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Case Reports

The Urea Cycle Disorders (UCD): A Case Report

MD. TARIQUL ISLAM[1], MD. IMNUL ISLAM[2], SEIKH AZIMUL HOQUE[3], ABU SADAT MD SALEH[4], ZOBAYDA PARVIN [5], NARAYAN CHANDRA SAHA [6]

Introduction:

The urea cycle is composed of five catalytic enzymes, a cofactor producer, and at least two transport proteins.[1] The urea cycle disorders (UCD) result from inherited molecular defects which compromise this clearance and resulting nitrogen accumulation in the form of ammonia, a highly toxic substance in the body. Urea cycle disorders are included in the category of inborn errors of metabolism. Severe deficiency or total absence of activity of any of the first four enzymes (CPSI, OTC, ASS, ASL) in the urea cycle or the cofactor producer (NAGS) results in the accumulation of ammonia and other precursor metabolites during the first few days of life. Because no effective secondary clearance system for ammonia exists, disruption of this pathway results in the rapid development of symptoms. The catabolism normally present in the newborn period combines with the immaturity of the neonatal liver to accentuate defects in these enzymes.[2-4] Infants with a urea cycle disorder often initially appear normal but rapidly develop cerebral edema and the related signs of lethargy; anorexia; hyperventilation or hypoventilation; hypothermia; seizures; neurologic posturing; and coma. About 50% of neonates with severe hyperammonemia have seizures.[4,5] The typical initial symptoms of a child with hyperammonemia are nonspecific: failure to feed, loss of thermoregulation with a low core temperature, and somnolence that progresses to lethargy and coma. Abnormal posturing and encephalopathy are often related to the degree of central nervous system swelling and pressure upon the brain stem.[4-6] In milder (or partial) urea cycle enzyme deficiencies, ammonia accumulation may be triggered by illness or stress at almost any time of life, resulting in multiple mild elevations of plasma ammonia concentration. In individuals with partial enzyme deficiencies, the first recognized clinical episode may be delayed for months or years. Although the clinical abnormalities vary somewhat with the specific urea cycle disorder, in most the hyperammonemic episode is marked by loss of appetite, cyclical vomiting, lethargy, and behavioral abnormalities. Sleep disorders, delusions, hallucinations, and psychosis may occur.[5,6] An encephalopathic (slow-wave) EEG pattern may be observed during hyperammonemia and nonspecific brain atrophy may be seen subsequently on MRI.[7] Defects in the fifth enzyme in the pathway cause arginase deficiency, a more subtle disorder involving neurologic symptoms.

Case Report:

Anhar 7 months' old boy hailing from Baridhara, 2nd issue of consanguineous parents presented on 01.05.2010 with vomiting since 8 hours of life following breast feed. He had a history of recurrent illness since birth. On 1st day of life he developed vomiting that persisted for 15 days. On 4th month of age he developed breathing difficulties, repeated convulsion for several days and loose motion with vomiting up to 6th month of age. He was admitted into different hospitals for several times and treated symptomatically. Mother had also complaints that the baby was not growing well. He was delivered at hospital by NVD. Antenatal and postnatal history was uneventful. Patient was completely immunized as per EPI schedule. He was on exclusive breast feeding up to 5 months of age. Milestones of development were not age appropriate.

On Examination at admission temperature was normal. There was no anaemia, jaundice, cyanosis, respiratory difficulties, abdominal distension, neck stiffness, convulsion, or any sign of meningeal irritation. Anthropometric measurement showed Z score of Height for age: - 3.4, weight for age: - 4.3 and OFC for age: - 6.2. From the physical examination and Ultrasonogram of whole abdomen we got no

1. Assistant Professor, Paediatric Cardiology, BSMMU, Shahbag, Dhaka.
2. Assistant Professor, Department of Paediatrics, BSMMU, Shahbag, Dhaka.
3. Assistant Professor, Department of Paediatrics, Dhaka Medical College and Hospital, Dhaka.
4. Postgraduate Trainee, Department of Paediatrics, Dhaka Medical College and Hospital, Dhaka.
5. Assistant Registrar, Department of Paediatrics, Dhaka Medical College and Hospital, Dhaka.
6. Associate Professor, Department of Paediatrics, Dhaka Medical College and Hospital, Dhaka.

