CASE REPORT

Neonatal-onset of Ornithine Transcarbamylase Deficiency: A Case of Severe Hyperammonaemia

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ABSTRACT

Severe hyperammonaemia, if untreated, rapidly leads to encephalopathy, cerebral oedema, and death. It can result from inherited or acquired disorders. A full-term baby boy, with Apgar score of 9, was intubated for transient tachypnoea of the newborn (TTN) at 30 minutes of life. He was extubated at 21 hours, began formula feeding, but developed seizures and respiratory distress 41 hours later, necessitating reintubation. Immediate investigations following the seizures revealed markedly elevated plasma ammonia (2796 µmol/L), respiratory alkalosis, hypocalcaemia and deranged coagulation profiles. Plasma amino acid analysis showed raised glutamine and alanine with undetectable citrulline levels; urine organic acid analysis revealed increased orotic acid, consistent with ornithine transcarbamylase (OTC) deficiency (OTCD). Unfortunately, he developed cerebral oedema and succumbed at 91 hours of life. This case report highlights the importance of clinical and biochemical suspicion of OTCD, an X-linked disorder that results in severe hyperammonaemia for early recognition and management of OTCD.
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INTRODUCTION

Ornithine transcarbamylase (OTC) deficiency (OTCD) is the most prevalent type of urea cycle disorder (UCD), affecting 1 in 14,000 to 80,000 people [1]. Recent newborn screening programs and date registries reported incidence rates of 1 in 62,000 in Finland, 1 in 63,000 in United States and 1 in 69,904 in Italy [1]. It is an X-linked genetic disorder with the affected gene located on the short arm of the X chromosome at Xp11.4. [1,2]. The disease exhibits significant phenotypic heterogeneity depending on the type of mutation, genetic background, and environmental factors [1,2]. Homozygous males with a complete absence of the OTC enzyme typically begin to exhibit neurological symptoms within 24 hours to a few days after birth. In contrast, late-onset OTCD occurs in males with partial deficiency and heterozygous females with mild neurocognitive symptoms [2].

The OTC enzyme plays a crucial role in converting ornithine and carbamoyl phosphate to citrulline within the urea cycle, the primary pathway for detoxification of ammonia and elimination of nitrogenous waste into water soluble urea. Consequently, typical biochemical changes include severe hyperammonaemia, reduced citrulline levels, increased glutamine levels, and elevated urinary orotic acid levels [1]. Early diagnosis and treatment of OTCD are vital to prevent hyperammonaemic crisis and minimise neurological sequelae. While genetic testing is typically confirmatory, recent diagnostic challenges underscore the need for strong clinical and biochemical suspicion [2].

CASE REPORT

A full-term baby boy, born via vacuum-assisted delivery (VAD) with Apgar scores of 8 and 9 at 1 and 5 minutes, respectively, was intubated at 30 minutes of life following respiratory distress (tachypnoea and grunting with the presence of nasal flaring and chest wall recessions). He was admitted to the neonatal intensive care unit (NICU) for transient tachypnoea of the newborn (TTN) and was commenced on intravenous antibiotics covering for presumed sepsis as the mother had experienced leaking liquor (<18 hours). He was extubated at 21 hours of life, and standard formula feeding was commenced soon after. Forty-one hours later, he developed several episodes

of seizures associated with generalised hypotonia and respiratory distress, requiring reintubation. He was his parent's first child, with no family history of metabolic disorders, early neonatal deaths or consanguinity. The mother's antenatal history includes gestational diabetes mellitus managed with dietary control, maintaining good blood sugar profiles throughout pregnancy.

Immediate investigations following the seizures revealed severe hyperammonaemia (2796 umol/L), respiratory alkalosis, hypocalcaemia and deranged coagulation profile (Table I). There was mild anaemia, but the white blood cell (WBC) count was not elevated, and C-reactive protein (CRP) level was normal. Apart from mild hypoalbuminaemia, liver enzymes were not elevated. There was no hypoglycaemia or renal impairment. Repeat investigations revealed worsening hyperammonaemia and coagulopathy, as well as increased lactate. Plasma amino acid analysis showed elevated glutamine, alanine and proline with undetectable citrulline and low normal arginine (Table II), while urine organic acid analysis showed increased excretion of orotic acid with orotic acid quantification of 3477.50 mmol/mol creatinine (reference interval 1.3-5.3), consistent with OTCD. Cranial ultrasound (USG) showed evidence of cerebral oedema. The immediate treatment goal was the rapid removal of excess ammonia; however, dialysis could not be performed due to the patient's worsening coagulopathy and cerebral oedema. He later succumbed at 91 hours of life.

