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Unraveling the complexity: A rare case of urea cycle defect and its clinical implications

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Abstract

Background: Argininosuccinate lyase deficiency is a rare urea cycle disorder that leads to severe hyperammonemia, particularly in neonates. Early identification and intervention are crucial to prevent neurological damage and improve long-term outcomes.

Case Presentation: This case presentation describes the clinical course of an 18-year-old male from South Africa, who was referred to the Adult Endocrine Unit for further management after being diagnosed with life-threatening hyperammonemia in the neonatal period. Presenting on the fourth day of life, the patient was ventilator-dependent and required peritoneal dialysis. Analytical results obtained during the hyperammonemia crisis showed considerable perturbements of metabolic parameters; potassium was 6.6 mmol/L, urea was <1 mmol/L and the peak ammonia level was 2590 µmol/L. The change in amino acid level showed that glutamine, alanine, and argininosuccinic acid were increased. Molecular genetic testing finally led to the diagnosis of argininosuccinate lyase deficiency, a urea cycle disorder. Mostly, dietary protein intake was restricted to about 1 g/kg/day, and the use of ammonia precursors such as sodium phenylbutyrate and sodium benzoate, L-arginine, and branched-chain amino acid supplementation.

The patient was treated and developed normally up to puberty, but he had mild neurocognitive delay that affected his school attendance in the mainstream schools. He ended up experiencing multiple hyperammonemia crises in his lifespan and the last admission with crisis in September 2024 ammonia increased to 228 umol/L (11-35umol/L), treated with Dextrose 10%infusion and ammonia scavengers, and protein restriction, ammonia dropped to 93 umol/L within 24 hours.

Conclusion: This case shows that urea cycle defect requires early diagnosis and continuing treatment to prevent episodes of hyperammonemia crisis. Our patient had normal physical growth but had neurocognitive dysfunction, which is why the management of this rare urea cycle disorder is challenging.

Keywords: Arginino-succinate lyase deficiency; Urea cycle disorder; Hyperammonemia; Neurocognitive impairment

1. Introduction

The urea cycle serves as the ultimate pathway for nitrogen metabolism, primarily occurring through the catabolism of amino acids, which leads to the creation and subsequent excretion of urea(1). Urea cycle conditions include a group of genetic defects in ammonia metabolism where a defect in one of the urea synthetic pathways leads to hyperammonemia (2). These defects may involve specific enzymes in the urea cycle or transport proteins linked to this metabolic procedure. The liver is the primary location for these enzymatic activities(2). As estimated, the prevalence of these genetic anomalies is about 1: 30,000 – 46,000 live births worldwide (3).

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Neonates affected with urea cycle genetic defect may present with poor feeding, vomiting, lethargy, irritability, respiratory alkalosis, abnormal neurological signs, and seizures(4). As they progress into late infancy, symptoms may include anorexia, failure to thrive, and poor developmental progress(5). In puberty and adulthood, patients can experience acute or chronic metabolic encephalopathy, leading to symptoms such as lethargy, agitation, behavioral issues, confusion, headaches, ataxia, fluctuating consciousness, and seizures(6). The chronic effects of UCDs often manifest as learning difficulties and varying degrees of neurocognitive impairment. Sometimes, UCDs can lead to metabolic decompensation in patients(6).

Regular reassessment is essential, and if there are any changes for the worse, a repeat clinical assessment and blood tests, including blood pH and gases, ammonia, urea and electrolytes, and glucose, are performed(7). In instances of hyperglycemia, treatment with an insulin infusion is preferred over reducing glucose intake. Potassium levels are monitored and corrected as necessary(7). Molecular genetic testing is the primary method for confirming diagnoses across the eight types of UCDs(8).

Sometimes, metabolic decompensation can cause UCDs often leading to hyperammonemia, a condition that can result in life-threatening encephalopathy(8). This decompensation often happens due to metabolic stressors such as intercurrent illnesses, vomiting, diarrhea, or fasting; however, in some cases, an obvious precipitating factor may not be identifiable. Patients presenting to the emergency department must be taken seriously, particularly if they exhibit vomiting or impaired consciousness(8). Early involvement is critical to preventing the establishment of cerebral edema, which can become irreversible(8).

