Neurology Asia 2026; 31(2) : 853 – 857

Fatal hyperammonemic encephalopathy triggered by valproic acid in adult-onset type II citrullinemia: A diagnostic pitfall

[1,2,3]Young-Soo Kim, [1,3]Minjung Kim, [4]Do-Hyung Kim, [2,3,5]Tae-Won Yang, [1,2,3]Oh-Young Kwon, [6]Hyung-Doo Park, [1,2,3]Soo-Kyoung Kim

[1]Department of Neurology, Gyeongsang National University Hospital, Jinju, Republic of Korea; [2]Department of Neurology, Gyeongsang National University College of Medicine, Jinju, Republic of Korea; [3]Institute of Health Science, Gyeongsang National University College of Medicine, Jinju, Republic of Korea; [4]Department of Neurology, Samsung Changwon Hospital, Sungkyunkwan University School of Medicine, Changwon, Republic of Korea; [5]Department of Neurology, Gyeongsang National University Changwon Hospital, Changwon, Republic of Korea; [6]Department of Laboratory Medicine and Genetics, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea

Abstract

Adult-onset type II citrullinemia (CTLN2) is a rare urea cycle disorder caused by *SLC25A13* mutations, often misdiagnosed due to fluctuating neuropsychiatric and metabolic symptoms. Hyperammonemia is its defining feature and can be fatal if unrecognized. A 30-year-old woman with intellectual disability presented with recurrent seizure-like episodes and behavioral changes. Brain MRI showed bilateral temporal lobe abnormalities suggestive of encephalitis or metabolic encephalopathy. Despite antiviral and antiseizure therapy, her consciousness deteriorated. On the sixth hospital day, valproic acid (VPA) was administered for seizure control, after which she rapidly progressed to coma and respiratory failure. Serum ammonia levels were markedly elevated (>615 μmol/L), and metabolic studies revealed increased citrulline and arginine levels. Genetic testing confirmed compound heterozygous *SLC25A13* mutations consistent with CTLN2. Despite aggressive management, the patient died 23 days after admission. This case underscores the diagnostic difficulty of CTLN2 and highlights the fatal risk of VPA-induced hyperammonemia in patients with unrecognized urea cycle disorders. Early metabolic screening should be considered in unexplained encephalopathy, especially when imaging and EEG findings are nonspecific, and VPA should be avoided to prevent catastrophic outcomes.

Keywords: Citrullinemia, hyperammonemic encephalopathy, valproic acid

INTRODUCTION

Adult-onset type II citrullinemia (CTLN2) is a rare autosomal recessive urea cycle disorder caused by mutations in the *SLC25A13* gene encoding citrin, a mitochondrial aspartate–glutamate carrier.[1] The disease manifests with variable neuropsychiatric and metabolic symptoms—ranging from altered mental status, irritability, and behavioral disturbance to, less commonly, seizures—making it a diagnostic challenge often mistaken for hepatic encephalopathy or psychiatric illness.[2,3] Hyperammonemia is the hallmark feature and may become fatal without prompt recognition and treatment.[4] Disease progression can be critically influenced by certain agents, including glycerol, fructose, alcohol, and hepatotoxic drugs.[5-9] Valproic acid (VPA), a broad-spectrum antiseizure medication, is known to induce hyperammonemia by impairing urea cycle enzymes, depleting carnitine, and altering glutamine metabolism.[10-14] However, its impact on CTLN2 has not been well established. We present a fatal case of CTLN2 in which administration of VPA appears to have precipitated catastrophic hyperammonemic encephalopathy, emphasizing the need for caution when selecting antiseizure

Address correspondence to: Soo-Kyoung Kim, Department of Neurology, Gyeongsang National University Hospital, Gyeongsang National University College of Medicine, Institute of Health Science, 79 Gangnam-ro, Jinju, Gyeongsangnam-Do, (52727) Jinju, Republic of Korea. E-mail: skkim.stroke@gmail.com

Date of Submission: 5 October 2025; Date of Acceptance: 6 January 2026

https://doi.org/10.54029/2026enj

medications in patients with or at risk for urea cycle disorders.

