Clinical Reasoning: A 27-year-old man with rapidly progressive coma

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SECTION 1

A 27-year-old man was brought to the emergency department by paramedics after being found wandering the street not communicative and with unsteady gait. At the scene, he was noted to have full body tremulousness, which improved after receiving midazolam. He was urgently transported to an emergency department and subsequently developed nausea, vomiting, and progressive deterioration of his mental status. On physical examination, he had tachycardia without fever, and was hemodynamically stable with normal oxygen saturation. He was stuporous; however, all brainstem reflexes were preserved with symmetrically reactive pupils of normal shape and size. He demonstrated spontaneous symmetrical limb movement as well as purposeful withdrawal. He had anicteric sclera, and his dermatologic evaluation showed no rash, needle track marks, or focal signs of external trauma.

Two weeks prior to this admission, he had presented to an emergency department for an upper respiratory illness with signs of mild confusion that spontaneously and completely resolved shortly thereafter.

His only prescription medication was bupropion for depression. His medical history included tetralogy of Fallot with an associated ventricular septal defect that was surgically corrected in youth, as well as pulmonic valve repair 4 years prior. He was employed as the CEO of a start-up Internet company and consumed occasional alcohol and marijuana socially. He had no familial history of neurologic disease.

Questions for consideration:

1. What are your differential diagnoses at this point?
2. What other investigations would help narrow the differential?

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SECTION 2

The differential diagnosis for rapidly progressive stupor and coma in young adults is broad (table 1).¹ Meningoencephalitis, toxic ingestion or substance abuse, or a severe systemic metabolic process were the leading diagnostic considerations. Initial evaluation with basic laboratory studies, urine toxicology, and brain imaging are helpful in narrowing the diagnosis.

Our patient's initial complete blood count, metabolic panel with liver enzymes and coagulation studies, cardiac biomarkers, and chest X-ray were normal. An ECG revealed sinus tachycardia with a right bundle-branch block and precordial T-wave inversions. The initial cranial CT was unremarkable. He was found to have lactic acidosis of 5.5 mmol/L (ref: 0.5–2.2 mmol/L) and low thyroid-stimulating hormone but normal

free T4 levels. Urinalysis and toxicology screening identified sterile ketonuria, the presence of benzodiazepines and tetrahydrocannabinol, and a normal salicylate level. Shortly after presentation, he developed airway compromise due to progressive obtundation requiring endotracheal intubation and was admitted to the intensive care unit for suspected meningoencephalitis. CSF analysis immediately following empiric initiation of broad-spectrum antimicrobial therapy yielded largely noninflammatory findings (3 leukocytes, 0 erythrocytes, 72 mg/dL glucose, 54 mg/dL protein). Serologic and PCR studies for herpes simplex virus, varicella-zoster virus, West Nile virus, and syphilis were negative, as well as the presence of HIV antibodies.

Although viral meningoencephalitis can present in an indolent manner, a fulminate bacterial process was unlikely given the diagnostic results thus far.

Table 1 Causes of stupor and coma in adults¹

Primary brain disorders	Metabolic derangements	Drugs and toxins	Organ failure	Injury	Endocrinopathies	Infection
Postictal state	Hyperglycemia/hypoglycemia	Alcohol	Cardiac arrest	Asphyxiation	Myxedema coma	Bacterial meningitis
Status epilepticus	Hypernatremia/hyponatremia	Carbon monoxide	Heart failure	Head trauma	Thyroid storm	Viral meningitis
Ischemic stroke	Hypercalcemia/hypocalcemia	Ethylene glycol	Lung disease	Hyperthermia	Acute adrenal insufficiency	Sepsis
Intracranial hemorrhage	Hypoxia/hypercarbia	Opioids	Kidney failure	Hypothermia	Diabetic ketoacidosis and hyperosmolar hyperglycemic nonketotic coma	Waterhouse-Friderichsen syndrome
Subarachnoid hemorrhage	Acidosis/alkalosis	Sedatives	Liver failure			Typhoid fever
Tumor	Hypophosphatemia	Tranquilizers				Rabies
Abscess	Reye encephalopathy	Anticholinergics				
Vasculitis	Porphyria	Psychotropics				
Hydrocephalus	Lactic acidosis					
	Hyperammonemia					

Figure MRI of the brain

(A) Diffusion-weighted and (B) apparent diffusion coefficient MRI of the brain show extensive cytotoxic injury within the cortex of the bilateral frontal, temporal, and occipital lobes and insular cortex.

Antimicrobial therapy was further tapered to only acyclovir as all bacterial cultures remained negative. Moreover, a focal intracranial process was not seen on initial cranial imaging, making intracranial hemorrhage, tumor, and trauma unlikely.

The patient developed frequent nonstereotypic multifocal myoclonus of the face, trunk, and limbs. His eyes had persistent downward deviation throughout the adventitious body movements but were without accompanying nystagmus. Continuous EEG monitoring did not demonstrate an ictal correlate initially. A brain MRI obtained 12 hours after admission showed diffuse bihemispheric abnormalities (figure). He rapidly deteriorated nearly 48 hours following symptom onset and developed progressive signs of brainstem dysfunction with bilateral fixed and dilated

pupils and pathologic extensor posturing. Repeat cranial imaging confirmed the presence of new extensive cerebral edema and severe bilateral uncal herniation. Given the unusual pattern of diffuse cortical injury noted on MRI, an ammonia level was obtained and found to be markedly abnormal at 569 $\mu\text{mol/L}$, greater than 15 times that of normal levels (ref: 11–32 $\mu\text{mol/L}$). He subsequently developed electrographic status epilepticus refractory to 3 anticonvulsants.

