# Two Cases of Valproate Associated Non-Hyperammonemic Subacute Encephalopathy After Prolonged Use

**Alexander Baradei, MD; Benjamin Kalivas, MD**
Medical University of South Carolina Departments of Medicine and Psychiatry

MUSC Health
Medical University of South Carolina

## ABSTRACT

**Background/Significance:** Encephalopathy is an alteration in mentation affecting a patient's cognition or level of arousal caused by any neurologic or systemic disease that alters brain function or structure. It is a syndrome rather than a specific disease process and can have varying temporal patterns of onset; 'subacute encephalopathy' occurring over a span of weeks to months. Valproic acid is an anti-epileptic medication that is often used in psychiatry as a mood stabilizer. In the year 2020 Valproate was the second most prescribed mood stabilizer with > 6million prescriptions written in the US for > 900,000 patients. Valproic acid has many known side-effects with valproate associated hyperammonemic encephalopathy being a rare yet well documented side-effect. But what is less known and poorly described in the literature is 'valproate associated non-hyperammonemic subacute encephalopathy after prolonged use,' sometimes referred to as 'reversible dementia.'

**Methods:** We present two patients in their fifth and seventh decade of life, that were seen by the psychiatry consult service for altered mental status. Both patients had a history of bipolar disorder and had been stable on valproate for more than 15 years. Both developed worsening subacute cognitive impairment of unknown cause that progressed over the course of several months with associated considerable loss of independence. Neither patient met diagnostic criteria for delirium, but they both had impaired executive function and memory. Both patients had extensive medical work ups to determine the cause of their encephalopathy which was all negative including normal free VPA and ammonia levels.

**Results:** After ruling out all other causes, It was suspected that valproate was the culprit of their encephalopathy, and they both returned to their baseline within six to twelve weeks after discontinuation of valproic Acid with continued improvement in mentation months later.

**Conclusion/Implications:** These cases demonstrate the importance of considering sub-acute encephalopathy after prolonged use of valproic acid and to consider discontinuation even when the patient has been stable on the medication for many years.

## REFERENCES

Baumgartner, J., Hoeflich, A., Hinterbuchinger, B., Fellinger, M., Graf, I., Friedrich, F., Frey, R., et al. (2019). Fulminant Onset of Valproate-Associated Hyperammonemic Encephalopathy. *The American journal of psychiatry*, *176*(11), 900–903. United States: American Psychiatric Association.

Caruana Galizia, E., Isaacs, J. D., & Cock, H. R. (2017). Non-hyperammonaemic valproate encephalopathy after 20 years of treatment. *Epilepsy & behavior case reports*, *8*(C), 9–11. United States: Elsevier.

Erkkinen, M. G., & Berkowitz, A. L. (2019). A clinical approach to diagnosing encephalopathy. *The American Journal of Medicine*, *132*(10), 1142–1147.

Evans, M. D., Shinar, R., & Yaari, R. (2011). Reversible dementia and gait disturbance after prolonged use of valproic acid. *Seizure (London, England)*, *20*(6), 509–511. England: Elsevier Ltd.

Farooq, O., Zunga, P. M., Dar, M. I., Rather, A. Q., Rashid, S., Basu, J., Dar, I. H., et al. (2014). Non-Hyperammonemic valproate encephalopathy. *Annals of Neurosciences*, *21*(2), 76–79. United States: Annals of Neurosciences.

Häussinger, D., Kircheis, G., Fischer, R., Schliess, F., & Dahl, S. vom. (2000). Hepatic encephalopathyin chronic liver disease:a clinical manifestation of astrocyte swelling and low-grade cerebral edema? *Journal of Hepatology*, *32*(6), 1035–1038. Netherlands: Elsevier B.V.

Jalan, R., & Bernuau, J. (2007). Induction of cerebral hyperemia by ammonia plus endotoxin: Does hyperammonemia unlock the blood–brain barrier? *Journal of hepatology*, *47*(2), 168–171. Netherlands: Elsevier B.V.

Lockwood AH, Yap EW, Wong WH. Cerebral ammonia metabolism in patients with severe liver disease and minimal hepatic encephalopathy. J Cereb Blood Flow Metab. 1991 Mar;11(2):337-41. doi: 10.1038/jcbfm.1991.67. Erratum in: J Cereb Blood Flow Metab 1992 Jan;12(1):177.

Pinson, R. (n.d.). *Encephalopathy - mmhospitals.org*. Retrieved April 4, 2023, from https://www.mmhospitals.org/Portals/0/Documents/patientsafety/Delirium/ACP%20Encephalopathy%20Coding%20Article.pdf

Sean P. Kane, P. D. (n.d.). *Valproate*. Valproate - Drug Usage Statistics, ClinCalc DrugStats Database. Retrieved April 3, 2023, from https://clincalc.com/DrugStats/Drugs/Valproate

Sechi, G. (2008). *Drug-related encephalopathies*. New York: Nova Science Publishers.

