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Case Presentation
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A Case of Ornithine Transcarbamylase Deficiency with Transient Loss of Vision

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Abstract

We present a girl diagnosed with Ornithine Transcarbamylase deficiency (OTCD) at eight years of age. She presented to emergency department (ED) with vomiting, abdominal pain, erratic behaviour, and confusion. She had slurred and senseless speech. She was noted to have low Glascow Coma Scale (GCS), she was responsive to pain. She was vitally stable, respiratory, cardiovascular, and gastrointestinal system exam were normal, but neurological exam showed four limb hypotonia, hyperreflexia and ankle clonus. She had baseline bloods including ammonia and serum amino acids. She was started on intravenous (IV) antibiotics and IV Aciclovir to cover for both encephalitis and meningitis. Her CT brain was normal. However, her ammonia was elevated at 324 umol/l and her serum amino acids showed marked elevation of glutamine, low citrulline, and low arginine which were suggestive of OTC deficiency. She was started on IV ammonia scavengers. She showed marked improvement clinically with normal GCS and ammonia decreased to 123 umol/l after around 6 hours of treatment. Unfortunately, a week after admission she started complaining of headache, runny nose, temperature, photophobia, and bilateral visual loss. MRI brain and magnetic resonance venogram (MRV) showed slight restriction diffusion in occipital area. She had papilledema and high CSF opening pressure. She was started on acetazolamide and Co enzyme Q10. She responded well to

management and continues to make a good progress.

Keywords: OTCD; Transient visual loss; Urea cycle disorder

Introduction

Ornithine Transcarbamylase (OTC) deficiency (OMIM #311250) is a rare genetic, X - linked disorder caused by mutations in *OTC* gene (Xp21.1), which encodes Ornithine Transcarbamylase, responsible for catalysing the synthesis of citrulline and inorganic phosphate from carbamoyl phosphate and ornithine. Liver is the only site of the complete urea cycle. OTC is intra-mitochondrial enzyme and some other urea cycle enzymes are intra-cytosolic as in **Figure 1**. OTC deficiency can present from severe form in the neonatal period to a milder form in adult life. It is the most common form of urea cycle defect, and the prevalence estimates range between 1:56,500 to 1:113,000 live births worldwide **[1]**. Female carriers can present with the disorder due to skewed X chromosome inactivation. About20% of carrier females present with the disorder **[2]**. The clinical manifestations include poor feeding, lethargy, tachypnoea, hypothermia, irritability, vomiting, ataxia, seizures, hepatomegaly, and coma. The initial investigations include venous blood gas, blood glucose, serum ammonia, plasma amino acids, liver function and renal function tests **[3,4]**. Diagnosis is based on biochemical testing, including high ammonia level, plasma amino acid analysis (low citrulline and arginine, high glutamine) and increased excretion of Orotic acid in urine. Diagnosis is then confirmed by molecular genetic testing. If left untreated encephalopathy can lead to brain stem dysfunction and death **[1,2]**. OTCD is managed by protein restriction and the use of ammonia scavengers. Protein restriction is the principle of management of urea cycle disorders along with arginine or citrulline. Initial management includes stopping all protein intake for maximum 36-48 hours as prolonged protein cessation will induce catabolism. In addition, commencing on IV dextrose 10-25% and lipids 1-3 g/kg/day with ammonia scavengers is recommended. Furthermore, addition of IV arginine and oral/NG citrullineis given **[3,4]**. Sodium phenylbutyrate works by combing with glutamine to form phenylacetylglutamine which excreted in the urine. Ammonia scavengers is also associated with disadvantages like depletion of branched chain amino acids and aggravate catabolic crisis so essential amino acids supplementation is of essence in patients with OTCD **[5,6].** It also depletes branched chain amino acids, so regular monitoring is essential. Sodium benzoate combines with glycine to form hippuric acid which then is excreted in the urine **[7,8]**.

