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Case Report

Recurrent encephalopathy and hyperammonemia in new born: case of arginosuccinic aciduria

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ABSTRACT

Urea cycle disorders result from defects in the metabolism of waste nitrogenous compounds derived from the breakdown of proteins and other nitrogen-containing molecules. Argininosuccinic aciduria is a rare autosomal recessive heterogeneous urea cycle disorder, which leads to the accumulation of argininosuccinic acid in the blood and urine. It is caused by defect in the argininosuccinate lyase (ASL) gene, which regulates the breakdown of argininosuccinate to fumarate and arginine in the urea cycle. They are a heterogeneous group of disorders which are associated with hyperammonemia resulting in severe neurological dysfunction like encephalopathy, seizures, developmental and psychomotor delay. The severe central nervous system dysfunction is by alteration of amino acid and neurotransmitters pathways and interference with normal cerebral energy metabolism and oxidative stress. Ammonium toxicity to the brain provokes irreversible damage due to cortical atrophy, edema, and demyelination, resulting in seizures, coma, and even death. We report such a case of urea cycle defect in a newborn that presented with recurrent encephalopathy with hyperammonemia precipitated by minor infections. Detailed investigations including genetic analysis lead to the diagnosis of argininosuccinic aciduria.

Keywords: Arginosuccinic aciduria, Genetic analysis, Hyperammonemia, Recurrent encephalopathy

INTRODUCTION

Urea cycle disorders are associated with hyperammonemia resulting in severe neurological dysfunction like encephalopathy, seizures, developmental and psychomotor delay.[1] Ammonia is a metabolite resulting from the breakdown of proteins in the body.

Raised levels of ammonia are toxic for the body especially CNS resulting in range of symptoms from seizure to coma. It is through the urea cycle that this harmful metabolite is detoxified to urea and removed from the body.

Patients accumulate the nitrogen in the form of ammonia in plasma, which is a highly toxic substance that is not excreted. Six genetic forms have been identified, arising from inherited deficiencies of catalytic enzymes (CPS1, OTC, ASS1, ASL, ARG1) and a cofactor-producing enzyme (NAGS). With the single exception of OTC which is X-linked, all show autosomal recessive inheritance.[2]

Argininosuccinic aciduria occurs due to mutations in the argininosuccinate lyase (ASL) gene, the enzyme that cleaves argininosuccinate to fumarate and arginine in the urea cycle occurring in the liver. The prevalence of this disorder is 1 in 70,000 live births making it the second most common urea cycle disorder.[3]

The clinical presentation of patients with ASAuria is variable. Generally, the disease has two forms, a severe

neonatal form and a milder late onset form.[4] The severe neonatal form is characterized by hyperammonemia within the first few days of life with poor feeding, vomiting, lethargy, and seizures, with subsequent progression to coma. The late onset form manifests late in infancy or in childhood; it presents with mental retardation, vomiting, failure to thrive and behavioral problems.[5]

CASE REPORT

A term IUGR male neonate weighing 2.25 kgs was delivered by cesarean section to a 23-year-old second gravida mother with regular antenatal follow up. On day 2 of life, the neonate had feed intolerance with repeated vomiting. Clinical examination was normal with no evidence of sepsis, electrolyte imbalance or hypoglycemia.

Due to possibility of sepsis, empirical antibiotics were started after taking blood culture. Condition of the child gradually worsened with child developing features of encephalopathy on day 3 of life. There was history of death of first child at 3 days of life with similar complaints of repeated vomiting and progressive lethargy. Child was kept NPO and intravenous dextrose containing solution was given. Ultrasound transcranium was normal with normal CSF findings. ABG showed respiratory alkalosis with raised ammonia levels (320 umol/dl).

Suspecting a metabolic disorder, the child was referred to a higher centre where he was given oral sodium benzoate. TMS showed raised citrulline levels with normal levels of organic acids. The sensorium of the neonate gradually improved over the next few days and baby was gradually started on breast feeds. However, he continued to have frequent hospital admissions due to recurrent infections in the next few months.

At the age of 5 months again, he presented with encephalopathy, severe respiratory distress with severe apneas and was put on mechanical ventilator for 3 days. Investigations again revealed hyperammonemia with respiratory alkalosis. Urine GCMS was negative for organic acids and orotic acid. Aminoacidogram showed raised levels of citrulline and glycine. Genetic analysis of the baby showed recessive (compound heterozygous) missense mutation c. A857G/ (p. Gln286Arg) of exon 12 (NM_000048) in the ASL gene. The baby continues to have episodes of encephalopathy precipitated with infection. At the present age of 6 months, he has delayed motor and social milestones.

DISCUSSION

Urea cycle defects (UCD) have a high morbidity and mortality rate especially in the neonatal period.[1,3] Since the disease has similar features as sepsis there can be delay in the diagnosis and poses a diagnostic challenge for the pediatrician. At the same time, it causes delay in the initiation of treatment.

However, a high index of suspicion and a timely intervention can affect the prognosis and neurological damage that may occur because of hyperammonemia. UCD mostly has an early onset (<28 days) (except for OTC deficiency), and high mortality especially in the neonatal period.[6] Early diagnosis and urgent treatment are important in terms of prognosis and the influence of the accumulation of toxic metabolites.

Continuous veno-venous hemodialysis or PD should be initiated urgently in patients unresponsive to dietary and pharmacological treatment, and rising ammonia levels above 500 μmol/L. Because of the hemodynamic and technical complication during the neonatal period, continuous veno-venous hemodiafiltration is recommended instead of hemodialysis. Continuous veno-venous hemodialysis has been shown to be more effective and safer in the removal of toxic metabolites; the duration of dialysis is shorter, and the neurological outcomes are more favorable compared to those of PD.

Enzyme analysis and molecular genetic tests should be performed if available as it may be helpful in genetic counseling.[7,8] However, initial test be tested in cases of high ammonia level for the diagnosis of UCD include arterial, blood gas, blood sugar, plasma acyl carnitine profile, plasma and urine amino acids, urine organic acids, urine ketone and urinary orotic acid levels.[9,10] In addition, Plasma citrulline levels are markedly high in ASS deficiency (citrulline Type I) where as in absence of ASL (argininosuccinic aciduria), plasma citrulline levels increase moderately as was seen in our case.

If the plasma citrulline level is at or below traces level, carbamoyl phosphate synthetse CPS1 and OTC deficiency should be considered.[1] With modern techniques, mutation analysis based on Sanger sequencing is the method of choice for confirmation of the diagnosis. Management option in the long term involves reducing the ammonia levels either with sodium benzoate, sodium phenylacetate or peritoneal dialysis/hemodialysis.

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