CASE REPORT

Rebound hyperammonemia triggered by interruption of renal replacement therapy in adolescent ornithine transcarbamylase deficiency

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Abstract : Background : Ornithine transcarbamylase (OTC) deficiency is the most common urea cycle disorder (UCD) and may lead to life-threatening hyperammonemia. Refractory cases require prompt and aggressive treatment, including renal replacement therapy (RRT), to prevent irreversible neurological damage. Case presentation : We encountered a 14-year-old girl with OTC deficiency who presented with severe hyperammonemia (649 μg/dL ; 382 μmol/L). Pharmacological therapy and emergency intermittent hemodialysis (IHD) were followed by continuous hemodiafiltration (CHDF), resulting in rapid ammonia clearance. However, a 4-h interruption of CHDF due to catheter replacement led to rebound hyperammonemia (>500 μg/dL ; >294 μmol/L), requiring resumption of RRT on day 4. OTC deficiency was subsequently diagnosed based on plasma amino acid and urine organic acid analyses on day 12. After intensifying the pharmacological therapy and achieving stable ammonia levels, RRT was discontinued on day 17. The patient recovered without apparent neurological sequelae and was discharged from the intensive-care unit. Conclusions : This case highlights the importance of uninterrupted RRT in managing acute hyperammonemia and suggests that even short pauses in CHDF can provoke clinically significant rebound. Early initiation of RRT, continuous monitoring of ammonia levels, and individualized treatment strategies are critical for optimizing patient outcomes. J. Med. Invest. 72 : 443-446, August, 2025

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INTRODUCTION

Ornithine transcarbamylase (OTC) deficiency is an X-linked urea cycle disorder (UCD) (1). UCDs have an estimated prevalence of 1 in 8,000 live births, with OTC deficiency being the most common subtype, affecting approximately 1 in 80,000 live births (2). The condition typically presents in early infancy and is characterized by recurrent episodes of hyperammonemia resulting from disruption of the urea metabolism pathway (3, 4). The rapid accumulation of ammonia and its precursors can lead to acute cerebral edema, which presents with a spectrum of neurological manifestations, including encephalopathy, seizures, and coma (3, 5, 6). Hyperammonemia is a medical emergency that requires prompt intervention, —even before a definitive diagnosis is established, —to prevent irreversible neurological damage (5, 7). Current therapeutic approaches include dietary protein restriction, administration of pharmacological ammonia scavengers, and renal replacement therapy (RRT) which are effective for extracorporeal ammonia detoxification (8, 9). However, while RRT can rapidly lower serum ammonia levels, there is a recognized risk of rebound hyperammonemia during or after RRT modification.

We herein report a pediatric case of refractory hyperammonemia caused by OTC deficiency that was successfully managed with a combination of pharmacological therapy and RRT, resulting in a favorable neurological outcome.

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CASE PRESENTATION

A 14-year-old girl with autism spectrum disorder and attention-deficit/hyperactivity disorder was admitted to our intensive-care unit (ICU) with repeated vomiting, altered mental status, and hyperammonemia (649 μg/dL ; 382 μmol/L). The purpose of admission was to initiate RRT. She weighed 45 kg and was 148 cm tall. She had no relevant history of inherited metabolic diseases, and her family history was negative.

On admission, her vital signs were as follows : blood pressure, 96/50 mmHg ; heart rate, 135 bpm ; respiratory rate, 35 breaths/min ; peripheral oxygen saturation, 99% on room air ; Glasgow Coma Scale score E4V2M5, and body temperature, 36.5 °C. Blood tests showed no significant abnormalities in the inflammatory markers (white blood cell count 10,500/μL, C-reactive protein <0.05 mg/dL), coagulation screen (prothrombin time/international normalized ratio 1.18, activated partial thromboplastin time 34.0 sec), or liver function tests (alanine aminotransferase 17 IU/L, aspartate aminotransferase 17 IU/L). Given the elevated ammonia level in combination with a normal anion gap and glucose level on an arterial blood gas analysis, UCD was suspected. Brain magnetic resonance imaging and a cerebrospinal fluid (CSF) examination were unremarkable (Figure 1).