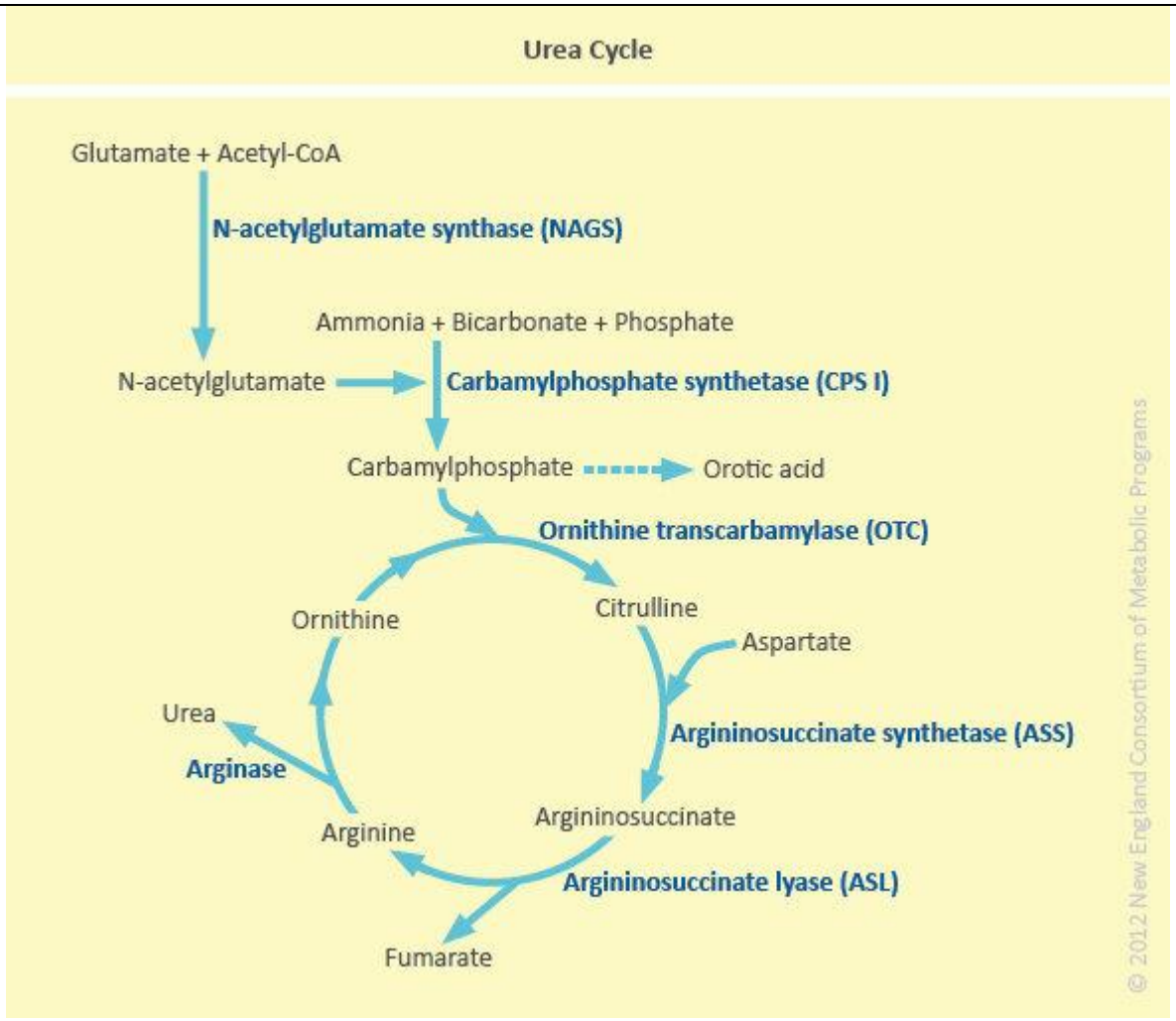

Figure 1: urea cycle.

Glycerol phenyl butyrate (Ravicti) has similar pharmacokinetics as sodium phenylbutyrate as it combines with glutamine to form phenylacetylglutamine which excreted in urine. It is not used for children less than 2 years old. Side effects include vomiting and somnolence with higher doses. Long term management with protein restriction and ammonia scavengers would not protect from crises, hence the use of liver transplant as a cure [9,10].

Case Presentation

An eight-year-old girl presented to CHI at Temple Street Hospital. She presented with her father to the Emergency Department with behavioural changes. She went to school that day and was complaining of abdominal pain that morning. When she arrived at school, she was reported to be erratic and aggressive. Her parents brought her home. Her parents noted slurred speech and confusion. She kept repeating to her parents that she wanted to be outside in garden and was pacing, walking, and bumping into things. On the previous day, the school informed the parents that she fell asleep in class and was brought home, where she slept most of the day. She started vomiting on that occasion, but she had no temperature and no diarrhoea. There was no history of viral illness or contact with sick person. Mum mentioned similar episodes in the previous year, but those were not as severe as this

episode. Mum described her on previous occasions as being lethargic, drowsy, and appeared' as if she was drunk' with slurred speech. On both occasions, she was brought to ED, with no admission on either occasion. As per parents, between these episodes, she had no issues. But they noticed that she avoided protein containing foods like sausages. In addition, she had difficulty seeing the board in school. There was no obvious trigger for these events identified.