Management of UCDs focuses on reducing ammonia production through low-protein food and medications that promote nitrogen removal via substitute pathways(2). General management consists of maintaining anabolism by carbohydrate intake, limiting protein, removing ammonia, providing arginine replacement, and providing adequate vitamins and minerals(2). Medical treatment consists of treating dehydration with intravenous 0.9% NaCl, administrating intravenous dextrose, and stopping natural protein intake. In suspected hyperammonemia, IV ammonia scavengers should be given according to the specific urea cycle defect(9). The management of UCDs often requires a tailored approach and different deficiencies require different doses and combinations of medications including sodium benzoate and sodium phenylbutyrate(10). Patient clinical status and laboratory values need continuous monitoring and reassessment for effective management and timely intervention of potential complications. This case presents the clinical course of an 18-year-old male who was diagnosed with life-threatening hyperammonemia in the neonatal period and was given treatment, including ammonia-lowering therapies and dietary management, to stabilize his condition and prevent neurological damage

2. Case Presentation

An-18-year-old male patient from South Africa was referred to the Adult Endocrine Unit for ongoing care. He initially presented on day 4 of neonatal life with life-threatening hyperammonemia that required ventilatory support and peritoneal dialysis.

His blood tests during this initial hyperammonemic crisis:

Na 143 (135—147 mmol/L), K 6.6 (3.7—5.9 mmol/L), Urea <1 (1.4 – 4.3 mmol/L), Creatinine 88 (44 – 106 mmol/L) Ca 1.69 (2.21—2.30 mmol/L) Total protein 52 (46 – 70 g/l), Ammonia 2590 mmol/l

Amino acid profile: elevated levels of glutamine, alanine and argininosuccinic acid

He was subsequently diagnosed with argininosuccinate lyase deficiency. He was stabilized on ammonia scavengers and arginine supplementation but has had multiple subsequent hyperammonemic crises over the years, most recently in 2021 when his ammonia level peaked at 246umol/L (11-35umol/L). Despite his condition, he has done very well with normal growth and pubertal development, although he does have mild neurocognitive impairment preventing him from attending mainstream schooling.

- Molecular genetic confirmed the diagnosis.
- Our patient's regular treatment plan includes the following:
- Protein restriction to approximately 1g/kg/day

Ammonia scavengers

- Sodium Phenylbutyrate 3.8g 6 hourly
- Sodium Benzoate 3.0g 6 hourly

L-arginine 3.2 g 6 hourly

Branched chain amino acid supplementation 30 tablets per day which equivalates to:

- Leucine 16.2 g/day
- Isoleucine 10.8 g/day
- L-valine 9 g/day

Potassium chloride 50 mg/ml 30 ml bd po

The medications are given via a percutaneous gastrostomy MIC-KEY tube.

The key side effects of treatment include essential and branched chain amino acid deficiency, hypokalemia, and progressive liver failure.

In September 2024 he had another crisis precipitated by chest infection, had dizziness, confusion, vomiting, sleep disruption, ammonia increased to 228 umol/L (11-35umol/L), treated with Dextrose 10%infusion and ammonia scavengers, and protein restriction, ammonia dropped to 93 umol/L within 24 hours.

After stabilization, molecular genetic testing confirmed argininosuccinate lyase deficiency, a rare urea cycle disorder. He was placed on a treatment regimen of dietary protein restriction of approximately 1 g/kg/day to manage his condition and prevent future crises. His medication regimen included ammonia scavengers, sodium phenylbutyrate at 3.8 g every six hours, and sodium benzoate at 3.0 g every six hours. L-arginine (3.2 g every six hours) and branched-chain amino acid supplementation (30 tablets per day, yielding 16.2 g leucine, 10.8 g isoleucine, and 9 g L-valine daily) were also given. Potassium chloride was also prescribed at a concentration of 50 mg/ml, and 30 ml was taken twice daily by mouth. The medications were given through a percutaneous gastrostomy MIC-KEY tube.

Despite his ongoing extensive treatment, the patient showed normal growth and development during puberty. However, he developed mild neurocognitive impairment, which prevented him from attending mainstream schooling. Over the years, he experienced multiple hyperammonemia crises, with the most recent episode occurring in 2024, when his ammonia level peaked at 220 μmol/L. Although the patient achieved normal physical development, continuous monitoring was crucial in this case to effectively manage his biochemical parameters and mitigate potential complications associated with his treatment. Regular follow-ups and adjustments were also made according to his management plan to optimize his health outcomes.

