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CASE REPORT

Type II citrullinemia presenting with psychiatric disorder in the emergency department: a case report

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Abstract

Background: Hyperammonemia, characterized by elevated ammonia levels in the blood, may result from various conditions, including adult-onset type II citrullinemia (CTLN2), a rare autosomal recessive disorder due to mutations in the *SLC25A13* gene. **Case**: We present a case involving a 57-year-old woman with a history of psychiatric disease who arrived at the emergency department with recurring episodes of decreased consciousness and seizures, all accompanied by hyperammonemia. Initial investigations, including brain computed tomography, magnetic resonance imaging, electroencephalography, cerebrospinal fluid analysis, and toxicology screening, yielded normal results. Despite urgent interventions, including continuous renal replacement therapy and enemas, her hyperammonemia and altered consciousness persisted. Metabolic testing indicated elevated citrulline levels, prompting genetic analysis that confirmed a mutation in *SLC25A13*, leading to a CTLN2 diagnosis. After diagnosis, ammonia levels were successfully normalized with dietary modifications and sodium phenylbutyrate and sodium benzoate, each administered at 3 g three times daily. **Conclusions**: In cases of persistent hyperammonemia with recurrent consciousness disturbances, especially in patients with psychiatric backgrounds, early metabolic testing should be considered. Treatment should include sodium pyruvate and a low-carbohydrate diet as part of a comprehensive diagnostic and therapeutic strategy.

Keywords

Hyperammonemia; Citrullinemia; Seizure; Emergency department

1. Introduction

Elevated ammonia levels are potent neurotoxins, and a rapid rise exceeding 170 μg/dL can induce encephalopathy, which is reversible if detected and treated early. As hyperammonemia progresses, cerebral edema may develop, potentially resulting in brainstem herniation and fatal outcomes. Early detection and management of acute hyperammonemia are critical, as patient prognosis is closely associated with the duration and severity of hyperammonemia [1–4]. Acute hyperammonemia is often observed in urea cycle disorders and organic acidemias, although it can also present in conditions such as fatty acid oxidation defects and mitochondrial diseases.

In Kobayashi's study, the *SLC25A13* gene on chromosome 7q21.3 was identified as the pathogenic gene for citrin deficiency, which is categorized into two clinical phenotypes based on age: neonatal intrahepatic cholestasis caused by citrin deficiency (NICCD) and adult-onset type II citrullinemia (CTLN2) [5]. NICCD typically presents with intrahepatic cholestasis in infancy and is responsive to treatment with medium-chain triglyceride (MCT) supplementation and lactose-restricted formulas [5]. Following recovery, some patients may experience symptoms such as fatigue, recurrent hypoglycemia and short stature.

CTLN2, an autosomal recessive disorder, results from mutations in the *SLC25A13* gene, leading to elevated plasma citrulline and ammonia levels due to liver-specific argininosuccinate synthetase deficiency. This disorder is characterized by recurrent hyperammonemic encephalopathy, and its prevalence is notably higher in East Asia, particularly Japan. Nagata *et al.* [6] reported the incidence of CTLN2 as 1 in 100,000 to 1 in 230,000, with a carrier rate of approximately 1 in 42 among the Japanese population. The estimated prevalence of citrin deficiency in this population is 1 in 7100 [7, 8]. Here, we describe the diagnostic and therapeutic approach to emergency patients with psychiatric symptoms, recurrent episodes of altered consciousness, and seizures associated with hyperammonemia, focusing on the rare presentation of CTLN2 in adulthood.

2. Case description

We report a case of a 57-year-old female with a history of schizophrenia and depression who had been under follow-up in our psychiatric department since 2013. Following the initiation of antipsychotic therapy, the patient developed extrapyramidal

symptoms, characterized by muscle rigidity, gait disturbances, and episodes of altered consciousness. Comprehensive neurological evaluations did not reveal significant abnormalities. In 2014, the patient experienced a seizure, leading to the initiation of levetiracetam therapy, with no further seizures documented thereafter. In 2017, she discontinued anticonvulsant treatment but remained on psychiatric medications.

