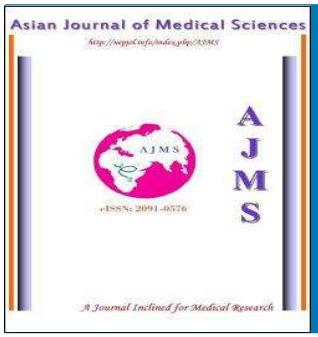

CITRULLINEMIA AND HYPERGLYCINEMIA PRESENTING WITH SEIZURES- CASE REPORT OF A 4 DAY OLD BABY

CASE REPORT AND LITERATURE REVIEW, Vol-3 No.1

Asian Journal of Medical Science, Volume-3(2012) http://nepjol.info/index.php/AJMS

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ABSTRACT

Inborn errors of amino acid metabolism (IEM) are of concern in India, the spectrum being wide, varied and poorly diagnosed. Since aggregate incidence of inborn errors of metabolism is relatively high, in countries such as India, a high degree of suspicion is essential to correctly diagnose an inborn error of amino acid metabolism. We report a case of citrullinemia, glycinemia with hyperammonaemia and seizures in a 4-day-old previously asymptomatic baby, with a brief review of the literature.

Key words: citrullinemia, hyperammonaemia, inborn error,aminoacid

"Since the aggregate incidence of inborn errors of metabolism is relatively high, a high degree of suspicion is essential to correctly diagnose an inborn error of amino acid metabolism. Coupling it with biochemical screening tests will help clinicians to act fast."

INTRODUCTION

Population based studies indicate tyrosinemia, maple syrup urine disease and phenylketonuria to be the commonest inborn errors of amino acid metabolism among newborns in India[1]. Citrullinemia is a rare autosomal recessive inborn error of the urea metabolism due to a deficiency in argininosuccinic acid synthetase (AAS). As a group, urea cycle disorders are estimated to occur 1 in 30,000 live births. Citrullinemia occurs in the general population with a frequency of 1 in 250,000 live births. There are 25 million births in India annually, of which 25,000 have metabolic disorders.[2] In India biochemical screening of 4400 cases of mental retardation revealed that 5.75% (256 cases) were due to various inherited metabolic disorders[3]. Our objective in reporting this case study is to highlight the importance of early detection of the IEM by pediatricians and biochemists in a sick child, to raise awareness and to prevent late complications by simple treatment.

CASE REPORT

Our case is a 4-day-old baby, born to 2nd degree consanguineous parents at 36 weeks by caesarian section. His birth weight was 3.25 kg and he reportedly breathed and cried immediately after birth. Since the baby was feeding well and had good cry and activity, He was discharged on 2nd day of life. From the 4th day of life, he developed generalized tonic-clonic seizures. It was, occasionally focal, multiple episodes during the day. The baby was brought to the emergency department of The Mission Hospital, Durgapur. There was no history of fever. The child was lethargy and there was history of poor feeding and excess cry. At admission, the baby weighed 2.65 kg. He was having active seizures which were generalized. Heart rate was 126/min, regular; all peripheral and femoral pulses were felt. Respiratory rate was 36/minute; SpO2 was 94 % in air. There were no obvious dysmorphism or neurocutaneous markers. There was no cyanosis, jaundice or significant lymph node enlargement. The baby had excess of hair in the face and forehead with low hairline and low set ears. There was no rash and he had no abnormal odour.

Anterior and posterior fontanelles were open, head circumference was 38.7 cm, pupils were equal and reacting well to light. There was no facial asymmetry and spine was normal. There were no bruits over the skull and transillumination test was negative. Abdomen was soft with no visible peristalsis and liver felt just below the right costal margin. Respiratory System Examination showed normal vesicular breath sounds bilaterally.