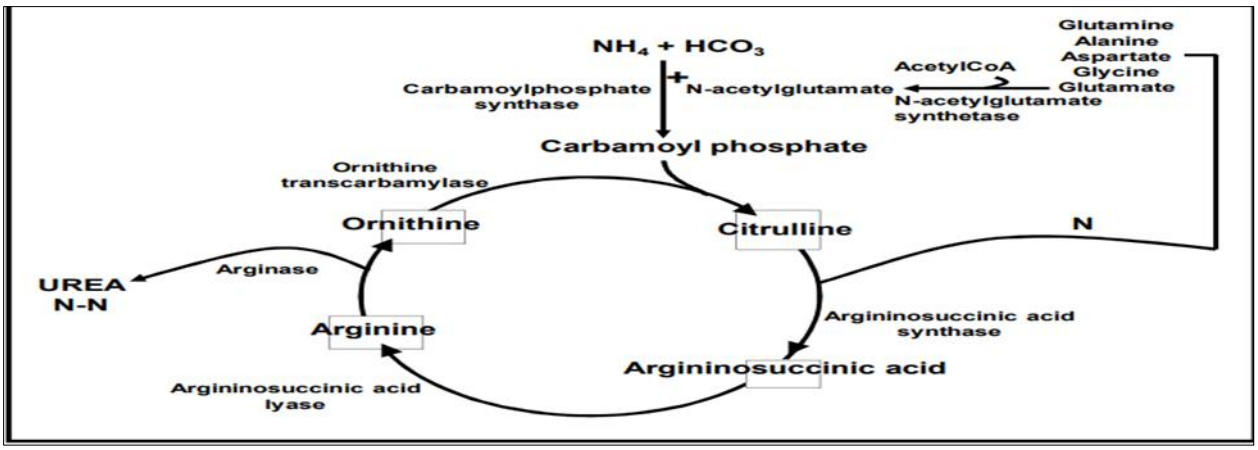

Figure 1 The urea cycle of the liver

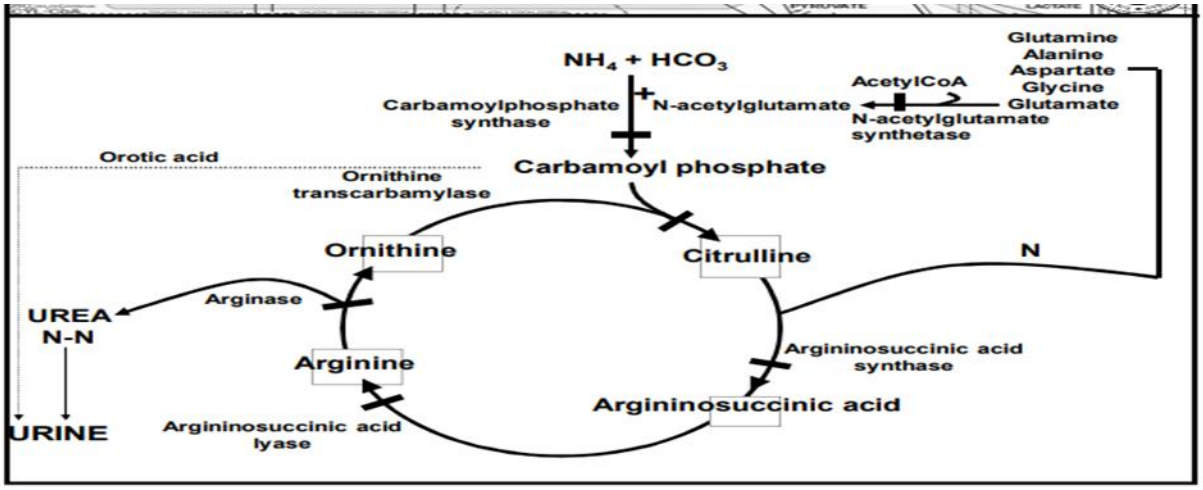

Figure 2 The urea cycle of the liver

3. Discussion

Urea cycle disorders are a group of inherited metabolic diseases in which the synthesis of urea, which is necessary to excrete nitrogen from the body, is defective(11). UCDs can manifest in a wide variety of ways, ranging from agitation to coma during acute bouts, which is a prevalent cause of newborns that exists in these patients(12). The most characteristic clinical feature of UCDs is hyperammonemia with elevated blood ammonia levels causing severe neurological symptoms because of its toxic effects on the central nervous system(13). There can also be different levels of mental impairment over time, even when the dietary intake is managed correctly. Our patient also experienced multiple hyperammonemia crises and developed mild cognitive impairment.

Typically, patients who have this sort of metabolic issue tend to build a tolerance to elevated ammonium levels. So, patients can totally show no symptoms even when their levels are around 200 µg/dL(14). These episodes happen quite often, even in mild cases of UCD, because there are many factors like fever, surgery, fasting, and infections, that can disrupt the metabolic balance(15). Additionally, it's often challenging to ensure that these young patients stick to their treatment plans over the long term(16). The damage to the central nervous system can be at least partially reversed if ammonium levels stay below 200-400 µg/dL. Still, we can't completely dismiss the possibility of mild neurological damage occurring even when ammonium levels are lower. The resulting neurological decline is related to how often acute episodes occur and the levels of ammonia present. Some symptoms that are specific to certain diseases are linked to unique metabolic issues, which usually arise from having too much or too little of certain amino acids(17).In our case, the ammonia levels peaked at 2590 µmol/L which is quite high. That is why, our patients had mild neurological impairment.

Initial investigations include measuring blood pH and gases, with ammonia samples sent urgently to the laboratory on ice, accompanied by a notification to ensure prompt processing(18). Additional tests include urea and full blood count, electrolytes, glucose, and quantitative amino acids(18). Other investigations are conducted as indicated by clinical findings, such as C-reactive protein (CRP) levels and blood and urine cultures(18).

