

Stabilized schizoaffective disorder; later confusion and depression appears

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Mr. D, age 42, has a history of schizoaffective disorder, which was stabilized with medication. He later presents with acute mood, cognitive, and behavioral changes. What could be the cause?



How would you handle this case?

Answer the **challenge questions** throughout this article

CASE Disoriented and confused

Mr. D, age 42, presents to our emergency department (ED) accompanied by his family with recent onset of disorientation, confusion, depressive mood with labile affect, sleep disturbances, purposeless movements, and grossly reduced kinetics/verbal output. He has a history of schizoaffective disorder, bipolar type, and recurrent admissions for psychotic mood instability.

A few months earlier, Mr. D was treated at our facility for acute exacerbation of his schizoaffective disorder. He was stabilized and discharged with aripiprazole, 30 mg/d, and mirtazapine, 15 mg/d—he had been taking both medications for some time—and newly started extended-release divalproex, 500 mg in the morning/1000 mg nightly (13.2 mg/kg). His trough valproic acid serum level was 70 µg/mL at discharge. He continued on this medication regimen until he returns to our ED with his family.

Mr. D has several medical problems, such as type 2 diabetes mellitus and hypertension, for which he has been receiving metformin, 1,000 mg/d, lisinopril, 10 mg/d, and simvastatin, 20 mg/d. He has no history of alcohol or substance abuse and does not smoke.

Serum and urine analyses are unremarkable and include finger-stick blood glucose, complete blood count, urinalysis, urine drug screen, comprehensive metabolic panel, mag-

nesium, γ -glutamyl transpeptidase (GGTP), amylase, thyroid-stimulating hormone, and blood alcohol level. Random valproic acid serum level taken in the ED is 64 µg/mL. Non-contrast head CT is interpreted as non-acute. There are no documented abnormal findings during the physical exam.

What could be causing Mr. D's altered mental status?

- symptoms of a medical illness
- medication, undetected substance intoxication, or withdrawal-related symptoms
- acute exacerbation of schizoaffective disorder
- delirium
- catatonia of undetected and/or multiple causes

The authors' observations

The differential diagnosis was broad at the time of Mr. D's presentation to the ED

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Disclosures

The authors report no financial relationship with any company whose products are mentioned in this article or with manufacturers of competing products.

Clinical Point

VHE is a rare and potentially lethal idiosyncratic event unrelated to duration of VPA treatment, dosage, or valproic serum level

Table 1

Summary of available psychiatric VHE case literature (14 reports)

Patient profile (N = 17)	
Age	21 to 46 (mean 46)
Sex	14 women (82%)
General medical comorbidity ^{5,7,10,12,15,17,18}	8 patients (47%)
Polypharmacy ^{5,7-12,15-18}	14 patients (82%; mean, 4.3 medications)
Anticonvulsant polytherapy ^{9-11,15,18}	5 patients (29%)
VPA exposure profile	
Duration of exposure before VHE onset (when reported) ^{5-11,13,15,17,18}	Range 1 day to 11 years (most commonly within 1 week, 46% of patients)
VPA dosage	Range, 750 to 3000 mg
Serum VPA level at time of noted VHE, when reported ^{5,6,8-13,15-18}	Range, 73 to 145 µg/mL (mean, 104 µg/mL)
Clinical findings	
Ammonia level at time of noted VHE, when reported with units ^{5,6,8-15,17,18}	Range, 58 to 445 µg/dL (mean, 239 µg/dL)
Transaminase levels at time of noted VHE, when reported ^{5,6,8-10,14-18}	14 (85%) cases normal; 2 cases documented transaminase abnormalities, including AST/ALT 37/35 U/L ¹¹ and an unquantified “mild” AST elevation ¹²
Management and outcome	
Treatment involved discontinuation of valproate ^{5-10,12-18}	16 patients (94%); use of lactulose was not uncommon (8 patients, 49%) ^{5-8,12,15,17} ; use of carnitine was uncommon (2 patients, 11%) ^{8,18}
Mortality	None (0%)
Time to recovery, when reported ^{5-15,17,18}	16 patients (94%) within 1 week or sooner
For standardization, micrograms per milliliter (µg/mL) for VPA levels and micrograms per deciliter (µg/dL) for ammonia levels were used in our review	
ALT: alanine aminotransferase; AST: aspartate aminotransferase; VHE: valproate-related hyperammonemic encephalopathy; VPA: valproic acid	

