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Case Report

Severe Hyperammonaemia with Metabolic Acidosis in a Neonate: a Case Report of Ornithine Transcarbamylase Deficiency (OTCD)

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***Abstract*— Ornithine transcarbamylase (OTC) deficiency (OTCD), the most common urea cycle disorder, is an X-linked genetic disorder due to complete or partial lack of the OTC enzyme. Its clinical presentation depends on the degree of enzyme deficiency and ranges from an acute neonatal metabolic crisis with a high mortality rate through to an asymptomatic adult. We present a case of a newborn baby boy who presented with poor feeding, vomiting, lethargy, and respiratory distress. Laboratory investigations revealed severe hyperammonaemia, hyperglutaminaemia, hyperalaninaemia, absence of citrulline, and marked orotic aciduria. Family screening confirmed the presence of an OTC disease-causing mutation in his mother. It was a heterozygous mutation, c.316G>A. p. Gly106Arg in exon 4.**

***Keywords*— urea cycle disorder; OTC; hyperammonaemia; neonate.**

I. INTRODUCTION

Severe hyperammonaemia is a life-threatening event in neonates. The underlying aetiologies can be classified into primary (metabolic disorders—urea cycle defect, fatty acid oxidation defect, organic acidaemia) and secondary (liver injury due to infection or toxins, transient hyperammonaemia of the prematurity) categories.

Ornithine transcarbamylase (OTC) deficiency (OTCD) (OMIM #311250), the most prevalent urea cycle disorder (UCD) [1,2] results from the hepatic mitochondrial enzyme OTC deficiency which is responsible to convert ornithine and carbamoyl phosphate to citrulline [3]. This results in an excess of nitrogen in the blood in the form of ammonia. Patients usually present with non-specific neurological symptoms such as vomiting, poor feeding, progressive lethargy, respiratory distress, convulsion, and coma [4]. The estimated prevalence of OTCD is 1:14,000 live births [5]. The mortality rate depends on the time of presentation as it is

higher in the neonatal (74–90%) compared to the late-onset (13%) period [6].

II. CASE REPORT

A 72-hour-old baby boy presented with a history of poor feeding associated with persistent vomiting, lethargy, and increasing respiratory distress. He developed seizures at the emergency department and was subsequently intubated. He was lethargic, dehydrated, and with neurologically abnormal posturing, hypertonia, and jerky movement of all limbs and lips smacking.

His mother had multinodular goitre which remained biochemically euthyroid antenatally. Otherwise, the intrapartum and immediate postnatal periods were uneventful. Further family enquiries revealed recurrent neonatal deaths on the maternal side (an uncle and five granduncles). He was the only son in his family, and he had four sisters who were free of the disease.

A complete blood count showed haemoconcentration with no evidence of infection. Blood gas revealed severe high anion gap metabolic acidosis. Initial plasma ammonia level was significantly elevated at 1794 umol/L, and plasma lactate was 12.1 mmol/L (Table 1). His serum urea, electrolytes, and liver function tests were normal with only mildly elevated aspartate aminotransferase.

TABLE 1:
SERIAL SERUM AMMONIA AND LACTATE

Admission (day)	Ammonia (umol/L)	Lactate (mmol/L)
1	1847	11.39
2	Peritoneal dialysis done	
3	234	11.63
4	256	9.70
5	311	5.87
6	398	7.00
7	681	4.91
8	748	5.70

Reference ranges are 6.5–35.0 umol/L for ammonia, and 0.65–2.44 mmol/L for lactate.

Plasma amino acids showed marked elevation of glutamine, alanine, and lysine, with absence of citrulline (Table 2). This was highly suggestive of UCD, and possibly OTCD. Similar findings were observed from his dried blood spot test—i.e., moderate elevation of glutamine and alanine with low citrulline and arginine.

Urine organic acid reported severe lactic aciduria with marked orotic aciduria: orotic acid/creatinine was 85.76 mmol/mol creatinine (normal range 1.3–5.3 mmol/mol creatinine) (Figure 1).

TABLE 2:
SERIAL PLASMA AMINO ACID

Admission (day)	Glutamine (umol/L)	Alanine (umol/L)	Citrulline (umol/L)	Arginine (umol/L)
1	4184	1890	0	51
2	3288	3703	0	51
4	4825	2106	0	82
5	4839	1634	0	69

Reference ranges are <700 umol/L for glutamine, 132–455 umol/L for alanine, 3–36 umol/L for citrulline, and 17–119 umol/L for arginine.