Regarding her development, gross motor, speech, and social development were age appropriate. She had coordination difficulties including, difficulty kicking a ball, pedalling a bike, using zips, and tying laces. She had been recently diagnosed in school with poor coordination and linked in with appropriate services. She was born at full term by spontaneous vaginal delivery, with no complications. Her vaccinations were up to date, and she has no known drug allergies. Regarding her family history, she has two sisters, one older, one younger. Her mum has no history of miscarriages, her grandmother had few miscarriages, and all were boys. She is in 3rd class in mainstream school.

On arrival, her Glasgow Coma Scale (GCS) was 11/15. She was responsive to pain. Physical examination was unremarkable apart of neurological exam which showed hypotonia of both upper and lower limbs, with brisk reflexes in both upper and lower limbs, with ankle clonus and negative meningeal signs. The overall impression was that she was encephalopathic. CT brain was normal, and she was resuscitated with fluid. Baseline bloods including ammonia and serum amino acids were done. Her VBG showed slight alkalosis of pH 7.49 (7.28-7.4), pCO2 4.5 (5-7.2 kPa) and Hco3 26.2 (20-27 mmol/l), lactate 1.4 mmol/l. She had high transaminases, ALT 271 u/l (0-35) and AST 83 u/l (0-40) and CRP<1. Her ammonia was 324 umol/l (0-65) and her serum amino acids showed marked elevation of glutamine at 2987 umol/l (544-836), low citrulline at 11umol/l (12-30), low ornithine at 22umol/l (27-103) and low arginine at 27umol/l (32-128) which was suggestive of OTC deficiency diagnosis. She also had a high alanine level, the highest being 906 umol/l (176-480) and it took 6 days to normalise. Her glutamic acid was normal at 41 umol/l (6-130) and glycine was also normal at 302 umol/l (97-389). Her urine showed high orotic acid excretion. Her management was guided by Inherited Metabolic Diseases Team, and she was commenced onammonia scavenger medications - Sodium Benzoate, Sodium Phenylbutyrate and Arginine, she had a loading dose of these followed by a maintenance dose. She showed great improvement with improved ammonia levels. Her GCS normalised in about 6 hours after commencing the treatment.

One week later while in the hospital, she began to have a runny nose. A nasopharyngeal aspirate was done, and she was found to be Rhino/Enterovirus positive. In addition, she started complaining of headache and decreased sleeping time. This was attributed to her viral illness initially. However, she started vomiting and complaining of blurred vision and photophobia. Two days later she mentioned that she could not see. Her Mum told us that she was walking towards the bathroom and bumped into the door. She could see after night sleep, but her vision was gradually getting worse as the day went on. If she had an afternoon nap her vision was noted to improve. On clinical examination, her GCS was 15/15, she was vitally stable. Meningeal signs were negative. She had no nystagmus, and both pupils reacted to light. Neurological examination revealed brisk reflexes and up going planters. Gait was normal with no ataxia. Furthermore, she was discussed with both Ophthalmology and Neurology teams, and her management was switched to IV ammonia

scavenger mediations instead of oral medications as she did not tolerate her oral medication. Her ammonia level was normal at this time. She was commenced on IV lipids and IV dextrose 10% for extra calories. A thorough ophthalmology examination was difficult, as she did not tolerate the light. She had papilledema on fundus examination. She was reviewed by the Neurology Team, who advised a lumbar puncture and MRI. She was started on IV Aciclovir and IV antibiotics. On MRI/MRV, there were no signs of venous sinus thrombosis, but there was an area of decrease diffusion in the right occipital cortex - query encephalitis due to the viral illness or possibly due to the OTC deficiency as in **Figure 2**. Cerebrospinal Fluid (CSF) microscopy was normal. CSF PCR and culture were all negative, however elevated opening pressure at 28 cm of H2O was observed. On further discussion given the headache, papilledema, and elevated opening pressure. She was started on Acetazolamide of 250mg twice a day and showed good improvement of the headache post same. Her vision improved slowly-she began to see colours first and started to have a better vision in the morning, however, it was noted to deteriorate at night. She was started on Co enzyme Q10100 mg twice a day as it was felt that there may be a secondary mitochondrial dysfunction and she reported improvement after being commenced on same. She regained her vision completely within 12 days.