She immediately underwent endotracheal intubation due to

altered consciousness and was initiated on a combination of treatments, including dietary management, medication, and RRT to eliminate excess ammonia. Intermittent hemodialysis (IHD) was initially performed. A 13-Fr, 15-cm quad-lumen catheter (BA/UK UB-1315-QHJ™ ; NIPRO Corp., Osaka, Japan) was inserted via the right internal jugular vein for IHD. IHD was performed using the DBB-200Si™ system (NIKKISO Co., Ltd., Tokyo, Japan) with an FX-140™ dialyzer (1.4 m² polysulfone membrane ; Fresenius Medical Care AG & Co. KGaA, Bad Homburg, Germany). The blood and dialysate flow rates were set to 120 and 500 mL/min, respectively. Anticoagulation was maintained with unfractionated heparin to keep the activated clotting time between 150 and 200 s. In addition, she received intravenous administration of arginine hydrochloride, carglumic acid, and total parenteral nutrition, including 50% glucose, thiamine, pyridoxine, cyanocobalamin, ascorbic acid, and fursultiamine. Four hours after initiating IHD, the serum ammonia level rapidly decreased to 146 μg/dL (86 μmol/L) (Figure 2).

Subsequently, we alternated between IHD and continuous hemodiafiltration (CHDF) in response to serum ammonia levels. CHDF was performed using the ACH-Σ™ system (Asahi Kasei Medical Co., Ltd., Tokyo, Japan) in combination with

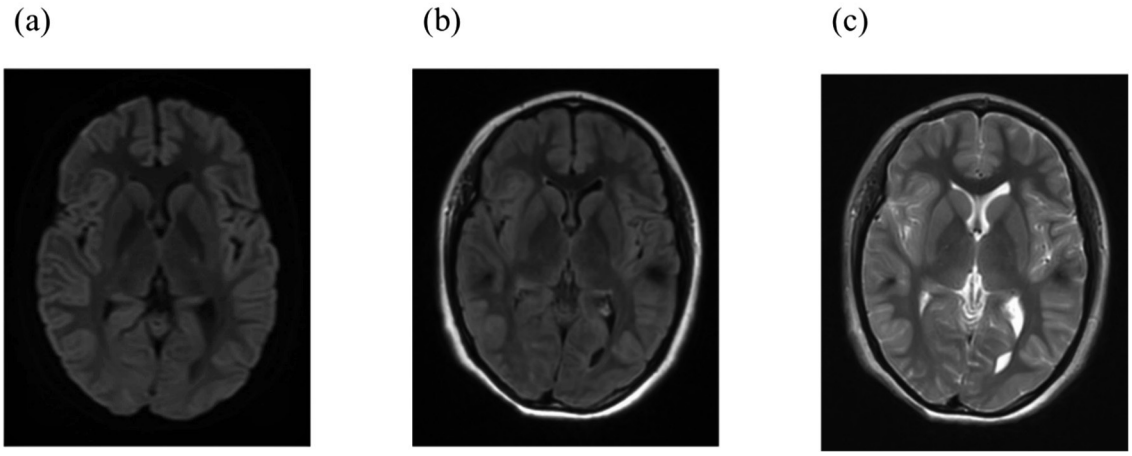

Figure 1. Brain magnetic resonance imaging showed no acute abnormalities.
a) diffusion-weighted imaging (DWI). b) fluid attenuated inversion recovery (FLAIR). c) T2 star-weighted imaging (T2*WI)

