Pearls & Oy-sters: Chemotherapy-associated hyperammonemic encephalopathy

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Pearls

- Hyperammonemic encephalopathy (HE) is a metabolic condition precipitated by elevated blood ammonia, which may be idiopathic or secondary to increased production (e.g., infection with urease-positive bacteria) or decreased elimination of ammonia (e.g., liver failure), or drug-induced (e.g., valproic acid).
- Chemotherapy-associated HE is a rare but highly fatal condition requiring rapid identification and neurocritical care.

Oy-ster

- Although uncommon in the adult population, hyperammonemia can be triggered by a metabolic stressor in the context of a previously undiagnosed urea cycle disorder, particularly heterozygous ornithine transcarbamylase deficiency.

A 55-year-old, right-handed, functionally independent woman was brought to the emergency department by her sister, who found her acutely disoriented and agitated. The patient's medical history was significant for major depression and dyslipidemia. One year prior to presentation, the patient completed a full course of chemotherapy (bendamustine and rituximab) for follicular B-cell lymphoma. Six months later, hypermetabolic retroperitoneal lymph nodes were found on a PET scan, suggesting relapse or persistent disease activity. A lymph node biopsy confirmed transformation to Hodgkin lymphoma. The patient received a first cycle of ABVD chemotherapy (doxorubicin, bleomycin, vinblastine, dacarbazine) 1 month prior to presentation. Two weeks before presentation, she was briefly hospitalized for a deep venous thrombosis of the left arm and chemotherapy-induced pancytopenia. The patient's sister reported that the patient had complained of mild fatigue and nausea following her second cycle of ABVD, administered 6 days prior to presentation. Her home medications were apixaban, dexlansoprazole, citalopram, rosuvastatin, pregabalin, prophylactic trimethoprim-sulfobactam, valaciclovir, and filgrastim. She did not use illicit drugs or alcohol. On presentation, the patient's vital signs were normal. She did not exhibit signs of meningismus, she was alert but was disoriented in all spheres, she uttered incomprehensible sentences, and she was mildly agitated. No cranial nerve deficits were observed. She exhibited paratonia, moved all 4 limbs forcefully, and withdrew to painful stimuli symmetrically. Deep tendon reflexes were normal and she had flexor plantar responses. No abnormal movements were observed. Her general physical examination was unremarkable.

Laboratory investigations revealed stable pancytopenia, respiratory alkalosis (pH 7.65), and elevated ammonia (NH₃) levels (221 μmol/L). Liver enzymes and liver function tests were normal. Noncontrast brain CT scan and MRI did not show any abnormalities, apart from significant motion artifact. An abdominal ultrasound ruled out biliary duct obstruction and portosystemic shunt. Lumbar puncture was delayed as the patient's anticoagulation had to be withheld. In the context of known immunosuppression, she was empirically treated for infectious meningoencephalitis

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(ceftriaxone, vancomycin, ampicillin, acyclovir). Her hyperammonemia was addressed with lactulose and rifaximin. Over the course of the next day, the patient's level of consciousness rapidly deteriorated. A routine EEG was performed to rule out nonconvulsive status epilepticus. It showed a moderate to severe generalized slowing of cerebral activity with no evidence of epileptiform abnormalities. Gradually, over the following hours, the patient became unresponsive to stimuli. She was intubated because of her inability to maintain her airway and transferred to the intensive care unit. Continuous veno-venous hemofiltration was initiated to accelerate the elimination of serum NH_3 , with some success ($353 \rightarrow 189 \mu\text{mol/L}$). At this stage, off-sedation neurologic examination showed no signs of lateralization or additional brainstem dysfunction. A repeat brain MRI performed the next day revealed symmetrical diffusion restriction of both thalami and internal capsules (figure 1, A and B), with subtle corresponding hyperintensity on fluid-attenuated inversion recovery (FLAIR).

A lumbar puncture performed on postadmission day 2 was normal, including an absence of leukocytes and normal protein. CSF studies for herpes simplex virus, varicella-zoster virus, listeria, tuberculosis, JC/BK virus, human herpesvirus-6, cryptococcus, mycobacteria, and mycosis were all negative, as were serum tests for Epstein-Barr virus, cytomegalovirus, hepatitis B and C virus, HIV, respiratory viruses, and toxoplasmosis.