because his symptoms overlapped across clinical considerations. The initial medical evaluation was negative, which suggested an active primary mental illness. However, Mr. D's presenting symptoms warranted continued vigilance for concurrent or emergent delirium or catatonia, especially because of the potential morbidity if these conditions are not detected and managed.

EVALUATION Fluctuating status

Mr. D is admitted to the mental health unit for treatment of presumptive bipolar depression with catatonic features. The initial admitting

team continues aripiprazole, increased divalproex extended release to 1,000 mg in the morning/1,500 mg at night, held mirtazapine, and started lorazepam, 2 mg, 3 times daily, for catatonia. Metformin, lisinopril, and simvastatin are continued. Mr. D's mental status and behavior fluctuates over the next 48 hours prompting the treatment team to consider an emergent delirious process.

On day 3, the primary team assumes care and observes fluctuations in level of arousal with disorientation, inattention, labile affect, disorganized speech and behavior, and responsiveness to internal (visual) stimuli. Finger-stick blood glucose level remains sta-



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ble. Review of physical symptoms is notable for nausea and examination reveals unsteady gait and asterixis. His family denies that Mr. D used alcohol or drugs before admission. Collateral information from the family and review of Mr. D's outpatient records is consistent with an acutely fluctuating confusional state that began 10 days before admission.

At this point, what is your differential diagnosis for Mr. D's altered mental status?

- a) symptoms of a medical illness
- b) medication, undetected substance intoxication, or withdrawal-related symptoms
- c) acute exacerbation of schizoaffective disorder
- d) delirium
- e) catatonia of undetected or multiple causes

TREATMENT Valproate stopped

Mr. D's ammonia level is 119 µg/dL (reference range, 15 to 45 µg/dL) on hospital day 3. Divalproex and lorazepam are discontinued, and standing lactulose is started because it is evident that he has active valproate-related hyperammonemic encephalopathy (VHE), also known as delirium due to valproate-related hyperammonemia.

Awake and drowsy EEG within 24 hours reveals "diffuse irregular slow activity" without epileptogenic features. HIV, syphilis, and vitamin B₁₂ and red blood cell folate screening are negative. We confirm that Mr. D is not a vegetarian (dietary carnitine deficiency is a risk factor for VHE). He is not screened for a urea cycle disorder.

The authors' observations

Divalproex is a commonly used FDA-approved treatment for a variety of neurologic and psychiatric conditions including acute bipolar mania.¹⁻³ It also is used for off-label control of various psychiatric symptoms. It is a stable coordination compound composed of sodium valproate and

valproic acid that dissipates into the valproate ion in the gastrointestinal tract.¹ (In this article, references to valproate [VPA] include valproic acid and divalproex.) The drug is relatively well-tolerated; however, use may carry teratogenic risk and can adversely impact a variety of body systems, especially hematopoietic, gastrointestinal, and neurologic systems.¹⁻³ Adverse effects can be idiosyncratic or in part related to VPA serum levels.^{1,4} VPA toxicity increases the likelihood of some adverse health outcomes, such as nausea, diarrhea, and tremors.¹

Identifying and treating VHE

Asymptomatic elevations in ammonia without evidence of hepatic injury are common, might be related to valproic serum levels, and may occur in up to one-half of psychiatric patients receiving VPA.^{2,4} In contrast, VHE is a rare and potentially lethal idiosyncratic event unrelated to duration of VPA treatment, dosage, or valproic serum level.^{2,4} In addition, prior safe use might not protect against future VHE.^{3,4}