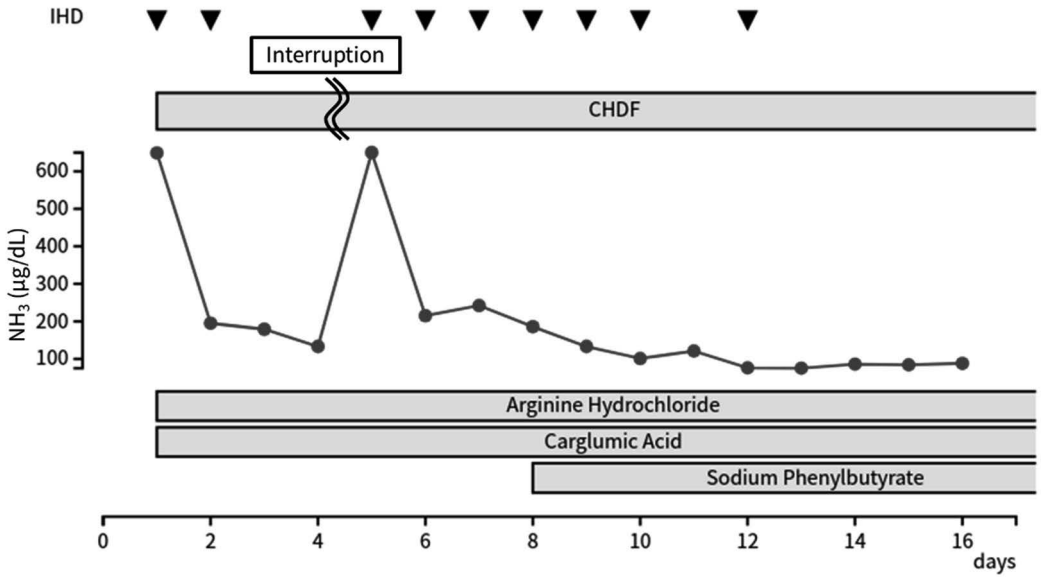

Figure 2. The clinical course of serum ammonia level and therapeutic interventions.
CHDF, continuous hemodiafiltration; IHD, intermittent hemodialysis

a UT Filter® A dialyzer (2.1 m² cellulose triacetate membrane ; NIPRO Corp.). During CHDF, the blood flow rate ranged from 80 to 120 mL/min, and the dialysate flow rate ranged from 2000 to 2500 mL/h. On day 3, the serum ammonia levels stabilized between 133 and 195 μg/dL (78 and 115 μmol/L).

On day 4, she was extubated following an evaluation of improved consciousness and confirmation that her condition met the extubation criteria. However, five hours later, she experienced sudden vomiting and was unable to take oral medications. Owing to frequent blood removal failure during CHDF, the hemodialysis catheter was replaced via the right internal jugular vein to the right femoral vein. This procedure took approximately four hours. She was re-intubated as her consciousness deteriorated and hemodynamic instability developed, with serum ammonia levels exceeding 500 μg/dL (294 μmol/L), which became unmeasurable. By promptly resuming CHDF and performing daily IHD, the serum ammonia levels decreased to 197-311 μg/dL (116-183 μmol/L). With the addition of sodium phenylbutyrate on day 8, the serum ammonia levels stabilized at approximately 200 μg/dL (117 μmol/L).

A plasma amino acid analysis revealed the following concentrations : citrulline, 8.8 nmol/mL ; ornithine, 25.8 nmol/mL ; argininosuccinic acid, 5.0 nmol/mL ; arginine, 40.1 nmol/mL ; glutamine, 60.6 nmol/mL ; and lysine, 212.6 nmol/mL. A urinary organic acid analysis revealed elevated levels of orotic acids. Based on the low plasma citrulline level and orotic aciduria, a diagnosis of OTC deficiency was confirmed on day 12.

After confirming alert wakefulness and administration of diuretics to reduce volume overload, re-extubation was successfully performed on day 14. Serum ammonia levels were successfully controlled within the range of 58-122 μg/dL (34-72 μmol/L), allowing for discontinuation of RRT (IHD on day 12 and CHDF on day 17). A low-protein diet was initiated on day 24, along with oral maintenance therapy, including L-arginine (approximately 4.6 g/day) and sodium phenylbutyrate (8.46 g/day). Thereafter, ammonia levels remained within normal limits.

