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# Valproate-induced hyperammonemic encephalopathy: an update on risk factors, clinical correlates and management☆

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**Abstract**

**Introduction:** Valproate (VPA)-induced hyperammonemic encephalopathy (VHE) is a serious drug-related adverse effect characterized by lethargy, vomiting, cognitive slowing, focal neurological deficits and decreased levels of consciousness ranging from drowsiness to coma.
**Methods:** We present a case series ($n$=5) and also review previous cases of VHE ($n$=30) in psychiatric patients to provide an update on risk factors, clinical correlates and management of VHE.
**Results:** To our knowledge, there are 30 (16 female, 14 male) previously reported VHE cases in psychiatric patients. Risk factors for VHE include VPA–drug interactions, mental retardation, carnitine deficiency and presence of urea cycle disorders. Length of VPA treatment, VPA dosage, serum VPA levels and serum ammonia levels do not appear to correlate with onset or severity of VHE.VPA discontinuation is the primary treatment of VHE, although, L-carnitine, lactulose and neomycin have been used adjunctively in some patients.
**Conclusion:** Clinicians should consider VHE in patients taking VPA who present with lethargy, gastrointestinal symptoms, confusion and decreased levels of drowsiness. VPA discontinuation is currently the mainstay of treatment for VHE, although more research is warranted to delineate the underlying risk factors for VHE and consolidate treatment modalities for this potentially life-threatening drug adverse effect.


*Keywords:* Valproic acid (VPA); Encephalopathy; Hyperammonemia; Altered mental status; Delirium

## 1. Introduction

Valproate (VPA) is an antiepileptic drug which is widely used in the treatment of psychiatric disorders including bipolar disorder and schizoaffective disorder. It is usually well tolerated but it has been associated with idiosyncratic side effects (not strictly related to serum VPA levels) involving hematopoietic, hepatic and digestive systems [1].

Hyperammonemia without clinical or laboratory evidence of hepatoxicity is an important idiosyncratic side effect of VPA treatment [1]. It can lead to valproate-induced hyperammonemic encephalopathy (VHE), which is a serious drug-related adverse effect characterized by lethargy, vomiting, cognitive slowing, focal neurological deficits and decreasing levels of consciousness ranging from drowsiness to coma in patients on VPA treatment [2]. VHE has been associated with electroencephalography (EEG) changes suggestive of severe encephalopathy with continuous generalized slowing, a predominance of theta and delta activity, occasional bursts of frontal intermittent rhythmic delta activity, and triphasic waves [2]. The clinical symptoms, hyperammonemia and EEG findings are reversible if a timely diagnosis is made [3], which requires a high suspicion for VHE.

Untreated VHE can lead to life-threatening coma, thus warranting an understanding of the pathophysiology and treatment of this uncommon but potentially fatal drug-related complication. We add five new cases ($n$=5) to previous VHE cases ($n$=30) and review the current literature to provide an update on risk factors, clinical correlates and management of VHE.

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## 2. Case reports

### 2.1. Case 1

Ms. R, a 19-year-old female, was admitted to a medical unit for evaluation of cognitive slowing, ataxia, lethargy, drowsiness, nausea and vomiting. She was diagnosed with bipolar affective disorder 1 week prior to her medical admission. She was started on VPA, which was titrated to 1500 mg/day (serum VPA level 87 μg/ml; normal range 50–100 μg/ml). She was also prescribed clonazepam 0.5 mg bid for management of anxiety symptoms. Her ammonia level was 124 μmol/L (normal range 9–35 μmol/L) with normal AST/ALT on admission. Her symptoms resolved and the serum ammonia level normalized within 1 day of discontinuing VPA.