A plain non-contrasted CT brain scan showed hyperdense and dilated cerebral veins involving superior sagittal sinus, straight sinus, bilateral transverse sinus, internal cerebral, and cortical veins (Figure 2), suggestive of thrombosis. There was no evidence of haemorrhage or ischaemia in the scan.

Subsequently, his liver function worsened, and he developed coagulopathy. His ammonia remained in refractory status despite him receiving chelation with sodium phenylbutyrate and L-arginine as well as peritoneal dialysis. His condition deteriorated further, and he required high ventilator settings, maximum inotropes, and regular blood product transfusion. Unfortunately, he died on day 10 after his birth.

OTC mutation analysis of the mother confirmed a heterozygous disease-causing mutation, c.316G>A. p. Gly106Arg in exon 4.

III. DISCUSSION

The initial patient's presentation was indistinct and could mimic other common neonatal illnesses, such as sepsis. Nevertheless, recurrent neonatal deaths in the maternal side of the family triggered the discovery of an underlying metabolic disease.

Any defect in urea cycle enzymes can lead to hyperammonaemia and is often accompanied by respiratory alkalosis due to respiratory centre stimulation. Conversely, our patient presented with hyperammonaemia and metabolic acidosis, which may have misled us to the organic acidaemia diagnosis. However, metabolic acidosis can occur in decompensated UCDs due to accumulation of lactic acid secondary to hypoxic tissue injury, as seen in this case evidenced by severe lactic aciduria in urine organic acid [7].

The timing of arterial blood sampling is also important because in the post-resuscitation period the respiratory centre is controlled by a ventilator and obliterates the typical respiratory alkalosis. A delay in the sample analysis and a manually heparinised blood gas syringe are pre-analytical factors that can contribute to metabolic acidosis.