CASE REPORT

A 30-year-old woman with lifelong intellectual disability was transferred for evaluation of recurrent seizure-like episodes. Four months earlier, she had developed frequent lip-smacking and behavioral changes interpreted as focal seizures. Other hospital brain MRI showed multifocal hyperintense lesions in the bilateral temporal lobes on FLAIR and DWI, leading to an initial diagnosis of viral encephalitis (Fig. 1). After transferring our hospital, cerebrospinal fluid analysis was normal, and although the possibility is low, empirical antivirals and steroids were administered. Her mental status transiently improved, and oxcarbazepine 150 mg bid was maintained for seizure control. On the second hospital day, she experienced worsening seizures. She was found making loud lip-smacking sounds, lasting approximately 20 minutes, responsive to lorazepam. Follow-up MRI on the fourth day demonstrated progression of cortical hyperintensities involving both hemispheres (Figure 2). Despite supportive management, her alertness declined, and she became increasingly agitated and unresponsive. EEG revealed continuous diffuse delta slowing. On the sixth day, VPA was introduced as an additional antiseizure therapy. Within hours, her consciousness deteriorated rapidly, progressing to coma and respiratory failure requiring intubation. Brain pre-contrast CT showed severe diffuse cerebral edema consistent with global metabolic injury (Figure 3). Serum ammonia, checked at this stage, was markedly elevated (>615 μmol/L). No evidence of hepatic dysfunction or infection was found, suggesting a metabolic etiology. Information regarding whether newborn screening had been performed and whether any abnormalities were detected during infancy was not available in the patient's past medical records. Metabolic work-up revealed markedly elevated plasma citrulline (253 nmol/L), arginine (229 nmol/L), and lysine (698 nmol/L). Genetic sequencing of SLC25A13 identified compound heterozygous pathogenic variants, confirming CTLN2 (Figure 4). Despite high-dose thiamine, ammonia-lowering agents, and supportive measures, her neurological function did not recover, and she died on hospital day 23.

DISCUSSION

This case illustrates the diagnostic difficulty and fatal potential of CTLN2. The patient presented with nonspecific neurological symptoms and MRI findings suggesting encephalitis, delaying recognition of a urea cycle disorder. Her condition worsened with declining consciousness and myoclonus. Administration of VPA for

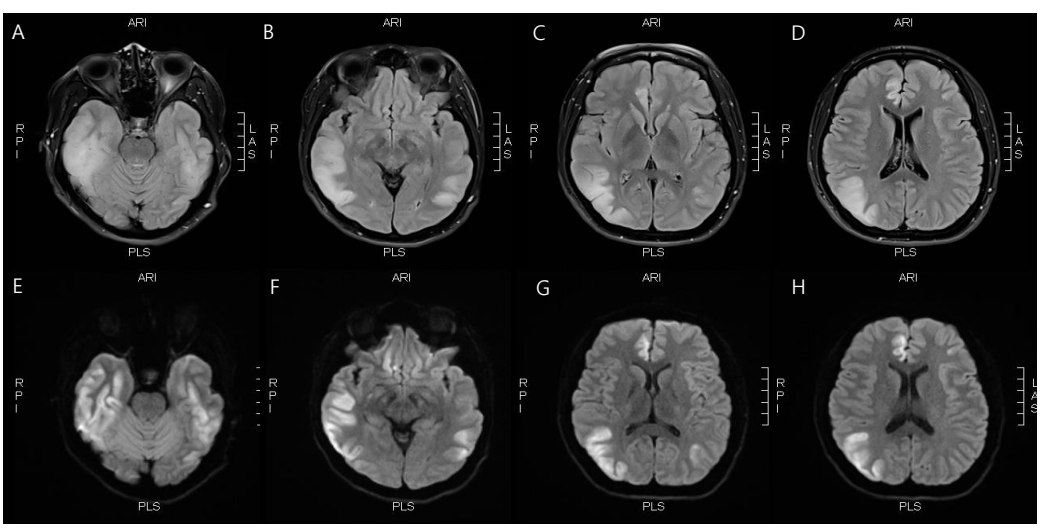

Figure 1. Initial outside MRI with FLAIR and DWI on one day before admission.
FLAIR and DWI images showed multifocal high signal lesions mainly in the bilateral basal temporal and right frontal area. (A-D are FLAIR, E-H are DWI)