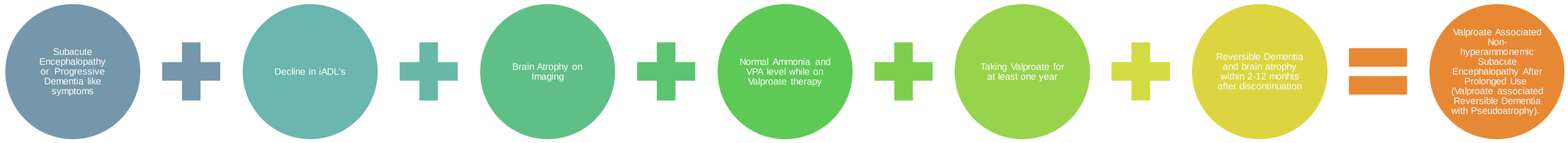
Sepehrinezhad, A., Zarifkar, A., Namvar, G., Shahbazi, A., & Williams, R. (2020). *Astrocyte* swelling in hepatic encephalopathy: molecular perspective of cytotoxic edema. *Metabolic brain disease*, *35*(4), 559–578. New York: Springer US.

Sztajnkrycer, M. D. (n.d.). *Valproic Acid Poisoning*. UpToDate. Retrieved April 3, 2023, from https://www.uptodate.com/contents/valproic-acid-poisoning?search=valproate+toxicity&source=search_result&selectedTitle=1~29&usage_type=default&display_rank=1

Tondelli, M., Vaudano, A. E., Sisodiya, S. M., & Meletti, S. (2020). Valproate use is associated with posterior cortical thinning and ventricular enlargement in epilepsy patients. *Frontiers in Neurology*, *11*.

Wai Yue, Y., Wai, C., Peter, W., Tung, W., & Yau, C. (2017). A fatal case of valproate-induced hyperammonemic encephalopathy: An update on proposed pathogenic mechanisms and treatment options. *International Journal of Epilepsy*, *04*(02), 181–183.

Zafar F, Billadeau BM, Ahmed AU. A Case of Valproate-Induced Hyperammonemic Encephalopathy. Cureus. 2020 Jul 10;12(7):e9114.




## Case 1

PRESENTATION
73 year-old woman with Bipolar disorder type 1 presented to the ED due to AMS, fall and abdominal pain. Four months prior to presentation she was independent and able to partake in all ADLs. Her mentation slowly began to decline with worsening memory. She was moved to an assisted living facility, but became increasingly lethargic and hyper-somnolent, sleeping ~16-18 hours per days.

| Past Medical History | Home Meds: | Significant labs: | Exam: | Imaging: |
|---|---|---|---|---|
| • Bipolar Disorder 1<br>Epilepsy<br>Obstructive sleep Apnea<br>Factor V Leiden<br>Hypothyroidism | • -Depakote 1500mg qhs (~15 years)<br>-Olanzapine 7.5mg qhs<br>-Venlafaxine 75mg qd<br>-Eliquis 2.5mg bid<br>-Synthroid 50mcg qd | • -WBC: 14.5<br>-Hgb: 11.5 MCV 107<br>-Lipase 556<br>-Ammonia 20.3<br>-Total VPA level 70.6<br>-Albumin 2.5<br>-Free VPA: 12 | • A&O x4, cooperative with good eye contact. Fluent with no language deficits and mood was "fine." She was logical and denied AVH, but did show thought blocking with latency in speech. | • **-CT head: Global parenchymal volume loss**<br>-CT Abdomen: Acute pancreatitis<br>-RUQ US: Cholelithiasis and bilary sludge, positive sonographic murphy's sign |

CASE RESOLUTION
Depakote was held, and she was transitioned to lacosamide for seizures, and her Olanzapine dose was increased for mood stabilization. She was discharged to rehab. When she was seen in clinic 4 weeks later her MOCA score was 23/30, but her mentation was very much improved. When seen another 3 months later, she was living independently once again, with much improved memory and cognition. Her MOCA score another 3 months later was 27/30, and a repeat CT head imaging one year after her hospital admission showed almost complete reversal of parenchymal volume loss with normal ventricular size.