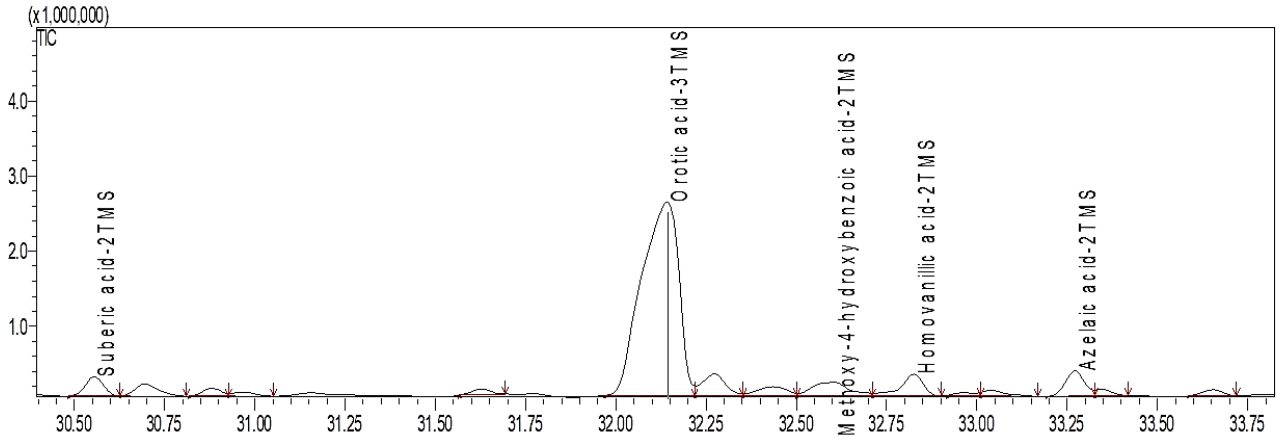
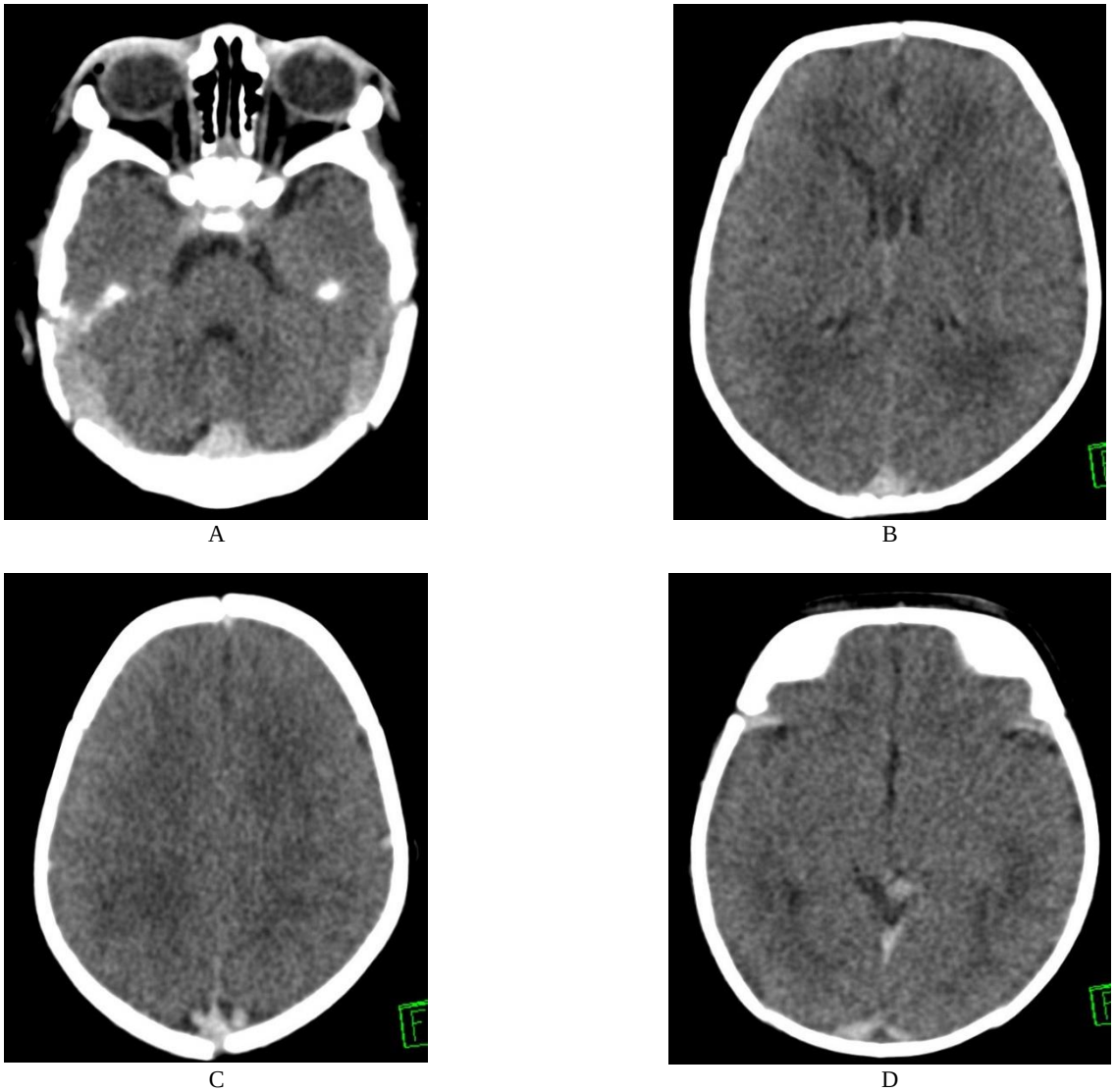


Figure 1: Organic acid chromatogram showing a high orotic acid level in this patient.



A B C D

Figure 2: Non-contrasted CT brain scans showed dilated straight sinus, bilateral transverse sinus (A and D), and superior sagittal sinus (B and C) with hyperdensity within, suggestive of thrombosis.

