

Citrullinemia Type 1: A Rare Case.

Garima Biyani¹, Syed Md Azad¹, Souvik Guha¹, Rohit Kapoor¹

¹Junior Resident, Department of Pediatric Medicine, Institute of Child Health, Kolkata.

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ABSTRACT

Here we presented a case of Citrullinemia type 1 in a full term male neonate who presented with an acute catastrophic collapse on the 3rd day of life. The key features of increasingly poor feeding, vomiting and progressive lethargy with or without seizures should quickly direct towards a metabolic origin. This case report also shows the importance of early biochemical and metabolic screening in newborns, to reach an early and definitive diagnosis of IEM and proper management of such cases.

Keywords: Citrullinemia type 1, neonatal IEM, metabolic screening.

INTRODUCTION

Here we presented a case of Citrullinemia type 1 in a full term male neonate who presented with an acute catastrophic collapse on the 3rd day of life. It is an inherited urea cycle disorder where the enzyme argininosuccinate synthetase is deficient. The key features of increasingly poor feeding, vomiting and progressive lethargy with or without seizures should quickly direct towards a metabolic origin. Hence, whenever performing blood gas analysis or a sepsis work-up in a newborn aged 2 to 7 days of age with signs of progressive encephalopathy, measurement of serum ammonia concentration should be included.

Name & Address of Corresponding Author

Garima Biyani
Institute of Child Health 11, Dr. Biresh Guha Street
City: Kolkata, PIN: 700017,
State: West Bengal
Country: India

CASE REPORT

A full term 3.2 kg male neonate was born to a primigravida mother by normal vaginal delivery after an uneventful pregnancy. History of consanguinity was present. He needed no resuscitation at birth and was breastfed in the delivery room and showed vigorous sucking. However, after transfer to the maternity ward, the mother expressed concerns as the child consistently refused to feed and regurgitated abundantly. Baby was admitted to neonatal intensive care unit (NICU) at 50 hours of life for retching, lethargy and poor feeding. On examination, he weighed 2.84 kg (11% weight loss), was lethargic and jittery with stable

vital signs, the fontanel and pupils appeared normal, diminished sucking and moro reflex were observed and had a blood glucose of 94 mg/dL. Baby was started on intravenous fluids and antibiotics. Initial laboratory exams included a complete blood count, C-reactive protein and blood chemistry. One hour after admission he developed multifocal clonic fits after which Phenobarbitone was loaded.

Baby had a progressive worsening of sensorium, frequent tonic posturing despite giving Phenobarbitone, worsening tachypnea requiring oxygen, and respiratory arrest needing mechanical ventilation three hours after admission. Blood gas showed pH of 7.45, Pco₂ of 25 and bicarbonate of 13 meq/L. Sepsis screen came out to be negative. His serum results showed marked hyperammonemia: 927 µmol/l, increased lactate concentration of 3.8 mmol/l, sodium: 158 meq/l, potassium: 3.8 meq/l urea: 9 mg/dL and creatinine: 1.8 mg/dl. CSF study was normal.

As there was no acidosis and no evidence of an infection or liver failure, a urea cycle disorder was strongly suspected. Metabolic screening profile for inborn error of metabolism (IEM) was planned. Blood and urine spot tests on filter paper were sent on the very next day. Umbilical venous catheterization(UVC) was done. Ammonia increased to a maximal value of 2567 µmol/l 24 hours later. After excluding Rh incompatibility, partial exchange was done with baby's blood group through UVC line to remove ammonia from body rapidly. After exchange, ammonia level decreased to 400 µmol/l. Ammonia scavenging therapy (intravenous sodium benzoate and arginine) was planned to commence as soon as possible. But before the drugs could be made available, unfortunately the baby died after 3 days of admission due to cardiac arrest.

By the time, metabolic laboratory results revealed markedly increased plasma citrulline of 1002(normal 6-28) $\mu\text{mol/l}$ and glutamine of 1142(158-551) $\mu\text{mol/l}$; increased urinary excretion of uracil, orotic acid and ornithine, consistent with urea cycle defect, The clinical course and biochemical profiles of the patient indicated the diagnosis Citrullinemia type 1 (CTLN1).