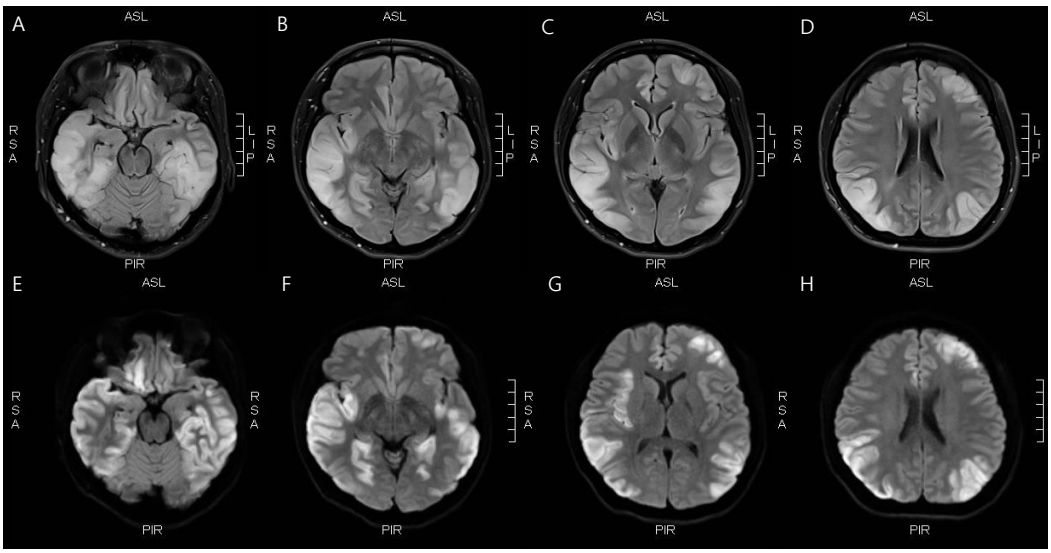

Figure 2. Follow-up MRI with FLAIR and DWI on 4th day of hospitalization.
FLAIR and DWI images showed more extended lesions seen in the initial outside MRI. (A-D are FLAIR, E-H are DWI)

seizure control led to rapid deterioration and severe hyperammonemia, revealing underlying CTLN2. This case emphasizes the need for early suspicion of urea cycle disorders in unexplained encephalopathy and cautions against VPA use, which can exacerbate hyperammonemia and cause catastrophic outcomes.

CTLN2 remains rare outside East Asia[15], and is easily overlooked due to its fluctuating neuropsychiatric manifestations.[5] Its hallmark—hyperammonemia—results from impaired ammonia detoxification caused by *SLC25A13* mutations.[1] Environmental and metabolic stressors, including infection, high-carbohydrate