VHE presents as delirium with characteristic acute changes in mental status, including alterations in cognition or level of consciousness ranging from lethargy to coma, along with possible focal neurological findings or vomiting.^{1,3,4} Although more common among patients with a seizure disorder, VHE also might be associ-

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VHE emergence is unpredictable and can occur within days or up to years of use with therapeutic VPA dosing and valproic serum levels

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Clinical Point

Pathophysiological descriptions of emergent VHE have been hypothesized, but the definitive causal mechanism remains unclear

Table 2

Systematic review methods and results of published VHE literature

Relevant articles published between 1996 and February 2015 were identified using Ovid MEDLINE

4 Primary search terms were employed:

1. divalproex (then adding “or” valproic acid from the populated list)
2. hyperammonemia
3. delirium
4. encephalopathy

Search terms number 1 and 2 were combined and that combination then was independently combined with terms 3 and 4

A priori excluded studies that did not involve:

- psychiatric patients
- non-adult (age <18)
- non-English language studies

Search method results:

- 85 abstracts which resulted in 12 reports that met criteria for review⁷⁻¹⁸
- examination of citations revealed 2 additional unique case reports^{5,6}
- all detected publications were case literature

We extracted subject profile, VPA exposure, clinical findings, and management/outcome data from these reports

VHE: valproate-related hyperammonemic encephalopathy; VPA: valproic acid

ated with new seizure activity in patients who do not have a seizure disorder.⁵

Although symptomatically acute in onset, emergence is unpredictable and can occur within days or up to years of use with therapeutic VPA dosing and valproic serum levels.^{2,4} Complicating identification, laboratory transaminase or ammonia elevations may or may not be present^{2,4}; however, VHE typically occurs in the setting of hyperammonemia and normal transaminase levels.² Reversible EEG findings are nonspecific² and could show generalized slowing with occasional bursts of frontal intermittent rhythmic delta activity and triphasic waves.^{2,4}

Pathophysiological descriptions of emergent VHE have been hypothesized,^{2,4} but the definitive causal mechanism remains unclear.⁶ Published VHE risk factors²⁻⁶ include:

- polypharmacy (especially anti-convulsants)
- inherited or dietary-based carnitine deficiency
- urea cycle disorders
- mental retardation.

Evaluating for urea cycle disorders may be more relevant in adult females because males with urea cycle disorder often die in the neonatal period.⁴ The FDA has issued warnings about emergent VHE in individuals with known urea cycle disorders or when VPA is administered with topiramate.¹ Anticonvulsant polypharmacy likely is the most commonly identified risk factor; however, this might be because it is easier to identify than other putative risk factors. In part because of the reported low incidence of VHE and methodologically limited evidence base, it is difficult to say with certainty what risk factors exist. Importantly, the literature also reports cases of VHE without established risk factors.^{5,6} This is consistent with our updated systematic review that only detected case literature.⁵⁻¹⁸ There remains a need for methodologically sound characterization of the prevalence, identification, and management of VHE in psychiatric patients.

Although some associations were more common, there is wide variability among patients—including risk factors—and exposure data within our review and earlier reviews^{5,19} of emergent VHE in psychiatric⁵ and mixed¹⁹ neurological/psychiatric cases series. Our review methods and summary findings can be found in *Table 1*⁵⁻¹⁸ (page 64) and *Table 2*,⁵⁻¹⁸ respectively.

How would you treat VHE?

- a) cholinesterase inhibitors
- b) antipsychotic therapy
- c) supportive care

- d) ammonia-reducing agents such as lactulose, carnitine, and neomycin
- e) discontinue valproate

OUTCOME Normalized ammonia

Four days after discontinuing divalproex and starting lactulose, Mr. D's fluctuating level of arousal, orientation, attention, and perceptual disturbances resolve along with restoration of environmental relatedness in setting of normalized ammonia level to 39 µg/dL. He is euthymic, non-psychotic, and without cognitive impairment at time of discharge. An "allergy" to divalproex is entered in his electronic medical record in an effort to discourage future retreat.