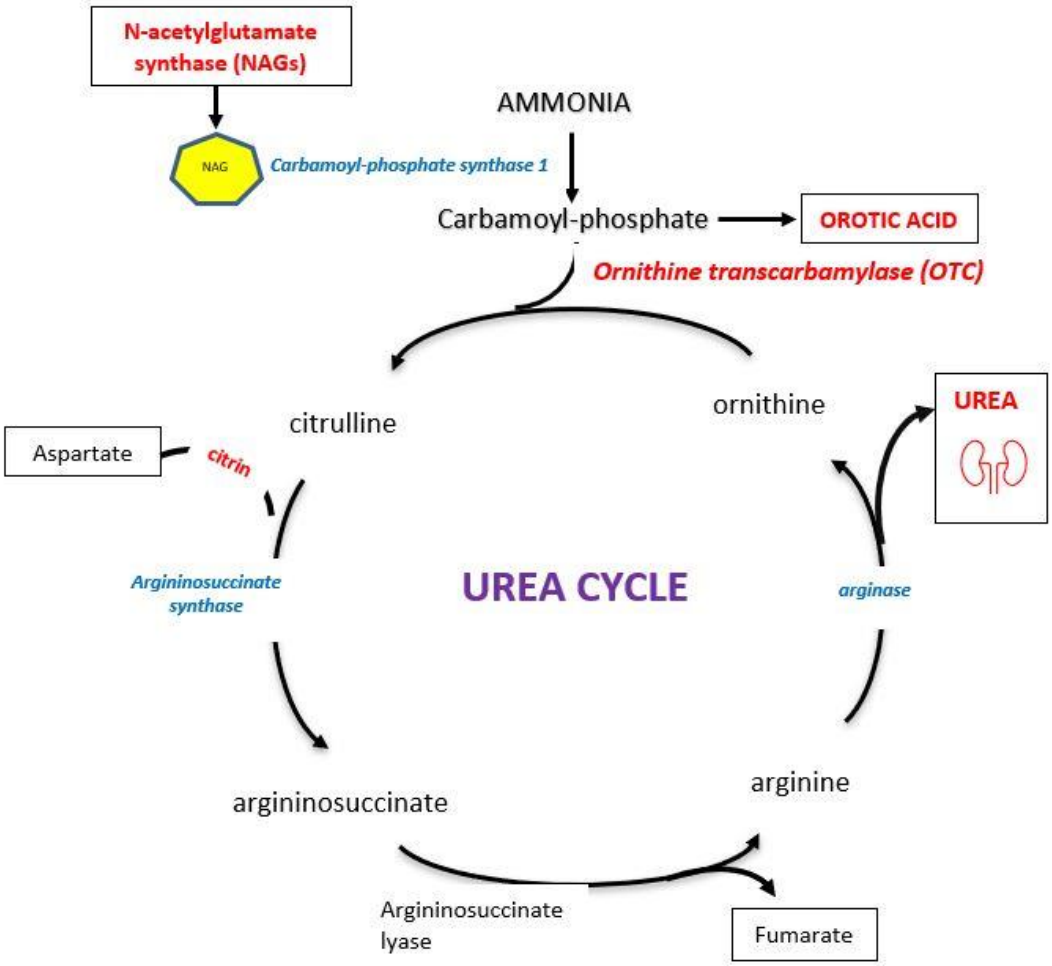


Figure 3: Urea cycle.

The urea cycle (Figure 3) plays an important role in the detoxification of ammonia to urea. It comprises enzymes [carbamoyl phosphate synthase 1 (CPS1), OTC, argininosuccinate synthase (ASS), argininosuccinate lyase (ASL), and arginase (ARG1)]; amino acid transporters [ornithine translocase (ORNT10) and citrin]; and cofactor producing enzyme [N-acetylglutamate synthase (NAGS)] [8].

Any enzyme deficiencies in the cycle results in UCDs. In UCDs, ammonia enters the central nervous system (CNS) in excessive amount, causing astrocyte toxicity. Ammonia is metabolized in the astrocytes via the reaction of glutamine synthase to form glutamine. Oxidative stress, bioenergetic failure and excessive accumulation of glutamine that occur because of this reaction contribute to cerebral oedema, intracranial hypertension and cerebral hypoperfusion, resulted in encephalopathy [7, 12, 20].

These reversible or irreversible effects on the CNS depends on the age of onset, duration, and level of hyperammonaemia exposed. Characteristic radiological abnormalities resemble ischemic infarcts in the insular cortex and cingulate gyrus [13]. OTCD has been documented to cause thrombotic complications [14] as seen in this patient. The proposed thrombotic pathophysiology is due to hypoargininaemia that results in insufficient nitric oxide production which leads to platelet hyperaggregability, endothelial dysfunction and vascular thrombosis [15].

In UCDs, specific abnormal patterns of amino acids in plasma amino acid analyses help to identify the degree of the defect. A repeatedly undetectable plasma citrulline with elevated ammonia and glutamine reflected a proximal cycle (CPS1, OTC, and NAGS) defect in our case. Excess carbamoyl phosphate is channelled into the pyrimidine biosynthetic pathway forming orotate (Figure 4). An analysis of increased orotic acid in urine organic acid strongly suggests the diagnosis of OTCD [9].