Table I: Laboratory Investigations

Investigations	Day 3 of life		Reference Interval
	0500 h	1800 h	
FBC			
While cell count	13.36	16.51	5-23 10^3/uL
Neutrophils	8.99	9.95	3-5 10^3/uL
Lymphocytes	1.66	3.25	2-8 10^3/uL
Haemoglobin	13.6	13.4	15.0-21.0 g/dL
Haematocrit	37.2	36.6	45-67 %
Platelet	296	338	210-500 10^3/uL
Coagulation profile			
PT	20.8	23.5	11.9-15.3 s
APTT	43.4	88.6	32.0-42.0 s
INR	1.56	1.77	
Fibrinogen	135	276	200-400 mg/dL
D-dimer	0.90		<0.5 ug/mL
ABG			
pH	7.51	7.42	7.35-7.45
pCO2	32	43	35-45 mmHg
$HCO3^-$	25.5	27.9	22-26 mEg/L
Ammonia	2796	4183	18-72 umol/L
Lactate	2.17	6.96	0.63-2.44 mmol/L
Random blood sugar	4.8		<11.1 mmol/L
Renal profile			
Sodium	135	134	135-150 mmol/L
Potassium	5.8	4.5	3.5-5.0 mmol/L
Urea	1.5	2.1	1.4-4.3 mmol/L
Creatinine	37	42	22-90 umol/L
Adjusted Calcium	1.68	1.60	1.90-2.60 mmol/L
Magnesium	0.77	0.98	0.79-1.56 mmol/L
Phosphate	2.15	1.97	1.76-3.37 mmol/L

CONTINUE

Table I: Laboratory Investigations. (CONT.)

Investigations	Day 3 of life		Reference Interval
	0500 h	1800 h	
Liver function test			
Albumin	30.7	28.2	31-43 g/L
Total protein	47.2	54.9	52-79 g/L
Total bilirubin	163.4	120.0	4.0-253.0 umol/L
ALP	181	140	76-233 U/L
ALT	12.6	17.5	6-30 U/L
AST	55	66	30-146 U/L
CRP	0.32		0.00-0.50 mg/dL

APTT: Activated partial thromboplastin; PT: Prothrombin time; INR: International normalised ratio;
ALP: Alkaline phosphatase; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; ABG: Arterial blood gas; CRP: C-reactive protein; FBC: Full blood count

Table II: Plasma amino acid profiles

Amino acid	Results	Reference Interval
Glutamine	2869	<700 µmol/L
Alanine	1115	132-455 µmol/L
Citruline	0	3-36 µmol/L
Lysine	1026	37-272 µmol/L
Proline	762	77-329 µmol/L
Arginine	37	17-119 µmol/L

DISCUSSION

Hyperammonaemia is characterised by a plasma ammonia concentration exceeding 110 µmol/L in term-born neonates [3]. It is neurotoxic and can lead to irreversible damages to the central nervous system [3]. The underlying cause can be inherited (e.g., metabolic disorders such as UCDs, fatty acid oxidation disorders, organic acidaemias) or acquired (e.g., hepatic insufficiency and sepsis) [2,3]. Indicators that narrow the differential diagnosis to UCDs include respiratory alkalosis, normal blood glucose level and severely elevated ammonia levels [2], as demonstrated in this case. In fatty acid oxidation disorders, there is non-ketotic hypoglycaemia, whereas in organic acidurias, lactic acidosis is present. Nevertheless, the respiratory alkalosis initially seen in UCDs may later progress to acidosis in decompensated states due to lactic acid accumulation secondary to hypoxic tissue injury [1]. Further evaluation includes plasma amino acid profiles, urine organic acid and urinary orotic acid quantification [2]. A marked increase in plasma glutamine and low blood citrulline are also observed in other proximal UCDs namely carbamoyl phosphate synthase I (CPSI) deficiency [2]. However, quantifying urinary orotic acid excretion, which is significantly elevated in individuals with OTCD is a key parameter, as demonstrated in this case [2]. In suspected cases, genetic testing typically confirms the diagnosis; however, studies have shown that routine Sanger sequencing of the OTC gene sometimes fails to detect disease-causing variants [2]. Additionally, next-generation sequencing and UCD gene panels have been ineffective in diagnosing certain cases [2]. This highlights the crucial role of clinical and biochemical suspicion in identifying this rare but potentially severe disorder. Regrettably however, genetic testing was not performed in this patient. Additionally, genetic

counselling and screening among family members play a crucial role in detecting carriers which ultimately avert potential complication.

