Ornithine transcarbamylase deficiency in a neonate: A disease in disguise

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Abstract

Ornithine transcarbamylase (OTC) deficiency is a rare X-linked genetic disorder that accounts for nearly half of all inherited disorders of the urea cycle. We present a case of ornithine transcarbamylase deficiency in neonate who had presented withpoor feeding and convulsion with history of previous sibling death due to unknown cause, withhigh blood ammonia levels (>500µg/dl) and tandem mass spectroscopy suggestive of complete Ornithine transcarbamylase deficiency.

Key words: Ammonia, Neonate, Ornithine transcarbamylase(OTC) deficiency, Urea cycle.

Introduction:

Ornithine transcarbamylase deficiency is a rare disease with incidence of 1 in 50,000 to 80,000.

It was first reported in 1962 by Russell in 2 girls, aged 20 months and 6 years, who were found to have hyperammonemia associated with episodic vomiting, delirium, stupor, failure to thrive and mental retardation.[1]

Ornithine transcarbamylase (OTC) is one of six enzymes of urea cycle that play a role in the break down and removal of nitrogen from the body. The lack of the Ornithine transcarbamylase enzyme results in excessive accumulation of nitrogen, in the form of ammonia. Excess ammonia, which is a neurotoxin, results in the symptoms.[2]

Ornithine transcarbamylase (OTC) deficiency can occur as a severe neonatal onset disease in males and as a post-neonatal onset disease (partial deficiency) in males and females.[2] The infant becomes symptomatic after feeding has started because human milk provides a protein load. Severe neonatal onset Ornithine transcarbamylase deficiency typically presentson day two to three of life and are usually catastrophically ill by the time they come to medical attention.[3]

Case report: Here is a 3day old male baby born through normal vaginal delivery at 37 weeks of gestation with birth weight of 3.5 kg to a G2P1D1 mother with family history of male sibling death on day 5 of life. The baby cried immediately after birth. The antenatal Ultrasonography was normal. At day 3 of life the baby had irritability, refusal to feeds and had 1 episode of convulsion for which child was referred to us with the endotracheal tube in situ.

At the time of admission, the child had convulsions and was loaded with levetiracetam and phenobarbitone. The convulsions were controlled with these two anticonvulsants. Inborn error of metabolism (IEM) was suspected as there was no history of perinatal asphyxia and sibling death was present. So, the child was started on mocktail (L-Carnitine, Coenzyme Q, Biotin, Pyridoxine). The blood investigation showed elevated ammonia of >500µmol/l and deranged coagulation profile. The child had brownish nasogastric aspirates for which child was transfused with fresh frozen plasma and vitamin k injection was given. The child didn't have any further bleeding. The child was then started with sodium benzoate and peritoneal dialysis for high ammonia levels. Tandem mass spectroscopy of blood and urine sample was done which suggested ornithine transcarbamylase deficiency and Ornithine transcarbamylase (OTC) gene sequencing planned to confirm the diagnosis. Ornithine transcarbamylase deficiency was diagnosed by laboratory tests. The child succumbed to death on day 9 of life.

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Investigations:

Table 1: Follow-up investigations of the child

Day of admission→	Day 1	Day 2	Day 5
Hb(gm/dl)	26.9	15.4	
TLC (cells/cumm)	14100	26000	
Platelet (cells/cumm)	181000	98000	
CRP (mg/L)	2.1		
Na (meq/L)	141	144	144
K (meq/L)	6.2	6.5	4.8
Cl(meq/L)	105	106	107
Creat(mg%)	1.2	1.4	0.7
Blood culture	Gram negative bacilli isolated		
TSB (mg%)	17.3	7.7	
DSB/ISB (mg%)	1.3/16	1.2/6.5	
PT/APTT (sec)	42.1/66.3		
INR	3.6		
Ca(mg%)	8.0		
Mg (mg/dl)	1.8		
Blood ammonia (µ/dl)	>500		
Lactate (mmol/L)	7		
Urine for ketone body	Absent		
TMS Blood	Elevated levels of glutamine, alanine, malonylcarnitine, methionine, proline and tyrosine		
TMS Urine	Elevated levels of Orotic acid with generalized aminoaciduria		
TMS Interpretation	Observed profile is seen in Ornithine Transcarbmylase Deficiency/ Transient Hyperammonemia of Newborn, Liver or Renal Dysfunction.		

Figure 1: Peritoneal dialysis for Hyperammonemia.

Figure 2: Tandem mass spectroscopy report of the baby.

GAS CHROMATOGRAPHY MASS SPECTROMETRY SCREENING REPORT- SUMMARY

Observations:
In view of abnormal MSMS profile urine sample was taken up for GCMS analysis.
Urine sample shows elevated levels of Orotic acid with genaralised aminoaciduria. Elevation in excretion of Glutamine, Glycine, Leucine, Lysine, Phenylalanine, Proline, 5-0xoproline,Threonine and Valine
Interpretation:
The observed profile can be seen in Ornithine transcarbamylase deficency/ transient hyperamrnonemia of newborn/liver or renal dysfunction /Hyperalimentation.
Suggestion:
It is recommended to do plasma Ammonia, Glucose estimation and monitor clinical, biochemical and metabolic pattern of the neonate.
OTC gene squencing can be done to confirm the diagnosis.
In view of transfusion history, it is recommended to repeat the test with another DES sample after 14 days of last transfusion.
Recommendation:
Please correlate the results with other clinical and diagnostic findings.

Discussion:

Clinical manifestations of ornithine transcarbamylase deficiency are mainly due to hyperammonemia[1]. Hyperammonemia manifests by lack of appetite, vomiting and neurological abnormalities like convulsion, irritability, coma. These episodes of hyperammonemia occur after ingestion of high protein diet.[3]

Our case presented with lethargy, poor feeding and convulsion on day 3 of life with elevated ammonia levels. A high glutamine levels and low citrulline levels are suggestive of proximal urea cycle defect. During acute encephalopathy, ammonia levels are typically above 200µmol/l. Oroticacid concentration is elevated in urine differentiates it from Carbamoyl phosphate synthetase1 deficiency.[4]

Thediagnosisisby Deoxyribonucleicacid(DNA)genetic testing. Mutation of Ornithine transcarbamylase gene has been identified in approximately 80% of patients. In rare cases Ornithine transcarbamylase deficiency may be detected by surgical biopsy and microscopic examination of tissue from liver, duodenum and rectum.[5]

The main stay of treatment is to rapidly lower the plasma ammonia to prevent the toxic effect on the brain. Hemodialysis is the fastest method for lowering ammonia. Nitrogen scavenger therapy with intravenous sodium phenylacetate, sodium benzoate or oral phenylbutyrate can be used.[6] Peritoneal dialysis can also be used when hemodialysis not available. Treatment with arginine or citrulline maintain normal rate of protein synthesis.[7]

Long term therapy combines dietary restrictions and methods of converting and excreting nitrogen from the body. Prompt and earlydiagnosis and treatment can avoid hyperammonemic coma and associated neurological symptoms. However those with complete enzyme deficiency, prompt treatment will not prevent recurrent episodes of hyperammonemia and development of serious complications.[8]

Conclusion: Ornithine transcarbamylase deficiency may present with very few clinical manifestations in newborn period. So recognition of leading signs like poor feeding, irritability, convulsions with significant family history like sibling death will provide early diagnosis, intervention and better outcome.

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