischemic injury.

Her acute clinical decompensation and high ammonia prompted extensive work up of her metabolic status, including amino acid defi-

ciencies. Other causes of acute hyperammonemia in adults were considered, such as malignancy, multiple myeloma, and valproate-induced hyperammonemia.<sup>4</sup> Her immunofixation revealed an IgA lambda monoclonal band, but there was no evidence of multiple myeloma or cancer. Her valproate level was less than 10, making this etiology unlikely. Less common causes, such as inborn and acquired errors of metabolism, were further investigated. A low carnitine level in the setting of hyperammonemia, a high creatine kinase (peripheral metabolism), a high triglyceride level (ketosis), and low BUN (2-3mg/dL) supported a metabolic defect and genetics was consulted. Quantitative amino acid

Figure 1a: Diffusion-weighted MRI.

HD #8



HD #15

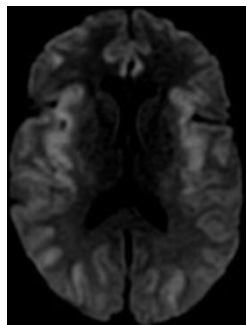
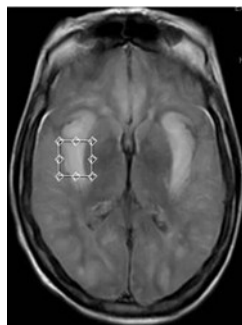


Figure 1b: FLAIR MRI.

HD #9



HD #17

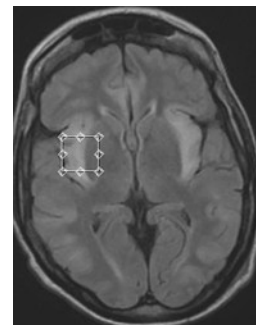


Figure 1: Radiographic changes in response to Ammonul. The boxed area in the FLAIR images reflects the area of interest, the insular cortex, analyzed on MR spectroscopy. HD = Hospital Day.

panels were obtained and the first three are shown in Table 1. With successive panels, taurine, hydroxyproline, proline, threonine, serine, glycine, alanine, citrulline, valine, cystine, methionine, isoleucine, leucine, tyrosine, phenylalanine, and arginine were observed to be low or downtrending overall. Aspartic acid, lysine, and histidine were consistently normal. Glutamate was initially elevated and ornithine became elevated late. The patient's amino acid panel (development of low citrulline and low arginine) indicated that she most likely had an ornithine transcarbamylase (OTC) or carbamoyl phosphate synthetase I (CPS I) dysfunction. However, the patient did not exhibit orotic aciduria to support OTC deficiency and genetic testing from a liver biopsy failed to reveal any mutations to support CPS I deficiency. As a part of her treatment, she was given multiple doses of lactulose but failed to improve clinically. She was treated with Ammonul, an ammonia-scavenging agent consisting of sodium phenylacetate and sodium benzoate.<sup>5</sup> Her ammonia level improved to the normal range within 24 hours.

Follow-up diffusion-weighted MRI (Figure 1a) and FLAIR images (Figure 1b) demon-

strated decreased intensity in previously noted areas and no new lesions, leading to the hypothesis that MRI findings were the result of hyperammonemia rather than due to global hypoxic-ischemic injury.<sup>6</sup> Related to this finding, MR spectroscopy demonstrated peaks most strongly for glutamine rather than lactate, supporting glutamate toxicity as a result of a urea cycle defect as opposed to hypoxic-ischemic injury. Genetic testing failed to identify mutations for OTC or CPS I deficiency, which are the most commonly occurring genetic deficiencies. However, with the inability to detect variant polymorphisms as well as large deletions and duplications, the possibility of a urea cycle defect was still the likely diagnosis. Due to the patient's poor neurological prognosis, her family requested comfort measures only, and she subsequently expired.