Regrettably, his sample was not sent for confirmatory molecular testing. However, because OTCD is an X-linked disease, a mutation analysis of his mother confirmed her carrier status. Hitherto more than 400 disease-causing mutations were identified and the most reported were missense variants [10]. The OTC gene (Xp21.1) has 10 exons and 9 introns. It codifies 322 amino acid proteins, and it is expressed in the liver and intestinal mucosa [11]. Most of the missense variants result in amino acid substitution and affect the function or structure of the enzyme. However, mutations that completely abolish OTC production and enzymatic activity result in acute neonatal manifestations [12].

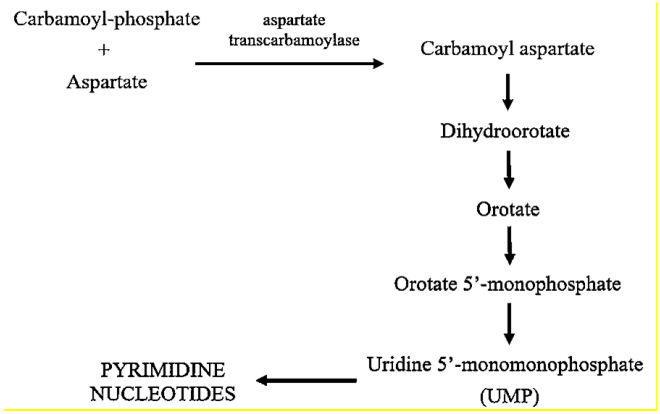


Figure 4: Pyrimidine pathway.

Currently, irrespective of the cause, the aim of severe hyperammonaemia therapy is to rapidly remove ammonium and its precursors [16, 17]. This is done by protein restriction, ammonia chelation, and hemo/peritoneal dialysis in refractory cases [18]. Hyperammonaemia is a neonatal emergency and without treatment and intervention, death usually occurs within the first week of life [16]. A suggested algorithm for the management of hyperammonaemia is shown in Table 3.

Delayed treatment will expose the infant to a poor neurological outcome: developmental delay, learning disability, cerebral palsy, and epilepsy [16]. Other strategies to counteract the adverse effects of hyperammonaemia have been proposed including using a NMDA receptor antagonist, nitric oxide inhibitors, or creatine and acetyl-l-carnitine, which were neuroprotective.

Current studies looking at novel therapies are ongoing. Genetic disease therapy on rat models delivering adeno-associated virus vector in OCTD mouse model hope to control the blood ammonia level as it restores the enzymatic activity [21, 22]. Other studies, such as cell therapy to populate functional hepatocytes in UCD patients, are also ongoing.

Finally, bioartificial livers are likely to be the future treatment of choice for acute hyperammonaemia [23].

IV. CONCLUSION

Hyperammonaemia is a neonatal emergency. OTCD is the most common inherited disease of newborns associated with severe hyperammonaemia. Nevertheless, its association with metabolic acidosis is unusual. The condition may occur because of lactic acid accumulation owing to hypoxic tissue injury in the case of decompensated disease. Without aggressive treatment, patients with OTCD usually die within the first week of life. Delayed treatment exposes the infant to poor neurological outcomes: developmental delay, learning disability, cerebral palsy, and epilepsy. Awareness of OTCD associated with severe hyperammonaemia requires multidisciplinary approaches to improve the neurological outcome and quality of life. Therefore, knowledge of the possible biochemical abnormalities in OTCD is vital in guiding the clinician towards effective treatment.

TABLE 3:
SUGGESTED ALGORITHM FOR MANAGEMENT OF HYPERAMMONAEMIA.

Plasma ammonia level (umol/L)	**Known/ Suspected UCD patient**
Above the upper limit of the reference range	Withhold protein intake a maximum of 48 hours Start IV glucose at appropriate dosage Monitor serial plasma ammonia level
>150≤250	Start IV arginine (+ L-citrulline and nitrogen scavenger) Consider nasogastric carbohydrate and lipid emulsions if tolerated
>250≤500	Prepare haemodialysis/continuous hemo filtration Start if no rapid drop of ammonia in 4 hours
>500≤1000	Start haemodialysis/continuous hemo filtration
>1000	Consider whether to continue specific treatment or opt for palliative care

Source: Adapted from Haberle J, Boddaert N, Burlina A, et al. Suggested guidelines for the diagnosis and management of urea cycle disorders. *Orphanet J Rare Dis*. 2012; 7:32.27

CONSENT TO PARTICIPATE

Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

CONFLICT OF INTERESTS

The authors declare that there is no conflict of interest.

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