In early September 2021, the patient developed acute disorientation, with symptoms fluctuating in severity. After seven days, she presented to the hospital in a stuporous state with significantly reduced consciousness. Initial brain computed tomography (CT) and magnetic resonance imaging (MRI) scans, along with toxicology screens, yielded normal results. However, laboratory testing revealed elevated ammonia levels at 449 μg/dL (reference range 27~90). Conservative management, including enemas, was implemented, resulting in symptomatic improvement, and the patient was discharged one week later. The following day, she returned to the hospital with an altered mental status and was readmitted. A diffusion MRI showed no abnormalities, yet her ammonia level had risen to 455 μg/dL (reference range 27~90). Symptomatic treatment with enemas and hydration led to an improvement in consciousness, and she was kept under observation. On the third day of readmission, the patient experienced a seizure managed with midazolam, prompting the re-initiation of levetiracetam at 500 mg twice daily. On the 12th day of readmission, her mental status declined to a semi-comatose state, with ammonia levels escalating to 479 μg/dL (reference range 27~90). Despite exhaustive investigations, the etiology remained unclear, and the patient was transferred to our institution for further evaluation.

Upon admission to our facility, the patient exhibited persistent reduced consciousness and hyperammonemia. Emergency interventions, including continuous renal replacement therapy (CRRT) and enemas, were administered. MRI findings revealed bilateral symmetric diffusion restriction with hyperintensities in the bilateral frontal and insular lobes, consistent with a diagnosis of hyperammonemic encephalopathy (Fig. 1). Gastroenterological assessment ruled out liver cirrhosis or vascular shunts, and an electroencephalography (EEG) was normal. Recurrent hyperammonemia on the third day of admission prompted a more in-depth metabolic investigation, including urea cycle-related amino acid assays and genetic testing. Results confirmed elevated levels of asparagine (84.4 nmol/mL; reference range 35–74), citrulline (161.4 nmol/mL; reference range 12–55), and lysine (296.6 nmol/mL; reference range 116–296), suggesting a urea cycle disorder. Subsequent genetic analysis identified a mutation in the *SLC25A13* gene, confirming the diagnosis. Following this, a conservative management approach was implemented, including CRRT and dietary modifications (total caloric intake of 1800 kcal, initially comprising 40% carbohydrates (720 kcal), 15% protein (270 kcal), and 45% fat (810 kcal), later adjusted to 30%/25%/45% for optimized ammonia control). The patient was treated with sodium phenylbutyrate 3 g and sodium benzoate 3 g, both administered three times daily. While liver transplantation was considered, a decision was made to proceed with dietary and conservative measures (Fig. 2). Over the subsequent three years, she consistently adhered to the prescribed medication doses and dietary regimen upon discharge, and the patient has remained free from episodes of altered consciousness and seizures. She continues on a minimal psychiatric medication regimen and maintains a normal lifestyle.

3. Discussion

This case of CTLN2 is characterized by a range of clinical manifestations, including hyperammonemia, neuropsychiatric disturbances, hepatic encephalopathy, metabolic derangements, nocturnal symptoms, aggressive behavior, hypersensitivity, excessive behaviors, delusions, memory impairment, asterixis, seizures and coma. In the present patient, psychiatric comorbidities were evident alongside intermittent, non-specific neurological symptoms commonly associated with psychiatric disorders. The recurrent episodes of altered consciousness raise the possibility that CTLN2 had manifested earlier, potentially contributing to the premature onset of clinical symptoms. Continuous monitoring of plasma ammonia concentrations and thorough evaluation for metabolic imbalances are critical in managing such patients.