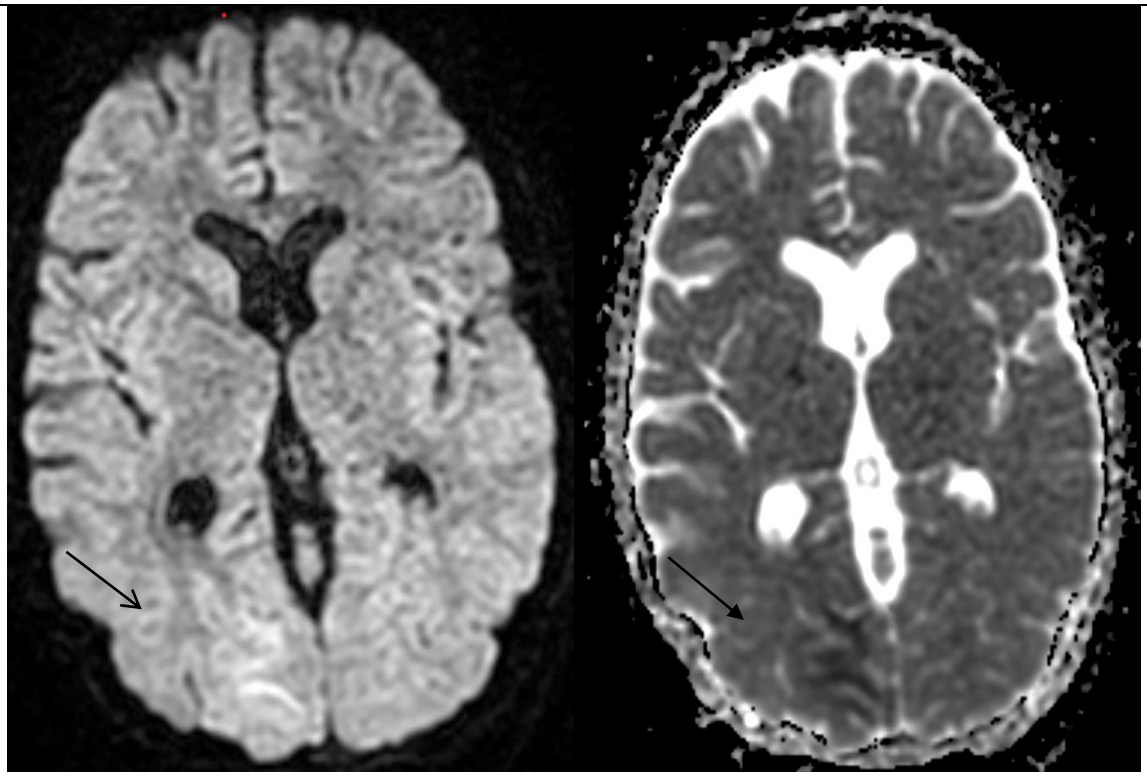

Figure 2: MRI brain showing area of reduced diffusivity on ADC (Apparent Diffusion Coefficient) involving right occipital lobe. No significant mass effect.

She was discharged home after approximately 5-week period of admission. She was back to school but for a half day initially and gradually this was extended to full day. She is enjoying school, and both parents are very happy with her progress. On examination in clinic shortly after discharge, there was no evidence of distress and systemic examination was normal. Her most recent weight

was 29.7 kgs (50th to 75th centile) and height was 130.5 cms (50th centile). She remains on Glycerol Phenylbutyrate, Sodium Benzoate, Citrulline and Co enzyme Q10. Her genetic testing (whole exome sequencing) revealed a loss of 47kb involving *OTC* gene, which is pathogenic and had not been previously described in the literature.

Discussion

Ornithine Transcarbamylase deficiency is a rare inherited metabolic disorder. It usually presents with hyperammonaemia. Our aim was to report a rare complication of transient visual loss despite normal ammonia level. In the literature there are only 4 cases described with same complication **[11-14]**. Our patient had signs of increase intra-cranial pressure and responded to Acetazolamide medication. This is first time the use of Acetazolamide had been described with OTCD. Her ammonia level was normal which is like the previous case described in the above cases. Healthy liver converts nitrogen to water soluble urea. Neurotoxicity of ammonia is not fully understood **[15]**. There are some explanations outlined in the literature. For example, neurotoxicity is due to change in osmolality as ammonia is taken by astrocyte to produce glutamine using glutamine synthase. Glutamine is an osmolyte that increases osmolality of both CSF and astrocyte resulting in cerebral oedema. Glutamine is converted to glutamate in neuron and released post synapse to release a molecule called GABA **[16]**. Furthermore, a study was done in adult patients with OTCD and asymptomatic women. They used MRI spectroscopy to study glucose and glutamine metabolism in asymptomatic female patients. It showed impaired glutamate metabolism and different spikes on MRS even in asymptomatic patients **[17]**.

Conclusion

Although Ornithine Transcarbamylase deficiency is an X - linked condition, it can present in females. We should consider it in any child with encephalopathy and/or acute visual impairment. It can occur in absence of high ammonia level and affect the occipital cortex. There are different opinions about the biochemical changes at cellular level, more research is required to further understand it. In our patient, the plasma amino acids showed secondary mitochondrial dysfunction, which could be responsible for visual loss, however, the question regarding occipital lobe involvement remains open. Further studies are required to understand this.

Take Home Message

For any child presenting to Emergency department with an episode of confusion checking serum ammonia is essential.

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