### 2.2. Case 2

Mr. K, a 36-year-old male, has a history of schizoaffective disorder, bipolar type, alcohol and cannabis dependence and hepatitis C, who was admitted to the medical ICU with slurred speech, drowsiness and slowed cognition. VPA was started 1 week prior to admission and titrated to 1000 mg with a serum VPA level of 114 μg/ml on admission. His psychotropic medications included risperidone (3 mg/day), clozapine (300 mg/day), clonazepam (3 mg/day), disulfiram (250 mg/day), topiramate (300 mg/day) and lithium (450 mg/day). His serum lithium level on admission was 1.2 mmol/L. His serum ammonia level was 111 μmol/L. His liver function test results including AST and ALT were within normal limits. An EEG revealed generalized dysrhythmia. Upon discontinuation of VPA, the ammonia levels normalized within 3 days and his cognitive symptoms resolved.

### 2.3. Case 3

Ms. V, a 53-year-old female, has a diagnosis of bipolar disorder type II and alcohol dependence who was maintained on VPA 750 mg daily and quetiapine 300 mg daily. She presented with nausea, vomiting, clumsiness and incoordination. She had a serum VPA level of 52 μg/ml. Her ammonia level was 97 μmol/L with normal AST, ALT and alkaline phosphatase. Her symptoms abated within 3 days of VPA discontinuation.

### 2.4. Case 4

Ms. E, a 41-year-old female, has a diagnosis of bipolar affective disorder and mild mental retardation. She presented with history of rapid cycling mood changes occurring repetitively over a 10-day cycle for the last 5 months. Her VPA dosage of 1000 mg/day (serum VPA level 96 μg/ml) was increased again to 1250 mg/day, and olanzapine 10 mg was added to control her manic symptoms. Within a day, she displayed bizarre behavior including disrobing herself on the unit and drawing with crayons on the walls. She also required seclusion and needed two point restraints. At this point, her ammonia level was elevated at 133 μmol/L. VPA was discontinued and her ammonia level dropped to 12 μmol/L within a day, but she continued to remain agitated with manic symptoms which abated with introduction of paliperidone over 2 week's duration.

### 2.5. Case 5

Ms. R, a 71-year-old female, has a diagnosis of schizoaffective disorder, bipolar type and mild mental retardation. She presented with declining alertness and reduction in functioning as compared to her baseline over 3 weeks. She was on VPA 1500 mg/day and lithium, which was increased from 300 mg/day to alternating doses of 300 mg and 450 mg/day (serum lithium level: 1.2 mmol/L). Her serum VPA level was 26 μg/ml and her ammonia level was 133 μmol/L. Her AST, ALT, alkaline phosphatase and bilirubin levels were within normal limits. An EEG revealed severe degree of generalized slowing and triphasic waves consistent with a diffuse disturbance of cerebral function suggestive of encephalopathy. VPA was discontinued and her mental state returned to baseline within 2 days, and ammonia level declined to 45 μmol/L.

## 3. Methods

A structured PubMed search was performed through May 2011 with keywords including "valproate," "valproic acid," "hyperammonemia," "altered mental status "and "encephalopathy." In this review, we have included VHE case reports [4–29] published in the English medical literature in psychiatric patients only. For standardization purposes, we have used micromoles per liter (μmol/L) for ammonia levels (normal levels: 9–35 μmol/L) and micrograms per milliliter (μg/ml) for VPA levels (normal levels: 50–100 μg/ml).

## 4. Results

To our knowledge, there are 30 previously reported cases of VHE in psychiatric patients (see Table 1). The mean age of these patients (16 female, 14 male) was 43.1 ±20.9 years. Four of 30 patients were aged <18 years, and three of them were aged >65 years. The mean VPA dosage ($n$=26) was 1336±575 mg and the mean serum VPA level ($n$=28) was 91±23 μg/ml. The mean serum ammonia level ($n$=25) was found to be 174±184 μmol/L. Majority of the VHE patients ($n$=18) recovered completely with discontinuation of VPA alone, and others received additional treatment with L-carnitine, lactulose and neomycin. The time to recovery from VHE ranged from 1 to 30 days.

We add five new VHE cases (four female, one male) with a mean age of 44±19 years. The mean valproic acid dosage was 1250±353 mg with a mean serum valproic acid level of 75±35 μg/ml. The mean serum ammonia level in these patients was 99±51 μmol/L. All of these patients had