The following day, a repeat EEG demonstrated generalized attenuation of cerebral activity, punctuated by 20- to 30-second trains of rhythmic delta activity, several per hour, with evolution in amplitude and frequency, with superimposed spikes, satisfying criteria for electrographic seizures (no clinical correlate noted on video-EEG). These were bilateral and independent

seizures but always maximal in the parietal head regions (figure 2). Propofol and midazolam infusions were successful in controlling the electrographic seizures and the patient was started on IV phenytoin followed by lacosamide. A third brain MRI, performed on postadmission day 3, demonstrated progression of the diffusion restriction in the thalami, internal capsules, cingulate gyri, and new abnormalities in the bilateral parietal, temporal, and occipital cortices (figure 1, C and D). Over the following days, attempts to decrease the chemical sedation resulted in increased electrographic seizures. The patient developed an infectious cellulitis of the leg, resulting in septic shock. She deteriorated despite antibiotic treatment and aggressive vasopressor support. Her NH_3 levels increased steadily to $1,600 \mu\text{mol/L}$ on postadmission day 8. A repeat brain CT scan demonstrated severe diffuse cerebral edema (figure 1, E–H). In light of this evolution, the family decided to transition to palliative care, and the patient died shortly after.

Discussion

The main source of NH_3 in humans is the gastrointestinal tract, where it is synthesized by enterocyte conversion of glutamine and gut bacteria catabolism of ingested proteins. Following absorption in the portal vein, the vast majority of NH_3 is converted to urea or glutamine by the liver. When liver metabolism is saturated or dysfunctional, catabolism and elimination of NH_3 is performed chiefly by the brain, muscles, and kidney. After crossing the blood-brain barrier, NH_3 participates in astrocytic catabolism of glutamate to glutamine, which is a potent osmotic agent. In the process, free radicals are also created. Osmotic and cytotoxic cerebral edema follow and may ultimately lead to seizures and intracranial hypertension.^{1,2}

Figure 1 Brain imaging

(A, B) Brain MRI (diffusion-weighted imaging [DWI] and apparent diffusion coefficient [ADC]) on postadmission day 1 reveals symmetrical diffusion restriction in the thalami and internal capsules. (C, D) Brain MRI (DWI and ADC) on postadmission day 3 demonstrates progression of the diffusion restriction in the thalami, internal capsules, and cingulate gyri, and new DWI abnormalities in the bilateral parietal, temporal, and occipital cortices. (E, G) Normal noncontrast brain CT on admission. (F, H) Noncontrast brain CT on postadmission day 8 demonstrates severe diffuse cerebral edema.

Figure 2 EEG

EEG performed on postadmission day 3 demonstrates generalized attenuation of the patient's cerebral activity (solid black arrow), punctuated by 20- to 30-second trains of rhythmic delta activity (outlined white arrow), several per hour, with evolution in amplitude and frequency, with superimposed spikes. These were bilateral and independent seizures but always maximal in the parietal head regions. Method: double banana referential montage with additional midline electrodes. Each interval is 1 second, notch filter is on, high frequency filter is at 70 Hz, and low frequency filter is at 1 Hz.

Hyperammonemia may be idiopathic, secondary to increased production or decreased elimination of NH_3 , or drug-induced.³ Excess production of NH_3 has been reported in the context of infection with urease-positive bacteria, increased protein catabolism due to gastrointestinal bleeding, burns, or sepsis, as well as hematologic neoplasms, particularly multiple myeloma. Bilateral tonic-clonic seizures can also transiently elevate NH_3 levels if measured up to 8 hours later, as the result of excessive muscular contractions.⁴ Inborn errors in metabolism, acute liver failure, chronic liver disease, and porto-systemic shunts are common causes of decreased NH_3 elimination. Ornithine transcarbamylase deficiency is the most prevalent inherited urea cycle defect. Mild enzymatic deficits can present in late adulthood if triggered by a metabolic stressor, particularly in heterozygous women, who tend to present later. Finally, drug-induced hyperammonemia is seen with medications that affect urea cycle enzymes (e.g., valproic acid, carbamazepine), cause hepatotoxicity (e.g., acetaminophen), or precipitate Reye syndrome (aspirin). Our patient had not recently taken any of these drugs.