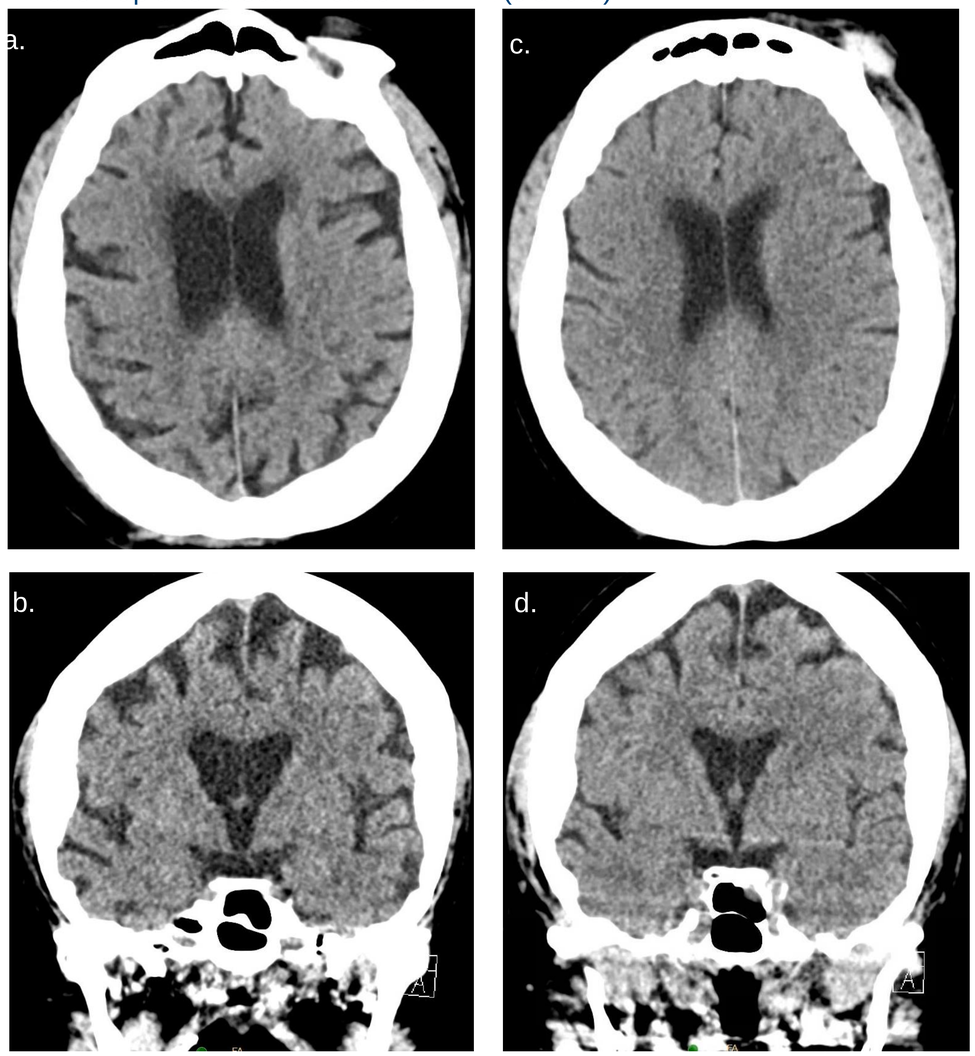
## Case 2

PRESENTATION
52 year-old man, presented to the ED with headaches, neck pain and cognitive decline over the span of several months. His headaches were left sided, constant and minimally responsive to over the counter medications. The cognitive decline included forgetfullness affecting short term and remote memory and increasing difficulty with iADL's including driving, preparing food, handling finances or completing tasks that require multiple steps. ROS was positive for fatigue, poor appetite, nausea, weight loss, light/sound sensitivity, worsening vision, slurred speech, balance problems and urinary incontinence.

| Past Medical History | Home meds | Labs | Exam | Imaging |
|---|---|---|---|---|
| • Bipolar Disorder 1<br>• Hypertension,<br>• Hyperlipidemia,<br>• Atrial fibrilation,<br>• Hypertrophic obstructive cardiomyopathy with implanted ICD,<br>• Cerebral vascular accident with residual left sided weakness,<br>• Peripheral vascular disease with implanted ilial stents,<br>• Lyme disease (treated 1 year prior) | • apixaban,<br>• atrovastatin,<br>• bumetanide,<br>• buspirone,<br>• depakote,<br>• empagloflozin,<br>• ezetimibe,<br>• gabapentin,<br>• lamotrigine,<br>• metoprolol tartrate,<br>• pantoprazole,<br>• prazosin,<br>• quetiapine,<br>• spirinolactone,<br>• trazodone,<br>• varenicline | • WBC 10.9;<br>• HGB 19.2;<br>• Ca 10.7;<br>• K 3.3;<br>• BNP 321;<br>• Ammonia 32;<br>• ceruloplasmin 27;<br>• TFTs WNLN<br>• UDS + Cannabinoids;<br>• vitamin levels WNL<br>• Trace metals WNL<br>• inflammatory markers Neg<br>• tick borne illnesses Neg<br>• Autoimmune work up Neg<br>• CSF studies Neg<br>• protein 14-3-3 Neg;<br>• urine prophyrin Neg; | • impaired frontal and execute function, flat affect, slow to respond to commands and clonus in right ankle, but was able to engage in conversation, recount recent events recently seen on television, and was oriented x4. | • CT head showed Moderate parenchymal volume loss out of proportion to age. |

CASE RESOLUTION
Due to the very thorough but largely negative work up, and the subacute nature of his decline in iADL's and associated atrophy on brain imaging in the context of taking Valproate for many years, it was suspected that his presentation was likely due to Valproate. Valproate was switched to Zyprexa then later to Lamotrigine. Upon 2 month follow up, patient had almost returned to his baseline, and is able to perform multi-step tasks, able to engage in an intellectual conversation, and is able to drive again. Unfortunately, there is no repeat head imaging to compare to the prior study, nor a MOCA score.

Figure 1: Coronal head CT at presentation (images a and b) and at follow up after discontinuation of VPA (c and d)




## DISSCUSSION