feature of intestinal obstruction except just palpable liver. Complete blood count and ESR showed normal. The laboratory evidence of Urinary ketones and serum electrolyte, anion gap, glucose, Co_2 and PH were normal. But there was higher level of serum lactate (19.30 mg/dl) and serum ammonia (95.0 µmol/L). IMD panel showed low level of citrulline 6.13 µmol/L and arginine 3.43 µmol/L. and undetectable Urinary Orotic acid level. Liver biopsy was not done.

Following Treatment was given:

- Counseling of parents
- Diet: Protein restricted (0.5-1 gm/kg/day), high carbohydrate and high fat contents.
- Oral Sodium Benzoate. (250-500 mg/kg/day) – life long.
- Follow-up: Clinical and Biochemical parameters

Comparison between previous and present status (after 10 months)

Topics	Previous status	Present status
Vomiting	Present	Absent
Loose motion	Present	Present but not so frequent
Edema	Present	Absent
Developmental mile stones	No neck control	Neck control is achieved; walk with support
Serum Ammonia	95µmol/l	25 µmol/l

Present Psychological assessment

Mental developmental index: 17 months

Psychomotor developmental index: 10 months

Behavior rating scale:

Orientation engagement area: 95 per (Within normal limit)

Emotional regulation area : 82 per (Within normal limit)

Motor quality area: 17 per (Questionable)

Total raw score area: 80 per

Present Developmental assessment

Gross motor : Can walk with support

Fine Motor : Pinching grasp

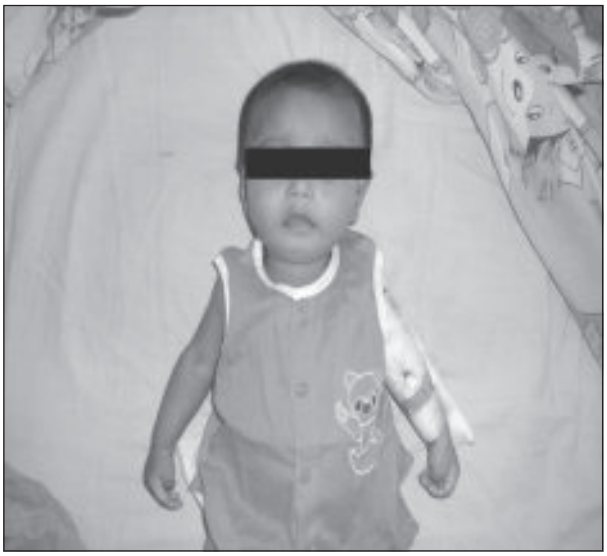
Vision: Age appropriate

Hearing : Age appropriate

Speech : 10 -15 single words

Cognition : Follow instruction ; no point body parts; no point picture; can peek a- boo.

Comment: Developmental age 10-11 months



Previous photo

Present photo

Discussion:

For the history of recurrent episodes of vomiting after breast feeding the case drives an attention to the neurological or gastrointestinal abnormality. But there was no evidence of meningeal irritation, intestinal obstruction or infection. There was increased serum lactate and ammonia level indicating a cellular metabolic error. Along with hyperammonemia associated with history of seizures at early infancy, failure to thrive, persistent vomiting and developmental delay was suggesting points in favor for Urea cycle disease. A plasma higher ammonia concentration, associated with a normal anion gap and a normal serum glucose concentration, is a strong indication