## Discussion

As described by our case, the presence of unexplained hyperammonemia raises the possibility of an inborn error of metabolism. Typically, with the urea cycle, glutamate is first combined with Acetyl CoA by N-acetylglutamate synthetase (NAGS) to create

N-acetylglutamate. Ammonia is then incorporated into N-acetylglutamate by carbamoyl phosphate synthetase I (CPS I) to generate carbamoyl phosphate. Ornithine transcarbamylase (OTC) then catalyzes a reaction between carbamoyl phosphate and ornithine to generate citrulline in the urea cycle. The ammonium ion is later transferred to form urea and is excreted. Deficiency in any five of the enzymes in the urea cycle results in the accumulation of ammonia which could be potentially fatal if untreated.<sup>7</sup> Although usually seen in neonates, later cases of childhood and adulthood have been described.<sup>1-3</sup> The presentation can be atypical, with chronic vomiting, developmental delay, seizure disorder, sleep disorders, or psychiatric illnesses following increased protein intake or during periods of stress such as acute or chronic illness.<sup>1</sup>

The most common deficiencies are N-acetylglutamate synthetase (NAGS) deficiency, carbamoyl phosphate synthetase I (CPS I) deficiency, and ornithine transcarbamylase (OTC) deficiency, all of which have an enzyme defect early in the urea cycle. OTC and CPS deficiency patients may display a low citrulline and arginine level in the metabolic panel, as in our patient. Urine studies in an OTC patient typically show a high level of orotic acid, which is a by-product of the cycle and is made from carbamoyl phosphate when OTC is not available. While our patient did not exhibit orotic aciduria, OTC is an X-linked disorder and can have a late presentation from carrier states in which there are varying amounts of residual enzyme activity.<sup>1</sup> The amount of organic acids (orotic acids) in the urine may be difficult to detect in these patients because of the varying degree of enzymatic activity (lyonization).<sup>7,8</sup> The OTC gene has been found to exhibit enormous variation. More than 340 mutations have been identified in families in which there was clinical OTC de-

ficiency.<sup>9</sup> A patient with CPS I deficiency (autosomal recessive) would likely demonstrate mutation of the CPS I gene. Although the mutation was not detected in the liver biopsy of our patient, this condition cannot be excluded, as altered transcriptional regulation of CPS I expression by polymorphisms is possible and the genetic testing does not detect large heterozygous deletions, duplications, or mutations within the promoter or deep intronic regions.<sup>10</sup> Lastly, a patient with NAGS deficiency would typically display a high alanine and glutamine level, which was not observed in our patient.

An early recognition of the toxic effects of hyperammonemia and investigation into etiology are critical for good prognosis. If untreated, patients may develop increased intracranial pressure, seizures and subclinical seizures (40% of cases), and eventually cerebral herniation and fatal outcome.<sup>3</sup> Our patient's symptoms of confusion, lethargy, and weight loss are consistent with a progressive hyperammonemic state. Further, quantitative evidence of continual elevation of ammonia was found. Response to treatment with sodium phenylacetate and sodium benzoate (ammonia scavenging agents) in patients with urea cycle dysfunction can potentially reverse the toxic effects of ammonia.<sup>11</sup> This patient's ammonia level was reduced to the normal range within 24 hours, and she exhibited radiographic improvement (Figure 1a and 1b). Hyperammonemia of this etiology that is treated promptly has a good prognosis. Urea cycle defects are treatable with a low-protein diet, amino acid supplementation, and/or liver transplant.<sup>12</sup> Unfortunately, in this case, because of prolonged toxicity, the patient's status epilepticus could not be resolved and she suffered a fatal outcome. Our case provides emphasis that early recognition of hyperammonemic encephalopathy without evidence of liver failure should prompt investigation for a urea cycle defect.

## Summary

Although most commonly associated with infancy, urea cycle defects should be considered in adults with unexplained encephalopathy and ammonia levels should be checked immediately. The signs and symptoms may be vague and atypical but patients may present with recurrent and fulminant presentations. Specific metabolic testing and enzymatic or molecular confirmation are necessary to establish the diagnosis but may not always be possible due to presently still undescribed mutations. Early recognition and treatment with medication, dietary protein restrictions, and/or liver transplant can improve long term outcome and prompt specialty care including neurology/genetics should be considered.

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