General management focuses on maintaining anabolism through carbohydrate intake, limiting protein consumption, removing ammonia from the body, replacing arginine and other essential amino acids, and ensuring adequate vitamins and minerals (18). Mediational treatment for ornithine transcarbamylase (OTC) and carbamyl phosphate synthetase I (CPSI) deficiencies involves administering L-arginine at 100 mL/kg/day, sodium benzoate at 250 mg/kg/day, and sodium phenylbutyrate at 250 mg/kg/day(7). For citrullinemia (argininosuccinate synthase deficiency) and argininosuccinic aciduria (argininosuccinate lyase deficiency), the treatment regimen includes L-arginine at 500 mL/kg/day, sodium benzoate at 250 mg/kg/day, and sodium phenylbutyrate at 250 mL/kg/day. In cases of arginine deficiency, sodium benzoate at 250 mg/kg/day and sodium phenylbutyrate at 250 mg/kg/day are administered(7). For N-acetylglutamate synthetase (NAGS) deficiency, the treatment consists of L-arginine at 100 mL/kg/day, sodium benzoate at 250 mg/kg/day, and sodium phenylbutyrate at 250 mg/kg/day(7). Our patient medication regimen also included ammonia scavengers, sodium phenylbutyrate at 3.8 g every six hours, and sodium benzoate at 3.0 g every six hours. L-arginine (3.2 g every six hours) and branched-chain amino acid supplementation.

Additionally, general guidelines recommend that if the patient is present in a state of shock or appears very ill, arrangements for admission to the Intensive Care Unit (ICU) or High Dependency Unit (HDU) are made. Management decisions primarily rely on the clinical status, particularly the degree of encephalopathy observed(18). For patients who are relatively well, treatment is conducted orally using their designated emergency regimen, which typically involves administering 200 ml of a 25% glucose polymer solution (e.g., Maxijul) every two hours. In cases where the patient is obviously unwell, intravenous glucose-containing fluids are necessary for treatment(18). Initially, dehydration is corrected with intravenous 0.9% sodium chloride. Natural protein intake is discontinued, and intravenous 10% dextrose is administered at a rate of 2 mL/kg/hr as quickly as possible (e.g., 140 mL/hr for a 70 kg individual) (19). Intravenous treatment with ammonia scavengers is initiated if plasma ammonia levels are substantially high or if hyperammonemia is suspected. Specific combinations and dosages of medications are necessary for various urea cycle defects(19). Any underlying infections or clinical problems are addressed, and analgesia, antipyretics, or antiemetics are administered as needed. In certain cases, hemofiltration or hemodialysis may be required, with careful consideration of the potential for refeeding syndrome in susceptible patients(19).