Questions for consideration:

1. What is the differential diagnosis for hyperammonemic crisis?
2. What additional testing would you pursue to narrow your differential diagnosis?
3. What therapy would you initiate?

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SECTION 3

There are numerous causes of hyperammonemia in adults (table 2).² An ammonia level should be considered in the initial evaluation of young adults who develop rapid decline in mental status without an obvious etiology, even in the absence of liver disease. Medications such as valproic acid can reduce the elimination of ammonia; however, the patient's history and toxicology profile did not suggest inadvertent medication ingestion, toxin exposure, or drug overdose. Herpetic infections and seizures may lead to secondary elevation of ammonia concentrations but not typically to such striking levels. An inborn

error of metabolism was now a much greater diagnostic possibility.

The patient received hyperosmolar therapy with mannitol and hypertonic saline along with other aggressive medical treatment for pathologic elevation in intracranial pressure (ICP) including chemical sedation, paralysis, and mild hypothermia (33°C). Despite this, he continued to demonstrate persistent signs of pathologic ICP elevation. Given the probable poor neurologic prognosis and family's wishes, further surgical intervention, such as ICP monitor placement, was not pursued. Ammonia levels continued to rise and peaked at 2,191 $\mu\text{mol/L}$ despite initiation of continuous renal replacement therapy 72 hours after symptom onset. Additional metabolic investigation revealed marked elevation of urinary orotic acid, consistent with the diagnosis of ornithine transcarbamylase (OTC) deficiency. He died 5 days after admission due to cardiovascular compromise from progressive cerebral herniation and likely brain death. An autopsy confirmed the presence of diffuse cerebral edema with patchy cortical ganglioneclerosis and uncal herniation. The liver was of average size and shape, and histologic examination demonstrated sinusoidal congestion but no cirrhosis.

Table 2 Causes of hyperammonemia in adults²

Increased ammonia production
Infection
Urease-producing bacteria
<i>Proteus</i>
<i>Klebsiella</i>
Herpes infection
Protein load
Extreme exercise
Seizure
Trauma and burns
Steroids
Chemotherapy
Starvation
Gastrointestinal hemorrhage
Total parenteral nutrition
Other
Multiple myeloma
Renal failure
Decreased ammonia elimination
Liver failure
Fulminant hepatic failure
Transhepatic intrajugular portosystemic shunt
Drugs
Valproate
Carbamazepine
Sulfadiazine
Salicylates
Glycine
Inborn errors of metabolism
Ornithine transcarbamylase deficiency
Carbamyl synthetase deficiency
Hypermethioninemia
Organic acidurias
Fatty acid oxidation defects

DISCUSSION OTC deficiency is caused by mutations of the *OTC* gene, located on the X chromosome, which is expressed in the liver and gut. The disease tends to affect neonatal boys severely; however, adult-onset disease has been described.³ In hyperammonemic crisis, rapidly progressive encephalopathy with signs of raised intracranial pressure is its most severe phenotype. Neurologic manifestations are common and include myoclonus,⁴ seizure, and status epilepticus, among other signs of cortical dysfunction. Prior case series suggest that OTC deficiency can be characterized on MRI by extensive cortical involvement that includes the insular and cingulate cortices, as these areas may be particularly vulnerable to hyperammonemic-hyperglutaminergic states.⁵ Refractory elevation of ICP and status epilepticus are challenging to manage and may lead to death. Although the precise mechanisms of ammonia-associated cerebral toxicity are not fully understood, it is believed to cause cerebral edema through glutamine accumulation within astrocytes and metabolic disturbances through a variety of mechanisms.⁴

Carriers of the genetic defect may develop mild, nonspecific symptoms that include confusion, nausea, irritability, cognitive deficits, bizarre behavior, and protein aversion. The more severe clinical manifestation is hyperammonemic crisis.⁴ The phenotypic variation seen in OTC deficiency, even among family members who share the same mutation, may result from the *OTC* genotypic heterogeneity as well as

variability in environmental and developmental factors.⁶ Stressors include the postoperative period,⁷ use of high-dose corticosteroids,⁸ and high protein consumption (e.g., Atkins diet).⁹ Plasma amino and urine organic acid levels are typically abnormal in OTC deficiency—elevated concentrations of plasma glutamine or alanine as well as urinary orotic acid and uracil are frequently seen. DNA sequence analysis often identifies an associated mutation. Treatment strategies involve reducing serum ammonia levels quickly with combination therapy including hemodialysis, dietary protein restriction, and sodium scavengers such as sodium phenyl acetate and sodium benzoate.¹⁰

Adult-onset OTC deficiency is rare but may have catastrophic neurologic consequences if not detected early. Early identification and aggressive treatment of hyperammonemia may potentiate its effects with reasonable neurologic outcome.

AUTHOR CONTRIBUTIONS

Dr. Jonathan M. Wong: drafting the manuscript, manuscript concept/design. Dr. Mekhala Chandra: critical revision of the manuscript. Dr. Rachael VanDeBogart: critical revision of the manuscript. Dr. Brandon Lu: critical revision of the manuscript. Dr. Alan H. Yee: manuscript concept/design, critical revision of the manuscript, manuscript supervision.

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DISCLOSURE

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