

## MORNING REPORT

# THE HYPE WITH HYPERAMMONEMIC ENCEPHALOPATHY: THE CASE OF THE CONFUSED VETERAN

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*(Written in call-and-response format with italicized text to be read by presenter)*

**A** 71-year-old veteran with multiple myeloma, heart failure with reduced ejection fraction, coronary artery disease, and atrial flutter presented to a large, urban Veterans Affairs Medical Center (VAMC) from his outpatient chemotherapy infusion clinic for confusion and lethargy. He was accompanied by a close friend who provided much of the history.

*Confusion, encephalopathy, acute brain failure, altered mental status, reversible dementia and acute confusional state are all terms indicating generalized brain dysfunction that is triggered by an acute illness. In an attempt to clarify these terms, diagnostic criteria for delirium were created in 1980 with the third edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM). It has since been updated to the DSM-5, defining delirium as diagnostic criteria that include an acute change from baseline with disturbances in attention and cognition (ie memory deficit, disorientation, language, perception). It is critical to know what a patient's baseline mental and functional status is when distinguishing between delirium and more chronic dementia.*

*An elderly patient coming in with acute delirium presents a broad differential diagnosis. It is important to consider organic, modifiable causes including medications, electrolyte abnormalities, hypoxia, alcoholism, liver disease, stroke and/or infection. Additional history, examination and lab findings will further develop the differential diagnosis. Delirium has been called the "canary in the coal mine" as it is a signal of an acute medical condition warranting evaluation and treatment. The difficulty often comes in identifying the medical condition it is signaling.*

Upon further questioning, the patient's friend noted a one-month decline in mentation and functional status. Prior to his decline he was living alone, driving, and

managing his own finances in an apartment with 17 stairs. At admission the patient had been living with his friend for the past "few weeks," who had taken over as his primary caretaker. He was originally diagnosed with Durie Salmon Stage IIa IgG light chain multiple myeloma three years prior and was transitioned to a new chemotherapeutic regimen of daratumumab/dexamethasone one week before admission. He subsequently became increasingly fatigued with a poor appetite. Then, while in the VAMC infusion clinic he was found to be lethargic and therefore sent to the emergency department (ED).

*The presence of anorexia and a new chemotherapeutic regimen in a subacute, progressive confusion can guide a differential towards an electrolyte abnormality, infectious, or medication induced etiology of acute encephalopathy. Relative risk data shows that patient's with electrolyte abnormalities have a 1.4-5.1 times higher likelihood of developing delirium compared to 3.1 times for infection and 2.9-4.5 times due to medication.<sup>1</sup> All of these must remain at the top of the differential diagnosis based off of this patient's clinical history.*

In the ED, the patient had a temperature 97.7, pulse 74, respiratory rate 16, and a blood pressure of 106/63. He appeared cachectic with temporal wasting and was noted to be oriented to person with tangential speech. Remote memory was intact as he was correctly able to name the entire 1955 Brooklyn Dodgers lineup. Physical exam was notable for coarse breath sounds in the right lower lobe. Further workup with a non-contrast CT head showed no intracranial process. Urinalysis was noncontributory, and comprehensive blood count was unrevealing other than a BUN of 29 and creatinine of 1.5. CT chest showed possible segmental pneumonia in

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RLL. Blood cultures were drawn and the patient was started on vancomycin and piperacillin-tazobactam for presumptive hospital acquired pneumonia.

*At this point a reasonable working diagnosis for this veteran would be delirium secondary to pneumonia. Delirium accounts for 30% of all elderly patients admitted to the hospital.<sup>2</sup> It is a poor prognostic indicator associated with one year mortality rates of 35-40%, higher nursing home placement (47% compared to 18%), and worse functioning/cognition.<sup>2</sup> A key concept in delirium is the idea that removal of the precipitating factor should lead to some improvement in mentation.*

The patient's mentation waxed and waned throughout his admission. On hospital day three, one of two blood cultures were positive for coagulase negative staph. This was deemed a contaminant. He displayed clinical resolution of the pneumonia, and his antibiotics were deescalated to amoxicillin-clavulanic acid. On day four of his admission, a MiniCog was performed due to persistent confusion. A MiniCog is scored out of five total points with a score of 3-5 indicating a lower likelihood of cognitive impairment. The patient scored 1/5 with poor clock draw and only one word on delayed recall. This was followed by the Montreal Cognitive Assessment (MOCA), where he scored only five out of 30 potential points. Any MOCA score less than 25 is considered abnormal, suggesting some form of cognitive impairment. He received only one point for visuospatial, naming, and attention cognitive domains and two points for orientation.