Table 1 Intravenous therapy: in an emergency the loading dose should be given initially followed by the maintenance dose

Drug	**Loading dose over 90 minutes**	**Followed by maintenance dose over 24 hours**	**Maximum daily dose (every 24 hours thereafter)**	**Sodium content of daily maintenance dose**
Sodium benzoate	250 mg/kg	250 mg/kg	500 mg/kg	3.5 mmol/kg/d
Sodium phenylbutyrate	250 mg/kg	250 mg/kg	500 mg/kg	2.8 mmol/kg/d
Arginine	-	150 mg/kg	250 mg/kg	nil

*Use of maximum doses would be exceptional and usually 250 mg/kg/d would be sufficient.

In the emergencies the doses given should always be MONITORING:

- Reassess regularly and if there are changes for the worse repeat the clinical assessment and blood tests, including Blood pH& gases. Ammonia Urea & electrolytes
- Glucose: should hyperglycaemia occur, treat with insulin infusion rather than reducing the glucose intake.
- Potassium: potassium concentration should be monitored and corrected as an increase from those used routinely. These should be divided into 2 hourly doses to reduce the risk of vomiting.
- Treat any infection, or constipation which increases the risk of ammonia absorption from the gut.

3.1. Monitoring

Reassess regularly and if there are changes for the worse repeat the clinical assessment and blood tests, including Blood pH& gases. Ammonia Urea & electrolytes

- Glucose: should hyperglycaemia occur, treat with insulin infusion rather than reducing the glucose intake.
- Potassium: potassium concentration should be monitored and corrected

If the patient is not improving within 24—48 hours consider using parenteral nutrition or essential amino acids supplementation to reduce the risk of ongoing catabolism from protein deficiency. If the foregoing therapy fails to produce any appreciable change in ammonia level within a few hours hemodialysis or peritoneal dialysis should be considered when the Ammonia level >500, or ammonia level >300,4 hours after ammonia scavenger introduced, or ammonia level between 100—300(encephalopathy, seizure, poor response to scavengers).

Liver transplantation: is a successful and definite treatment for patients with OTC deficiency who have been well controlled and have avoided multiple hyperammonaemia.

Consider the possibility of refeeding syndrome in susceptible patients.

3.2. Progress

There may be considerable lag between the normalization of the ammonia and the improvement in the neurological status of the patients. Several days may be required till the infant is fully alert.

3.2.1. Chronic therapy will involve

- Ongoing treatment with ammonia scavenger
- Providing appropriate carbohydrate diet with protein restriction (0.8 g/kg/day)
- Provide essential amino acids.

3.2.2. Prognosis

- OTCD has high morbidity and mortality, particularly in neonatal onset.
- Approximately 24%neonatal onset, 11% in later onset.
- The poorer prognosis the longer the ammoniemiac crisis in neonatal periods.
- European guidelines suggest goal of care discussion when:
- Coma >3 days
- Elevated intracranial pressure
- Ammonia > 1000
- Later onset has better prognosis as may be residual OTC activity.

4. Conclusion

This case emphasizes the importance of timely diagnosis and therapy of argininosuccinate lyase deficiency, a rare urea cycle disorder that can cause life-threatening hyperammonemia. The complexity of the required stabilization of ammonia levels and metabolic balance throughout a patient's clinical journey from a neonatal crisis to ongoing management as an adolescent is highlighted. While patients with this condition have normal physical growth and development during puberty, their presence of mild neurocognitive impairment and multiple hyperammonemia crises demonstrate the challenges that patients with this condition face. Regular monitoring and specially directed treatment are still important to achieve optimal health outcomes and avoid complications.

The majority of cases of urea cycle defect die early during childhood due to sepsis or late diagnosis. In our case the patient was diagnosed early and received appropriate management. In addition, patient family education and monitoring is very critical.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

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