for the presence of a UCD.[2] Then the IMD panel tests were done and the findings helped to rule out the diagnosis. [4,5,8-10] The plasma concentrations of arginine was low that was indicating all urea cycle disorders except ARG deficiency, in which it is elevated five- to sevenfold.[4,5] The Plasma concentration of citrulline in our patient was also very low. Citrulline discriminates between the proximal and distal urea cycle defects, because citrulline is the product of the proximal enzymes (OTC and CPSI) and a substrate for the distal enzymes (ASS, ASL, ARG). Plasma citrulline is either absent or present only in trace amounts in neonatal-onset CPSI deficiency and OTC deficiency and present in low to low-normal concentrations in late-onset disease.[5] That's why our case was identified as proximal urea cycle disorder. Urinary Orotic acid was also measured to distinguish CPSI deficiency from OTC deficiency. It is significantly elevated in OTC deficiency and normal or low in CPSI deficiency.[10] In our patient OTC was undetectable, so it was diagnosed as Urea Cycle Disorder due to CPSI deficiency. Urinary Orotic acid excretion can also be increased in argininemia (ARG deficiency) and citrullinemia type I (ASS deficiency)].[11] A definitive diagnosis of CPSI deficiency, OTC deficiency, or NAGS deficiency depends on determination of enzyme activity from a liver biopsy specimen; however, the combination of family history, clinical presentation, amino acid and Orotic acid testing, and, in some cases, molecular genetic testing is often sufficient for diagnostic confirmation, eliminating the risks of liver biopsy.

Conclusion:

Urea cycle disorders are included in the category of inborn errors of metabolism. There is no cure. Infants, children and adults with a known urea cycle disorder should be under the close monitoring of a pediatrician. Parents of infants and young children are often the most skilled at recognizing subtle changes that are symptomatic of rising blood ammonia levels in their children. In infants and young children vomiting, refusal to feed, listlessness, lethargy, episodes of vomiting frequently and irritability occur with rising ammonia level. If these symptoms persist over several hours, the physician should be alerted for direction on the possibility of UCD. It is believed that up to 20% of Sudden Infant Death Syndrome cases may be attributed to an undiagnosed inborn error of metabolism such a urea cycle disorder. In April 2000, research experts at the Urea Cycle Consensus Conference estimated the incidence of these disorders at 1 in 10,000 births. This represents a significant increase in case diagnosis in the last few years. Because many cases of urea cycle disorders were remain undiagnosed and/or infants born with the disorders die without a definitive diagnosis, the exact incidence of this disease is unknown and underestimated.

References:

1. Jackson MJ, Beaudet AL, O'Brien WE. Mammalian urea cycle enzymes. Annu Rev Genet. 1986; 20: 431–64.
2. Summar M, Tuchman M. Proceedings of a consensus conference for the management of patients with urea cycle disorders. J Pediatr. 2001;138(1):S6–S10.
3. Pearson DL, Dawling S, Walsh WF, Haines JL, Christman BW, Bazyk A, et al. Neonatal pulmonary hypertension - urea-cycle intermediates, nitric oxide production, and carbamoyl-phosphate synthetase function. N Engl J Med. 2001;344(24):1832–8.
4. Summar M. Current strategies for the management of neonatal urea cycle disorders. J Pediatr. 2001;138(1):30–9.
5. Batshaw ML, Berry GT. Use of citrulline as a diagnostic marker in the prospective treatment of urea cycle disorders. J Pediatr. 1991;118(6):914–7.
6. Brusilow SW. Disorders of the urea cycle. Hosp Pract (Off Ed). 1985; 20(10):65–72.
7. Bourrier P, Varache N, Alquier P, Rabier D, Kamoun P, Lorre G, et al. Cerebral edema with hyperammonemia in valpromide poisoning. Manifestation in an adult, of a partial deficit in type I carbamylphosphate synthetase. Presse Med. 1988;17(39):2063–6.
8. Steiner RD, Cederbaum SD. Laboratory evaluation of urea cycle disorders. J Pediatr 2001;138(1):S21-S29.
9. Tuchman M, Batshaw ML. Management of inherited disorders of ureagenesis. The Endocrinologist. 2002;12(2):99-109.
10. Bachman C, Colombo J.P. Diagnostic value or orotic acid excretion in heritable disorders of the urea cycle and in hyperammonemia due to organic aciduria. European Journal of Pediatrics. 1980;134(2):109-13.
11. Batshaw ML. Hyperammonemia. Curr Probl Pediatr. 1984;14(11):1–69.