*It is important to reevaluate diagnoses as patient's progress through admission. This patient's presumed precipitating factor for encephalopathy has resolved and yet he is still clinically unchanged. A broader differential must be evaluated and further workup pursued.*

Metabolic and hormonal contributors to delirium were evaluated, including serum vitamin B12 and TSH levels, and found to be within normal limits. CT head was repeated, this time with contrast, showing no evidence of myeloma metastasis to brain, subdural hematoma or intraparenchymal insult. Despite normal synthetic liver function, ammonia was drawn and found to be elevated to 105 umol/L (normal 11-32 umol/L). He had no prior serum ammonia levels charted. Ultrasound of the liver was then performed, showing hepatomegaly but no evidence of fibrosis. Liver synthetic function was evaluated with serum platelet count and INR within normal limits and albumin decreased to 3.1 g/dL.

*Elevated ammonia with normal hepatic function is an uncommon presentation seen in patients with advanced multiple myeloma, valproic acid overdose, and various urea cycle disorders.<sup>4</sup> It is postulated that in hyperammonemia secondary to multiple myeloma, the large population of plasma cells overproduce ammonia due to increased production of cytokines and immunoglobulins.<sup>5</sup> Elevated ammonia is thought to cause changes in astrocyte size and function, with resulting neurologic manifestations including confusion.<sup>4</sup> Hyperammonemic encephalopathy is treated with systemic chemotherapy; hemodialysis is effective only when used in concert with chemotherapy.<sup>5</sup> In contrast to encephalopathy related to cirrhosis, there is no role for lactulose in treating hyperammonemic encephalopathy associated with multiple myeloma.*

Lactulose was trialed, despite no direct evidence supporting its use in multiple myeloma, for five days. There was no improvement in mentation despite adequate bowel movements. Almost two weeks into the Veteran's hospital stay, repeat MOCA was performed. He continued to perform poorly with a score of 7/30. After goals of care conversations with

the patient's friend and healthcare power of attorney, it was decided to try chemotherapy again. He received daratumumab and dexamethasone on day 12. Within several days, he was noted to have improved wakefulness, attention and ability to interact. He was discharged to a skilled nursing facility on day 17 of his hospitalization with a primary diagnosis of hyperammonemic encephalopathy secondary to progressive multiple myeloma. Unfortunately, he was readmitted several weeks later with confusion and a serum ammonia level of 92 umol/L. He was enrolled in hospice and expired soon thereafter.

*This case elucidates an uncommon etiology of encephalopathy as well as the challenges in treating hyperammonemic encephalopathy. Hyperammonemia is a common cause of encephalopathy in veterans; however, it is usually attributed to severe liver disease. The patient's delirium was originally attributed to pneumonia, however when his condition did not improve with antibiotics, the decision was made to workup additional etiologies eventually leading to the diagnosis of non-cirrhotic hyperammonemic encephalopathy.*

**Discussion**

Hyperammonemic encephalopathy in progressive multiple myeloma has been documented in case reports for thirty years and is associated with a high mortality. There is no prevalence data or randomized controlled trials currently published, but the little research that has been published shows that it is more frequently seen in men and the most common subtype is IgG, as in this patient.<sup>5</sup> Treatment of hyperammonemic encephalopathy involves management of underlying etiology via chemotherapy rather than symptomatic treatment with lactulose. Early workup and initiation of chemotherapeutics is critical in symptom management. With this in mind a high index of suspicion for hyper-

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ammonemic encephalopathy should be given to patients with multiple myeloma admitted for altered mentation when more routine etiologies of delirium are not elucidated.

**References**

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