Previous studies, such as those by Kyo *et al.* [9], have documented cases in which patients with citrin deficiency were erroneously diagnosed and treated for schizophrenia for prolonged periods. Similarly, in this case, the patient had been treated for schizophrenia and depression for many years and had a history of a single seizure during adolescence [9]. However, no further investigations were conducted to explore underlying metabolic etiologies. Without prior assessments of plasma ammonia and citrulline levels, it remains challenging to definitively exclude citrin deficiency as a contributor to the patient's earlier psychiatric and neurological symptoms.

In the psychiatric population, comprehensive systemic evaluations are typically emphasized. However, the low prevalence of genetic metabolic disorders and their often non-specific initial presentations may delay accurate diagnosis. Furthermore, plasma ammonia testing is not routinely included in standard diagnostic panels, complicating the early identification of such metabolic conditions. Therefore, in cases involving atypical psychiatric presentations, a careful review of the patient's history for seizure episodes and a broader differential diagnosis, including ammonia testing, should be pursued when appropriate.

Dietary patterns in CTLN2 patients have been well-documented. These patients often display a preference for high-protein and high-fat foods while actively avoiding carbohydrate-rich diets. This dietary behavior is thought to represent a metabolic adaptation to impaired liver function. The macronutrient distribution in CTLN2 patients, with a notably lower intake of carbohydrates and higher proportions of fat and protein, contrasts sharply with that of healthy individuals [10–12]. For instance, CTLN2 patients typically exhibit a macronutrient ratio of 19:44:37 (protein/fat/carbohydrate), compared to 14:25:61 in the general population [10]. In one reported case, a patient presenting with hyperammonemia and altered consciousness was treated with a high-carbohydrate, low-protein diet, commonly employed in managing hepatic encephalopathy in end-stage liver disease. However, this dietary regimen led to a deterioration in the patient's clinical condition,