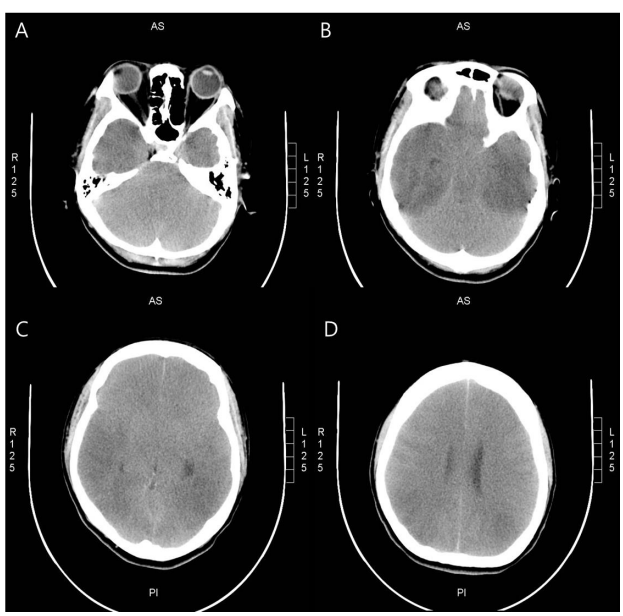

Figure 3. Brain pre-contrast CT on 6th day of hospitalization. CT images revealed intense low-density lesions in the bilateral temporoparietal area with severe diffuse brain swelling.

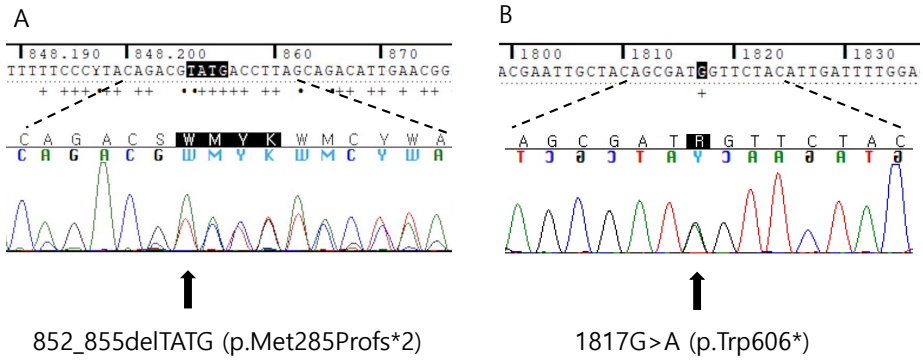

Figure 4. DNA analysis of SLC25A13 gene in patient.
Schematic representation of two pathogenic variants identified in the SLC25A13 gene: (A) c.852_855delTATG (p.Met285Profs*2) - a four-base pair deletion causing a frameshift and premature stop codon, and (B) c.1817G>A (p.Trp606*) - a nonsense mutation resulting in a truncated protein.

intake, or hepatotoxic medications, can precipitate acute crises. Certain agents such as glycerol- or fructose-containing solutions, high-dose glucose infusions, alcohol, and acetaminophen are known to trigger abrupt worsening and are strictly contraindicated in CTLN2.[5-9]

VPA poses particular danger in this population. Although widely used as a broad-spectrum antiseizure drug.[16] VPA can induce or exacerbate hyperammonemia through several mechanisms: inhibition of carbamoyl phosphate synthetase I, depletion of carnitine (vital for mitochondrial fatty acid transport), and increased glutamine metabolism, which liberates ammonia.[10-14] These effects are especially harmful in individuals with underlying urea cycle dysfunction, such as CTLN2, leading to profound metabolic derangement and fatal encephalopathy, as demonstrated in this case.

From a preventive perspective, clinicians should exercise caution when prescribing VPA to adults with unexplained encephalopathy. In particular, urea cycle disorders should be considered in patients presenting with hyperammonemia in the absence of liver disease, and careful drug selection may help prevent fatal outcomes.

This case has limitations, including unavailable newborn screening data and incomplete clinical information from prior residential care, which precluded identification of earlier triggers or clear reasons for symptom progression.

In conclusion, this case highlights VPA as a potential iatrogenic trigger for fatal hyperammonemic encephalopathy in CTLN2 and emphasizes the importance of tailored pharmacologic strategies in the management of rare metabolic disorders. Increased clinical awareness and careful drug selection are essential to prevent avoidable morbidity and mortality in this vulnerable patient population.

