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Neonatal Citrullinaemia of Consanguineous Parents: An Experience from Sri Lanka

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Introduction

Incidence of all urea cycle disorders (UCD) has been reported as 1:35 000 and out of that the incidence of citrullinemia is 1:250 000 births in the United States. [Summer M. L., et al. Molecular genetics and metabolism, 110 (1–2), 179–180]. Worldwide incidence of citrullinemia type 1 ranges between 1:44 300 to 1:200 000[Wasim, M., et al. Biochemical Genetics, 56 (1–2): 7–21]. The incidence or prevalence of UCD in Sri Lanka is not known. Citrullinemia is a UCD caused by the deficiency of argininosuccinic acid synthetase (ASS), an enzyme that catalyzes the third reaction of the urea cycle [Rizwani I, et al. Elsevier; 2012: 447–453]. There are three types of enzyme abnormalities causing citrullinaemia. The classic neonatal form is type I and type II is a milder form which presents later in life. Although even after a thorough literature search we were unable to find published data on citrullinaemia locally, there would be diagnosed patients. Hence, we present two case scenarios on neonatal citrullinemia focusing on the clinical presentation, diagnosis, genetic testing and outcome in Sri Lanka.

History of patient 1

First baby boy was born at term to 2nd degree consanguineous parents with a birth weight of 3600 grams. Birth history and clinical examination were unremarkable. On the second day of life with the commencement of breast feeding he developed intermittent excessive crying and lethargy, refusal of feeds and grunting. He was admitted to the Special Care Baby Unit (SCBU) where he went into cardiopulmonary arrest within hours of admission needing ventilator care which continued until he succumed to death on 7th day of life. Antenatal history was uneventful except of polyhydramnios at the 3rd trimester of pregnancy. One first cousin sister had died of an unknown cause on the 4th day of life, who was born to consanguineous parents between same families. After the death of the baby, parents got defaulted from carrier testing and genetic counseling.

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Investigations

Neonatal screening using a blood sample collected on a filter paper at the 4th day of life revealed high citrulline concentration. Quantification of plasma amino acids by high performance liquid chromatography with post column derivatisation showed citrulline 2945 µmol/L(3–55 µmol/L), glutamine 3723 µmol/L(200–1200 µmol/L), alanine 1153 µmol/L(131–710 µmol/L) with undetectable argininosuccinic acid confirming the diagnosis of citrullinemia type 1.

Analysis of urine organic acid based on Gas Chromatography Mass Spectromerty (GCMS) revealed markers of lactic acidosis and ketosis with undetectable orotic acid and uracil. In addition, his serum liver transaminases were elevated.

Genetic analysis confirmed autosomal recessive citrullinemia type I (CTLN1), the classical form due to *ASS1* variant c. 1168G>A p. (Gly390Arg).

History of patient 2

The second baby, a boy born to the same parents was admitted to SCBU to screen for citrullinemia.

Investigations

Analysis of plasma amino acid on 1st day of life after commencement of breast feeding showed a citrulline value of 370 µmol/L (3–55 µmol/L) with undetectable argininosuccinic acid suggesting argininosuccinic acid synthetase deficiency.

Management of patient 2

Immediately after sample collection for citrulline, breast feeding was stopped and intravenous (IV) infusion of 10% Dextrose was started on D1 (day one) itself. Administration of intra lipid and fluid cocktail (10% dextrose, 3% saline, KCl) was initiated on D2. From D6 onwards, breast feeding was reintroduced with oral rehydration solution (ORS), which were increased gradually. Oral sodium benzoate (200 mg/6 hrly), a nitrogen scavenger was added from D6 onwards. On D14, the baby's clinical condition deteriorated due to sepsis. As a result oral feeding was withheld and the baby was treated with intravenous(IV) antibiotics and IV fluid cocktail.

Second sample of blood for plasma citrulline which was taken on D15 showed a citrulline concentration of 2225 µmol/L (3–55 µmol/L). As the sepsis has settled by D22, oral therapeutic formula CYCLINEX-1 specially made for UCD was introduced. After one week of formula feeding, plasma citrulline on D28 revealed further elevation to 3473 µmol/L and the plasma ammonia concentration was 337 µmol/L (<100 µmol/L). As the baby was active & well, the therapeutic formula was continued. However, on D40 the baby had convulsions with high plasma ammonia concentration and died on D45 of life.