The baby had total white blood cell count 4100 cells / cumm and differential count showed 70 % lymphocytes and 27% neutrophils. Red cell count was 4.23 million/cumm and platelet count was normal. Initial investigations showed negative C-reactive protein, mild leucopenia and no evidence of coagulopathy, no blood group incompatibility and no evidence of hemolysis. The plasma glucose, creatinine, uric acid and serum electrolytes were normal. Serum Calcium levels were 9.2 mg/dl (normal 8.4-10.2 mg/dl), magnesium 2.3 mg/dl (normal 1.7-2.8 mg/dl). Total bilirubin was 7.6 mg/dl (normal upto 1 mg/dl) and direct bilirubin was 0.4 mg/dl (normal upto 0.3 mg/dl). Urea level was low at 9 mg/dl (normal 15-40 mg/dl) were normal. Urine on routine and microscopic study revealed acidic p H (6.6), with no ketones, sugar or albumin. At admission, the blood ammonia was elevated, at 131 µg/dl (normal 20-80 µg/dl) and plasma lactate levels were 31.9 mg/dl (normal 4.5-20 mg/dl) they rose to 217 µg/dl and 51 mg/dl respectively, on 6th day after admission. His, blood pyruvate was 0.42 mg/dl (normal 0.3-0.9 mg/dl) and lactate/pyruvate ratio 75.95, at admission. The patient's blood was submitted for investigati-

-ons by tandem mass spectrometry .It showed to contain analytes for amino acids, organic acids, and fatty acids oxidation disorders in normal concentrations except for high glycine and citrulline levels. Citrulline levels were 406 µmol/L (normal <70 µmol/L) and glycine levels were 855 µmol/L (normal <505 µmol/L). Arginine levels were low at 7.76 umol/L (normal <132 umol/L). Tyrosine levels were normal at 17.70 µmol/L (normal <550 µmol/L) and methionine levels were 14.60 µmol/L (<77 µmol/L). Ornithine wad 47.20 umol/L (normal <278 umol/L) .G6PD levels, TSH levels, biotinidase, 17 OHP, galactose, Immunoreactive trypsinogen were normal .Repeat testing on a second sample revealed similar result.

The baby was admitted with active convulsions which were controlled with loading dose of phenobarbitone and later he was started on maintenance dose. CSF analysis was done immediately to rule out meningitis. The CT scan of brain was normal. The baby did not have any focal deficits, anisocoria or any further seizures and improved clinically within 4 days. The baby was started on nasogastric feeds, which were slowly increased and changed to direct breast-feeds. The blood culture was negative and C reactive protein and blood counts were normal later on and therefore, antibiotics were stopped.

DISCUSSION

Citrullinemia represents the fourth most common anomaly of the urea metabolic pathway .[4] However, its prevalence remains unspecified in the literature, which only suggests that male and female cases seem to occur equally.[5] Citrullinemia is due to a deficiency in argininosuccinate synthetase (AS) (EC 6.3.4.5), which McMurray and coauthors [6] initially described in 1962.

Two clinically and genetically distinct forms of citrull-inemia have been identified. The classic form (type 1) is due to deficiency of the arginosuccinate enzyme [E.C 6.3.4.5]. The adult form (type II) is due to citrin deficiency (gene and location SLC25A13 gene- 7q21.3.) Citrin is a calcium dependent mitochondrial aspartate glutamate transporter that inactivates argininosuccinate synthetase activity only in the liver, presumably by disrupting mitochondrial export of aspartate and from defects in the malate aspartate shuttle. Classic Citrullinemia (CTLN1) presents in two major forms. The severe or neonatal form, which is the most common form, appears in the first few days of life with signs and symptoms of hyperammonaemia, while the sub acute or mild form symptoms like failure to thrive, frequent vomiting, developmental delay, appear gradually after 1 year of age. [7]

There is one report in an Indian neonate of a urea cycle defect of argininosuccinate synthetase deficiency by Balsekar, et al. [8] also based on clinical and biochemical profiles .Karnik et al [9] reported two cases of hyperammonaemia with citrullinemia in India.

Coude et al [10] reported 4 cases with similar clinical and biochemical findings. Symptoms started during the first day of life with acute metabolic acidosis and lethargy. Serum lactic acid was always high (10 to 20 mM) with a lactate-Pyruvate ratio between 50 and 100. Serum βOH butyrate was normal or slightly elevated but the βOH butyrate-acetoacetate ratio was constantly less than 1.

Our case was an apparently well, only 4 day old baby, suddenly deteriorating, that led us to the screening for IEM after sepsis was ruled out. In our case, the screening marker of high citrulline was followed up by tandem mass spectrometry analysis of plasma amino acids. Although enzymatic determinations and DNA analysis are considered confirmatory for metabolic and genetic disorders, we could not perform further tests due to financial constraints. With early detection we could protect

him from complications like cerebral palsy. Early diagnosis of these disorders can significantly improve the long-term prognosis of affected children, by early treatment. The authors stress on the importance of nation-wide large scale newborn screening for IEM.

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