The clinical presentation of OTCD may vary depending on the severity and the age of onset of the disease. An epidemiology study involving three countries in Europe (France, Turkey and United Kingdom), demonstrated that neonatal-onset cases accounted for 19%, 12% and 7% cases, respectively, while 39%, 42% and 67% had a late-onset presentation [1]. In addition, family history of OTCD, was reported between 36-60% of cases [1]. Patients with severe neonatal onset are typically asymptomatic at birth but manifest clinical manifestations related to hyperammonaemia within the first few days of life with tachypnoea, vomiting, hypotonia and lethargy, which may progress to seizures, development of respiratory alkalosis, hypothermia, and severe encephalopathy [2]. In this case, symptoms worsened 40 hours after feeding commenced, with acute episodes of seizures, respiratory alkalosis and hypotonia. In neonatal onset, the physiological catabolism of the newborn is considered to trigger the decompensation [4]. In contrast, patients present post-neonatally have various triggering factors such as febrile infections, protein loading, trauma and other catabolic situations [4].

The most important prognostic factors for patients in hyperammonaemic crisis are the extent of ammonia elevation and duration of elevated ammonia, with longer duration of hyperammonaemia associated with worse prognosis [2]. Prognosis is commonly poor in cases with extreme elevation of plasma ammonia level ≥1000 µmol/L and/or a duration of hyperammonaemic crisis of >24 hours [4]. These criteria were met in this case, with the infant presenting with life-threatening plasma ammonia levels of 2796 umol/L, with further increment noted a few hours later. In the acute stage of severe hyperammonaemia, rapid removal of ammonia is mandatory by providing adequate hydration, restriction of protein intake and haemodialysis. [1,2]. This child was kept nil by mouth and given intravenous fluids, and planned for dialysis which was abandoned due to worsening coagulopathy. Palliative care was opted for due to rapid elevation of ammonia level and evidence of cerebral damage.

OTCD, particularly the neonatal onset carries significant mortality and morbidity. Forty percent of infants pass away during the neonatal period, and 52% experience developmental delays by the age of one year [5]. Given the severe clinical complications associated with hyperammonaemia, early diagnosis prior to symptom onset is highly desirable [5]. Implementing a universal newborn screening for these disorders would be the optimal approach. However, OTCD is not included in the neonatal screening in most centres [2]. If available, newborn screening for OTCD involves measuring citrulline levels in dried blood spots. Additional testing using a glutamine-to-glutamate ratio is advised to identify individuals with a UCD [2]. A low citrulline and high glutamine levels on newborn screening suggest OTCD. However, because glutamine is inherently unstable and citrulline lacks sufficient specificity and sensitivity for OTCD, current consensus guidelines do not endorse routine newborn screening for this condition [2].

CONCLUSION

Neonatal onset of OTCD poses a considerable challenge to paediatric healthcare, requiring aggressive and comprehensive intervention. This case highlights the importance of continued efforts to raise awareness among healthcare providers and develop more effective therapeutic interventions for patients with this rare metabolic disorder.

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REFERENCES

1. Seker Yilmaz B, Baruteau J, Arslan N, Aydin HI, Barth M, Bozaci AE, et al. Three-country snapshot of ornithine transcarbamylase deficiency. Life (Basel). 2022;12(11):1721. doi: 10.3390/life12111721.
2. Donovan K, Vaqar S, Guzman N. Ornithine Transcarbamylase Deficiency. [Updated 2024 Feb 26]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan. Available from: https://www.ncbi.nlm.nih.gov/books/NBK537257/.
3. Del Re S, Empain A, Vicinanza A, Balasel O, Johansson AB, Stalens JP, et al. Irritability, poor feeding and respiratory alkalosis in newborns: Think about metabolic emergencies. A brief summary of hyperammonemia management. Pediatr Rep. 2020;12(3):77–85. doi: 10.3390/pediatric12030019.
4. Unsinn C, Das A, Valayannopoulos V, Thimm E, Beblo S, Burlina A, et al. Clinical course of 63 patients with neonatal onset urea cycle disorders in the years 2001-2013. Orphanet J Rare Dis. 2016;11(1):116. doi: 10.1186/s13023-016-0493-0.
5. Vasquez-Loarte T & Thompson JD, Merritt JL 2nd. Considering proximal urea cycle disorders in expanded newborn screening. Int J Neonatal Screen. 2020;6(4):77. doi: 10.3390/ijns6040077.