HE typically presents with acute to subacute neuropsychiatric symptoms, ranging from mild cognitive impairment and sleep-wake disorders in mild cases to agitation, psychosis, and eventually coma in moderate to severe cases. Some patients also present with abdominal discomfort, nausea, or anorexia, as well as hyperventilation, myoclonus, asterixis, or diffuse hyperreflexia.⁵ The differential diagnosis includes structural (e.g., stroke, CNS mass or neoplasm), toxico-metabolic (e.g., hypercapnia, hyperglycemia, uremia), infectious (e.g., sepsis, meningoencephalitis), and psychiatric (e.g., neurologic functional disorder) causes of altered level of consciousness. An elevated serum NH_3 concentration is required to make the

diagnosis of HE, but the absolute concentration does not always correlate with clinical severity. Brain MRI typically shows restriction of diffusion and T2/FLAIR hyperintensities in the insular cortex, cingular gyri, thalami, and posterior internal capsules,⁶ with the involvement of other cortical regions in more severe cases. Occipital and perirolandic regions are usually not involved. Approximately half of patients exhibit cortical or subcortical microbleeds. Cortical diffusion restriction can also be seen in status epilepticus. In our patient, cortical diffusion restriction could have been caused by HE, seizures, or both.⁶

Chemotherapy-associated HE is a rare condition. Typically, patients with hematologic or solid neoplasms present within 24 days of exposure to a chemotherapeutic agent with rapid-onset severe encephalopathy, with or without additional signs of hyperammonemia such as seizures and respiratory alkalosis. The diagnosis requires that NH_3 levels be greater than twice the upper limit of normal, and that hepatic dysfunction and other etiologies of hyperammonemia have been ruled out.^{7,8} The associated chemotherapeutic agents include vincristine and daunorubicin, respective structural analogues of vinblastine and doxorubicin, which our patient had received. Cytarabine, asparaginase, cytosine arabinoside, amsacrine, cyclophosphamide, etoposide, mitoxantrone, and prednisone have also been involved.⁷⁻¹¹ In the literature, other authors have proposed a multisystem dysfunction in the acutely ill patient on chemotherapy as a mechanism of hyperammonemia. Possible contributing factors include increased protein intake via parenteral nutrition, as well as increased protein catabolism caused by cancer cachexia, concomitant sepsis, or gastrointestinal bleeding.¹⁰ The specific management of hyperammonemia is multimodal, including reduction of protein intake, administration of lactulose and rifaximin, continuous

veno-venous hemofiltration, or conventional dialysis. Ammonia scavengers (sodium phenylacetate, sodium benzoate) should be considered in patients with inborn errors of metabolism. Despite optimal medical management, case series have reported poor prognoses, with peak NH_3 levels of 758–1,001 $\mu\text{mol/L}$ and 80% case fatality.^{7,8} However, a notable exception has been consistently described among patients exposed to 5-fluorouracil, where NH_3 is a direct metabolic product, and hyperammonemia is transient and nonlethal in 78% of cases.¹²

Physicians should be aware of chemotherapy-associated HE, a rare but highly fatal condition requiring rapid identification and neurocritical care.

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Disclosure

The authors report no disclosures relevant to the manuscript. Go to [Neurology.org/N](https://www.neurology.org/N) for full disclosures.

Appendix Authors

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Joel Neves Briard, MD	Université de Montréal, Canada	Author	Drafted the manuscript
Nastasija Lezaic, MDCM	Université de Montréal, Canada	Author	Presented the patient's case to the neurology service rounds and revised the manuscript
Mark Robert Keezer, MDCM, PhD	Université de Montréal, Canada	Author	Interpreted the video-EEG monitoring and revised the manuscript

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