DISCLOSURE

Financial support: This work was supported by the New Faculty Research Support Grant from Gyeongsang National University in 2025, GNU-NFRSG-0048

REFERENCES

1. Kobayashi K, Sinasac DS, Iijima M, *et al*. The gene mutated in adult-onset type II citrullinaemia encodes a putative mitochondrial carrier protein. *Nat Genet* 1999;22(2):159-63. doi: 10.1038/9699.
2. Arora S, Srivastava MVP, Singh MB, *et al.* Adult onset type II citrullinemia--a great masquerader. *QJM* 2020;113(1):49-51. doi: 10.1093/qjmed/hcz238.
3. Kyo M, Mii H, Takekita Y, Tokuhara D, *et al*. Case of adult-onset type II citrullinemia treated as schizophrenia for a long time. *Psychiatry Clin Neurosci* 2015;69(5):306-7. doi: 10.1111/pcn.12253.
4. Funabe S, Tanaka R, Urabe T, Kawasaki S, Kobayashi K, Hattori N. [A case of adult-onset type II citrullinemia with repeated nonconvulsive status epilepticus]. *Rinsho Shinkeigaku* 2009;49(9):571-5. doi: 10.5692/clinicalneurol.49.571
5. Hayasaka K, Numakura C. Adult-onset type II citrullinemia: Current insights and therapy. *Appl Clin Genet* 2018;11:163-70. doi: 10.2147/TACG.S162084.
6. Komine R, Minamimura K, Watanabe A, *et al.* Sudden development of adult-onset type II citrullinemia

after total gastrectomy: a case report. *Surg Case Rep* 2018;4(1):11. doi: 10.1186/s40792-018-0420-9.
7. Shiohama N, Sugita Y, Imamura N, Sato T, Mizuno Y. [Type II citrullinemia triggered by acetaminophen]. *No To Shinkei* 1993;45(9):865-70.
8. Takahashi H, Kagawa T, Kobayashi K, *et al.* A case of adult-onset type II citrullinemia--deterioration of clinical course after infusion of hyperosmotic and high sugar solutions. *Med Sci Monit* 2006;12(2):Cs13-5.
9. Yazaki M, Takei Y, Kobayashi K, Saheki T, Ikeda S. Risk of worsened encephalopathy after intravenous glycerol therapy in patients with adult-onset type II citrullinemia (CTLN2). *Intern Med* 2005;44(3):188-95. doi: 10.2169/internalmedicine.44.188.
10. Bezinover D, Postula M, Donahue K, Bentzen B, McInerney J, Janicki PK. Perioperative exacerbation of valproic acid-associated hyperammonemia: a clinical and genetic analysis. *Anesth Analg* 2011;113(4):858-61. doi: 10.1213/ANE.0b013e318228a001.
11. Iqbal K, Kummamuru H, Dasari N, *et al*. A case of valproic-acid induced hyperammonemic encephalopathy. *Cureus* 2021;13(12):e20380. doi: 10.7759/cureus.20380.
12. Mock CM, Schwetschenau KH. Levocarnitine for valproic-acid-induced hyperammonemic encephalopathy. *Am J Health Syst Pharm* 2012;69(1):35-9. doi: 10.2146/ajhp110049.
13. Yagi M, Nakamura T, Okizuka Y, *et al.* Effect of CPS14217C>A genotype on valproic-acid-induced hyperammonemia. *Pediatr Int* 2010;52(5):744-8. doi: 10.1111/j.1442-200X.2010.03157.x.
14. Yokoyama S, Sugawara N, Maruo K, Yasui-Furukori N, Shimoda K. Blood levels of ammonia and carnitine in patients treated with valproic acid: A meta-analysis. *Clin Psychopharmacol Neurosci* 2022;20(3):536-47. doi: 10.9758/cpn.2022.20.3.536.
15. Wong YC, Au WL, Xu M, Ye J, Lim CC. Magnetic resonance spectroscopy in adult-onset citrullinemia: elevated glutamine levels in comatose patients. *Arch Neurol* 2007;64(7):1034-7. doi: 10.1001/archneur.64.7.1034.
16. Romoli M, Mazzocchetti P, D'Alonzo R, *et al.* Valproic acid and epilepsy: From molecular mechanisms to clinical evidences. *Curr Neuropharmacol* 2019;17(10):926-46. doi: 10.2174/1570159X17666181227165722.