DISCUSSION

In our case, once hypoglycemia was ruled out as the cause of lethargy, sepsis was considered although there were no antecedents for early onset sepsis. On seeing the results (negative sepsis screen, normal CRP, normal CSF values) sepsis was unlikely. A cardiac cause was considered unlikely as the baby was not in shock or was not cyanotic and had normal pedal pulses. Increased serum creatinine was a “red flag” but with normal serum potassium, acute renal failure was thought unlikely. The onset of neurological symptoms after a symptom free interval of more than 12-24 hours following a normal delivery in a term baby with normal Apgar scores renders hypoxic-ischemic encephalopathy unlikely. Neonatal arterial ischemic stroke may also present with delayed focal seizures but in general with normal alertness up to the event and in between seizures. So, non-infective encephalopathy due to IEM with hypernatremic dehydration was considered. What was unexplained initially was the normal urea despite dehydration, weight loss and elevated creatinine. The normal urea with a disproportionately raised creatinine is probably due to defective synthesis of urea. Respiratory alkalosis due to hyperventilation is the key feature in urea cycle disorders and is the result of hyperventilation due to stimulation of the central respiratory drive by hyperammonemia.^[1] The low bicarbonate seen in our patient could be due to the metabolic compensation for the low pCO_2 in respiratory alkalosis.

The key features of increasingly poor feeding, vomiting and progressive lethargy with or without seizures should quickly direct towards a metabolic origin. Hence, whenever performing blood gas analysis or a sepsis work-up in a newborn aged 2 to 7 days of age with signs of progressive encephalopathy, measurement of serum ammonia concentration should be included.^[2] The differential diagnosis of metabolic causes of neonatal hyperammonemia is obviously not restricted to urea cycle defects, but also includes organic acidemias (propionic aciduria, methylmalonic aciduria), which cause secondary derangement of the urea cycle function, fatty oxidation defects, pyruvate carboxylase deficiency as well as several other enzymatic deficiencies. Organic acidurias are characterized by low blood pH, abnormal anion gap and elevated urinary ketones. In our patient, normal pH, absence of organic aciduria, elevated glutamine

and highly elevated citrulline and orotic acid pointed towards the diagnosis of CTLN1.

CTLN1 is an autosomal recessive disorder which often runs a rapidly fulminant course resulting in neonatal death as in our case.^[3] The underlying biochemical defect is a defect in the enzyme argininosuccinate synthetase (ASS) that converts citrulline to argininosuccinate (3rd step in the urea cycle). It is caused by a mutation in the ASS1 gene located on chromosome 9q34.^[4] The classical form is very rare with an incidence of 1 in 57,000 people worldwide³, but incidences may be higher in populations with greater consanguinity. Most patients with classical CTLN1 present with symptoms in 1st few days of life with acute hyperammonemia and life threatening encephalopathy. Seizures progressing to coma and death are typical in untreated patients.^[5] In the subacute or mild form, clinical findings such as failure to thrive, frequent vomiting, developmental delay and dry, brittle hair appear gradually after one year of age. Acute hyperammonemia, triggered by intercurrent catabolic state, may bring the diagnosis to light.^[4] In CTLN1, the plasma level of citrulline is markedly elevated, usually 50-100 times normal. Urinary excretion of orotic acid is moderately increased. The diagnosis is further confirmed by enzyme assay in cultured fibroblasts or by DNA analysis.^[4,7,8] Prenatal diagnosis is possible with the assay of the enzyme activity in the cultured amniotic cells or by DNA analysis of chorionic villi biopsy.^[3,4] Massive build up of ammonia resulting from this urea cycle defect causes cerebral edema and encephalopathy that is rapidly fatal if left untreated.^[6] Treatment consists of using intravenous sodium benzoate and/or phenylacetate. Hemodiafiltration is the therapy of choice in severe hyperammonemic encephalopathy and if it is not available hemodialysis or hemofiltration should be rapidly instituted to limit permanent neurological damage.^[6]

Organic aciduria or urea cycle disorders are not uncommon and often present fulminantly. Early diagnosis is crucial for three reasons, the condition is rapidly progressive and causes irreversible damage early in the course, the treatment can often be effective if commenced early and long term outcome may be improved, and correct early diagnosis helps in genetic counselling.^[9] Use of blood gases, electrolytes, ammonia, lactate, pyruvate, urine metabolic spot tests, gas chromatography mass spectroscopy(GCMS) for organic acids, aminoacid chromatography, enzyme estimation in white cells, skin fibroblasts and other tissues have made diagnosis possible.

In neonatal IEM pregnancy, delivery is uneventful. The newborn baby with IEM is normal for 1st three-four days after which disorder presents due to intake of dietary protein etc. Neonates with IEM are misdiagnosed to have sepsis or other disorders.

Sepsis often accompanies IEM and may confound diagnosis further. Pediatricians often think that neonatal IEM is rare. Though individual disorders may be uncommon, these disorders are fairly common when considered together. The neonate has a limited response to illness and predominant signs and symptoms are poor feeding, lethargy, failure to thrive, seizures, coma, acidosis or ketosis. Emergency adequate laboratory facilities to diagnose neonatal IEM are scarce and lacking in India leading to delay in diagnosis and treatment and hence a poor prognosis in most cases. Therefore, this case report shows the importance of early biochemical and metabolic screening in newborns, to reach an early and definitive diagnosis of IEM and proper management of such cases.

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