Neuropsychiatric Sequelae of Hyperammonemia: Clinical Pearls for the CL Psychiatrist

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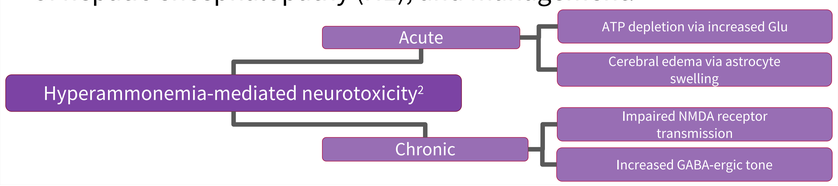
Background

Hyperammonemia is known to cause acute and chronic neurotoxicity, and valproic acid (VPA) has often been associated with inducing hyperammonemia. Here, we will present a case of patient with altered mental status and hyperammonemia, and literature review covering non-hepatic hyperammonemia, grading of hepatic encephalopathy (HE), and management.



Clinical Grading of HE[21]

00	**Covert** - altered psychomotor speed and/or executive functioning without clinical evidence of mental change	• Abnormal results of "established psychometric or neuropsychological tests" • No specific criteria
01	**Covert** - altered sleep, impaired arithmetic abilities, shortened attention, euphoria/anxiety, "trivial lack of awareness"	• Cognitive or behavioral decay on clinical exam, while still remaining oriented to time and space
02	**Overt** - lethargy/apathy, disorientation to time, personality change, dyspraxia, inappropriate behavior, asterixis	• Patient gets at least 3 of the following incorrect: day of the month, day of the week, month, season, or year (in addition to the other findings)
03	**Overt** - somnolence/semi-stupor (though responsive to stimuli), confusion, gross disorientation, bizarre behavior	• Gross disorientation includes disorientation to space; patient gets at least 3 of the following incorrect: country, state/region, city, or place
04	**Overt** - Coma	• Not responsive to painful stimuli

Case

A 74-year-old male with schizoaffective disorder, bipolar type, and past medical history of CKD stage III and COVID-19 associated cognitive sequelae was being evaluated for behavioral dysregulation and psychosis attributed to acute psychiatric decompensation. Home medications included benztropine, aripiprazole tabs with Aripiprazole Maintena long-acting injectable as well as VPA. After confirming medication adherence and obtaining a sub-therapeutic VPA level of 44 mcg/mL on admission, the VPA dose was increased from 1500mg qhs to 1750 mg qhs to manage agitation. After initial improvement, the patient developed lethargy with altered sensorium and inattention. Work-up revealed a VPA level of 106 mcg/mL, prompting discontinuation of VPA. Additionally, labs showed an ammonia level of 38 µmol/L, which increased to 51µmol/L a few days later. Ultimately, the patient was treated for urosepsis.

Discussion

Etiologies

- Infectious: Urinary tract infections with urease-producing bacteria[8,16]
- Metabolic: Urea cycle disorders, other enzyme disorders[3, 9, 15, 19]
- Enteral: GI bleed, bacterial overgrowth, constipation[1, 14]
- Anatomic: Urinary diversions[10, 17], porto-systemic shunt[4]
- Post-Op: Gastric bypass bariatric surgery[5, 6, 18], organ transplantation[12]
- Renal: AKI, CKD[12]
- Muscular: Burns, trauma, seizure activity, high intensity exercise[11]
- Other: Multiple myeloma[4]
- Medications:

Psychotropics	Other Medications
VPA, co-administration of VPA and risperidone, lamotrigine, gabapentin, methamphetamines, carbamazepine[4, 7, 11, 12, 13, 22]	Topiramate, cytarabine, asparaginase, 5-FU, salicylates, tacrolimus, cyclosporine, acetazolamide, cyclophosphamide, enflurane, halothane, sulfadiazine[4, 12]

Management*

Non-Pharmacologic	Pharmacologic
• Obtain thorough history from patient and/or collateral regarding medication changes, surgeries, potential ingestions • Complete review of psychiatric and non-psychiatric medications, including both new and chronic • Restrict protein intake[12] • Consider obtaining confirmatory ammonia levels if lower elevation (60-100 µmol/L), ensuring they are correctly drawn/transported[12] • Consider genetic testing for urea cycle disorders or other inherited disorders	• If applicable, treat underlying etiology (discontinuing medication if possible, IVF, treating GI bleed, etc.) • Consider empiric antibiotics if clinical suspicion of infection • Medications: lactulose, rifaximin, L-carnitine, sodium benzoate

*Generally, normal ammonia levels for adults range from 30-50 µmol/L - though this varies in the literature

Conclusion

Given the neurotoxic effects of ammonia, it is important for the Consultation-Liaison Psychiatrist to consider non-hepatic hyperammonemia as an etiology of altered mental status, especially considering the effects of medications such as VPA. Further research on the clinical presentation of non-hepatic hyperammonemia and the longitudinal effects of hyperammonemia is necessary to determine the role of trending elevated values.

References