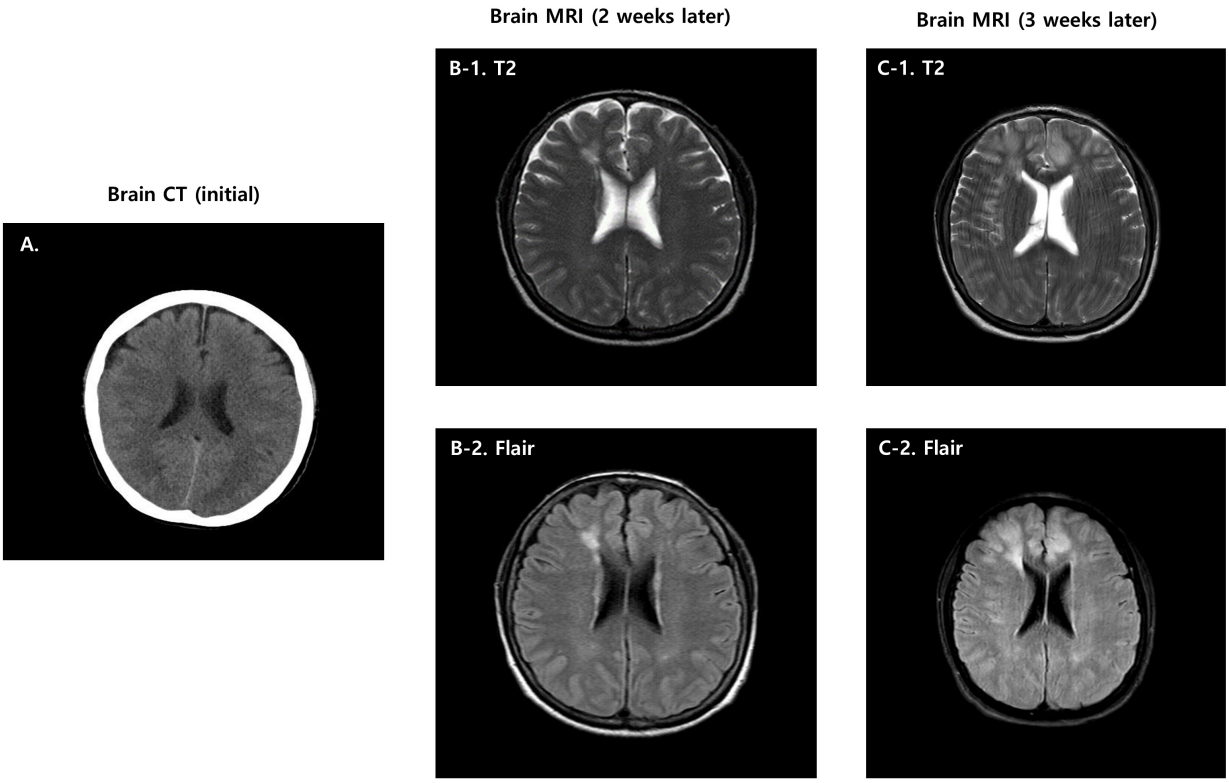

FIGURE 1. Brain image of the patient. (A) Initial Brain CT is non-specific. (B-1) T2 MRI findings (2 weeks later) showing bilateral symmetric diffusion restriction in the bilateral frontal and insular lobes. (B-2) Flair MRI findings (2 weeks later) showing hyperintensities in the bilateral frontal and insular lobes. (C-1) T2 MRI findings (3 weeks later) showing worsening bilateral symmetric diffusion restriction in multiple lobes. (C-2) Flair MRI findings (3 weeks later) showing hyperintensities in multiple lobes. CT: computed tomography; MRI: magnetic resonance imaging.