She was discharged from the ICU on day 16 and returned home on day 57, without any obvious neurological consequences. Following discharge, she was followed-up on an outpatient basis, with no hyperammonemic episodes observed to date.

DISCUSSION

We encountered a challenging case of refractory hyperammonemia secondary to OTC deficiency. This case demonstrates clinical instability that can result from a short interruption in RRT during the acute phase of hyperammonemia. Despite initial stabilization with pharmacological therapy and RRT, the temporary pause triggered rebound hyperammonemia with significant clinical consequences.

OTC deficiency is a congenital enzyme defect in the urea cycle that results in impaired ammonia metabolism and recurrent hyperammonemia (3). These episodes are typically triggered by catabolic stress, excessive protein intake, or certain medications (3, 10). The symptoms are nonspecific and include vomiting, anorexia, agitation, altered consciousness, and seizures (3, 5, 6, 11). As observed in this case, hyperammonemia with a normal anion gap and blood glucose suggests UCD (12). The diagnosis is confirmed through biochemical and genetic testing, including plasma amino acid and urinary organic acid analyses, and enzyme activity assays (13, 14).

Rapid elevation of serum ammonia levels leads to the accumulation of metabolic products, such as glutamine and glutamate, which contribute to cerebral edema through osmotic activity and vasodilatory effects (3, 15, 16). In the present case, the serum ammonia level reached 649 μg/dL (382 μmol/L) upon admission. Hyperammonemia lasting over 24 h or a serum ammonia concentration exceeding 360 μmol/L (613 μg/dL) has been reported to be associated with poor neurological outcomes and reduced survival rates (2, 17). In addition, failure to initiate RRT in cases in which serum ammonia levels exceed 180 μmol/L (307 μg/dL) is associated with increased mortality and intellectual disability (2). Therefore, a rapid reduction of serum ammonia levels is critical.

Ammonia is a small molecule (molecular weight = 17) that can be efficiently removed by RRT. The efficacy of RRT in treating hyperammonemia caused by UCDs has been reported even in neonatal and pediatric populations (5, 9, 16, 18). Several reports have suggested that continuation of CRRT after IHD is useful for maintaining stable control of hyperammonemia and preventing rebound hyperammonemia (19, 20). However, even when ammonia is rapidly removed using these methods, the risk of rebound hyperammonemia remains due to inadequate intracellular solute clearance. This risk is particularly concerning in the acute phase, when protein catabolism is accelerated. In pediatric patients, frequent monitoring of blood ammonia levels is recommended during the acute phase of hyperammonemia at intervals of 2-4 h (21). Once serum ammonia levels show a decreasing trend or stabilize at 200-300 μmol/L (341-511 μg/dL), the monitoring interval can be extended to every 4-12 h (5). If pharmacological therapy is effective and RRT is no longer required, once-daily measurement of serum ammonia levels may be acceptable (21).

In the present case, the serum ammonia level decreased to 100-200 μg/dL (59-117 μg/dL) on the day following ICU admission ; therefore, we extended the measurement interval from 3 h to 8 h. After extubation on day 4, the patient's oral intake was insufficient, but serum ammonia levels remained stable. Nevertheless, rebound hyperammonemia occurred during a four-hour interruption of CRRT, resulting in marked neurological deterioration. This case highlights that when discontinuing RRT or implementing a stepwise reduction in the RRT dose, the risk of rebound hyperammonemia must be carefully considered. It is essential to reinstitute RRT promptly upon the emergence of neurological signs or ammonia elevation.

CONCLUSION

Early and continuous RRT is vital in pediatric patients with OTC deficiency and severe hyperammonemia. Even short interruptions in CRRT can result in rebound hyperammonemia with life-threatening consequences. Clinicians should anticipate such risks, ensure uninterrupted therapy during critical phases, and tailor RRT strategies according to the patient's metabolic status.

CONFLICT OF INTERESTS

All authors have no conflict of interests

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