The authors' observations

Once identified, management of VHE invariably includes consideration for discontinuation of valproate^{1,2,4,19}; other adjunctive, expediting, ammonia-reducing strategies, including lactulose and carnitine, have also been described.^{2,4,5,20} Although lactulose is more commonly used, carnitine supplementation might be associated with a preferable dosing schedule and drug interaction and side-effect profile.²⁰ Rapidly deteriorating clinical status could indicate hemodialysis.⁴

Of critical importance, these management strategies rely on awareness of and prompt identification of the condition, which includes an ability to distinguish

Related Resources

- Thomas KL, La AQ, Punia S, et al. Valproic acid-induced hyperammonemia and minimal hepatic encephalopathy prevalence among psychiatric inpatients. *Ann Clin Psychiatry*. 2016;28(1):37-42.
- Holroyd S, Overdyke JT. Hyperammonemia associated with valproic acid use in elderly psychiatric patients. *J Neuropsychiatry Clin Neurosci*. 2012;24(3):372-374.

Drug Brand Names

Aripiprazole • Abilify	Metformin • Glucophage
Divalproex extended-release • Depakote ER	Mirtazapine • Remeron
Lisinopril • Zestril	Neomycin • Neo-Fradin
Lorazepam • Ativan	Simvastatin • Zocor
	Topiramate • Topamax

emergent VHE from the mental illness VPA is used to treat.

Stopping the offending agent generally results in complete recovery in VHE patients with psychiatric illness.⁴ Most (>90%, n = 31) psychiatric patients in our and prior⁵ case series reviews recovered within 2 weeks of intervention.⁵ Cautious resumption of divalproex could be considered if there is a compelling clinical indication and you suspect that a putative polypharmacy agent such as topiramate has been removed; otherwise future retreat of VPA should be avoided.¹⁴

Mr. D's case was consistent with a valproate-related hyperammonemic delirious event. He had preadmission acute onset, intra-daily fluctuating confusion, and visual perceptual disturbances with nausea, asterixis, gait disturbance, elevated ammonia, and a supportive EEG months

Clinical Point

Stopping the offending agent generally results in complete recovery in VHE patients with psychiatric illness

Bottom Line

Although emergent valproate-related hyperammonemic encephalopathy (VHE) is rare, it represents a potential missed opportunity to detect and correct a reversible delirious process. It is challenging to distinguish VHE from the psychiatric illness that valproate is used to treat. Providers should have a low threshold for checking an ammonia level in clinical scenarios that involve any alteration in mental status that may resemble delirium in psychiatric patients treated with valproate.

after starting divalproex. Similar to our case, some challenging aspects of identifying emergent VHE include:

- earlier safe use of divalproex over extended periods
- lack of elevated VPA serum level
- lack of transaminase elevation
- lack of apparent risk factors
- presence of background serious mental illness, which can distract from VHE detection via misattribution to uncontrolled primary mental illness.

This last point is critical because it can delay VHE identification and treatment or worse, result in misdiagnosis with accompanying continuation or escalation of VPA dosing as has initially occurred in Mr. D's case. Similar concerns have been raised^{2,5} and occurred,^{5,19} which is not surprising given the frequency of VPA use for psychiatric conditions and symptoms.

Providers should have a low threshold for checking an ammonia level in clinical scenarios that involve any alteration in mental status that may resemble delirium in psychiatric patients treated with valproate. From a preventative perspective, it may be prudent to avoid valproate in psychiatric patients with known VHE risk factors. Either way, promotion of VHE awareness and detection across medical disciplines is paramount.

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Clinical Point

From a preventative perspective, it may be prudent to avoid valproate in psychiatric patients with known VHE risk factors