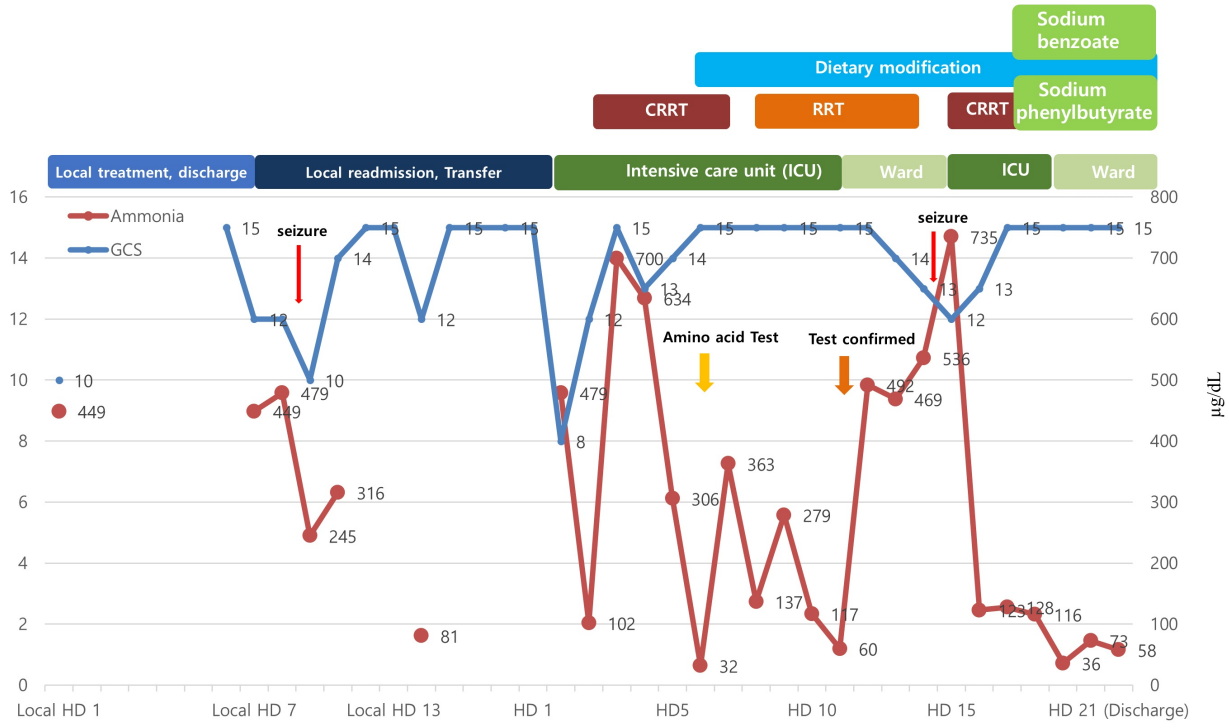

FIGURE 2. Clinical course of the patient following symptom onset. HD: hospital day; GCS: Glasgow coma scale; CRRT: continuous renal replacement therapy; RRT: Renal replacement therapy.

with a concurrent rise in alanine aminotransferase levels, suggesting that high-carbohydrate diets may exacerbate metabolic dysfunction in CTLN2 patients. Consistent with prior reports [13], our patient's management involved the successful implementation of a low-carbohydrate dietary regimen to stabilize metabolic control.

The use of sodium phenylbutyrate and sodium benzoate is well-established in the management of urea cycle disorders (UCDs), both agents being effective in reducing hyperammonemia [14, 15]. Both medications are beneficial in conditions involving hyperammonemia, such as citrin deficiency, due to their role in providing alternative metabolic pathways that bypass the urea cycle. By facilitating the conversion of ammonia to less toxic compounds, such as glycine and glutamine, both drugs support the diversion of ammonia into pathways that lead to its safe excretion as hippuric acid and phenylacetylglutamine in urine. Furthermore, another study has indicated that sodium pyruvate may also be effective. Exogenously supplied pyruvate has been reported to reduce the lactate/pyruvate ratio and subsequently lower the cytosolic NADH (nicotinamide adenine dinucleotide hydrogen)/NAD^+ (nicotinamide adenine dinucleotide-oxidized) ratio in the liver. This adjustment may alleviate the inhibition of glycolysis and enhance ureagenesis by providing cytosolic oxaloacetate and aspartate. Additionally, pyruvate may serve as an alternative energy source under certain conditions [5]. These pharmacological interventions are vital in preventing the life-threatening consequences of hyperammonemia. In this patient's case, both sodium phenylbutyrate and sodium benzoate were instrumental in achieving a significant reduction in plasma ammonia levels.

Progressive hepatic failure in CTLN2 can culminate in cerebral edema and death, necessitating liver transplantation as the only definitive treatment [16]. However, recent evidence suggests that a low-carbohydrate diet supplemented with MCTs can offer effective metabolic control in many cases, potentially delaying or averting the need for liver transplantation [15, 17–19]. Given that liver transplantation may not always be immediately available, patient management should prioritize pharmacological and dietary strategies while determining the appropriateness and timing of transplantation. Thus, a detailed dietary history and family medical history should be obtained to inform management decisions in patients presenting with hyperammonemia.

4. Conclusions

In conclusion, we present a case of adult-onset CTLN2 with psychiatric manifestations, which was successfully managed with oral sodium pyruvate and a low-carbohydrate diet. It is imperative for emergency physicians, psychiatrists, and other clinicians to recognize the clinical and biochemical hallmarks of CTLN2 and to consider this diagnosis when evaluating patients with unexplained psychiatric or neurological symptoms.

AVAILABILITY OF DATA AND MATERIALS

The authors declare that all data supporting the findings of this study are available within the paper and any raw data can be obtained from the corresponding author upon request.

AUTHOR CONTRIBUTIONS

SML—study conception and design. SWK, YSL—draft manuscript preparation. SWK—data curation. SML, HYL—critical review of the manuscript. All authors reviewed the results and approved the final version of the manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was approved by the institutional review board (IRB) of Chonnam National University Hospital (CNUH-EXP-2023-021). The requirement for informed consent was waived by the IRB due to the retrospective nature of the study and the anonymization of patient information prior to analysis.

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CONFLICT OF INTEREST

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