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Biochemistry

PROPIONIC ACIDEMIA ACCOMPANIED BY HYPERGLYCEMIA

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ABSTRACT A healthy male baby, which was the mother's first pregnancy and first live birth, was born at term. The child had rapid respiration, absence of suckling, and jaundice on the third day following delivery. The family history revealed parental consanguinity. The general status of the baby was poor, and he was pale and icteric. His physical examination revealed weakening of the neonatal reflexes, signs of hypotonicity, dehydration, tachypnea, and Kussmaul respiration. The patient was hospitalized in the neonatal follow-up clinic with a pre-diagnosis of sepsis. His laboratory analyses revealed metabolic acidosis, hyperglycemia, ketonuria, and hyperammonemia. The blood levels of C3-propionylcarnitine were high. An investigation of the urinary organic acids revealed high levels of 3-OH propionic acid, 3-OH isovaleric acid, propionylglycine, and methylcitrate. Considering these results, the patient was diagnosed as propionic acidemia. Hyperglycemia is rarely seen in propionic acidemia. Organic acidemias must be kept in mind if hyperglycemia and metabolic ketoacidosis are accompanied by hyperammonemia, if clinical improvement cannot be maintained despite proper treatment, and if family history reveals parental consanguinity or unexplained infant death.

KEYWORDS : .Propionic acidemia, hyperglycemia, metabolic acidosis

Introduction

Propionic acidemia (PA) is a metabolic disease with autosomal recessive trait and has a general incidence of 1/100.000-1/150.000 (1). This study presents a case with a pre-diagnosis of sepsis due to clinical signs of rapid respiration, absence of suckling, and jaundice, and who was diagnosed with PA regarding the results of laboratory investigations, because of the rare existence of this state, and because of the existence of hyperglycemia in the patient in contrast to the general expectation of hypoglycemia.

Case report

A healthy male infant was born at term as the mother's first pregnancy by spontaneous vaginal delivery and first live birth, with a weight of 2600 gr. The patient had rapid respiration, absence of suckling, and jaundice on the third day following delivery.

The family history revealed parental consanguinity, and there was no history of sudden infant death. The general status of the patient was poor, and he was pale and icteric. The case had signs of dehydration and a 12% loss of the body weight, and his physical examination revealed tachypnea, Kussmaul respiration, weakening in the neonatal reflexes, mild hypotonicity and hypoactivity. The patient was hospitalized in the neonatal follow-up clinic, with a pre-diagnosis of sepsis.

The results of the biochemical analysis were as follows: glucose 215 mg/dL, urea 153 mg/dL, creatinine 1.5 mg/dL, direct bilirubin 0.87 mg/dL, and ammonia 718 µg/dL. Metabolic acidosis was determined in the analysis of blood gases (Ph: 7.03, PCO2: 20.5 mmHg, HCO3: 7.5 mEq/L, base deficit (BD): -23.5 mEq/L). The urine analysis revealed (2+) protein and (3+) ketone. Urine and blood cultures of the patient were taken, and ampicillin-cefotaxime treatment was initiated. Proliferation was not present in the blood and urine cultures. The general status of the patient was poor. A cerebrospinal fluid (CSF) culture was taken, and CSF was investigated regarding the microscopy and biochemical parameters. No pathological signs were detected in the analyses of CSF. Since no proliferation was detected in the cultures, a pre-diagnosis of sepsis was excluded. The patient was administered treatments of sodium benzoate for detoxification, and sodium bicarbonate for metabolic acidosis. The peritoneal dialysis was initiated because of the maintenance of hyperammonemia and metabolic acidosis. The value of ammonia was < 100 µg/dL within 48 hours and the peritoneal dialysis was terminated.

Metabolic disease was considered primarily because of the presence of metabolic acidosis and hyperammonemia in the patient, and the presence of parental consanguinity. The patient thus underwent tandem mass spectrophotometry (Tandem MS), urinary organic acid analysis, and blood amino acid chromatography. Tandem MS analysis revealed a high level of blood C3-propionyl carnitine. Levels of branched chain amino acids were detected to be high in the analyses of blood amino acids (valine 987 mmol/L, leucine 829 mmol/L, and isoleucine 406 mmol/L). The levels of 3-OH propionic acid and 3-OH isovaleric acid were high in the urinary organic acid analysis, and propionyl glycine, methyl citrate, and tiglylglycine were positive, which are not normally present in urine. Considering these results, the case was considered to have propionic acidemia; he was thus initiated on a low-protein diet that did not include isoleucine, valine, methionine and threonine and was also administered treatment of biotin and L-carnitine. Metronidazole was added to the medication to reduce the production of propionic acid by the intestinal bacteria. The synthesis of N-acetyl glutamate, which is an allosteric activator of the rate-limiting step of the urea cycle, is inhibited in PA; therefore, carglumic acid, which is the synthetic structural analog of N-acetyl glutamate, was administered for the treatment of hyperamm onemia.

The enzyme PCC causes the carboxylation of propionyl CoA to produce methylmalonyl CoA. The alpha subunit of the propionyl CoA

carboxylase (PCC) is coded by 13q32 (PCCA), and its beta subunit is coded by 3q22 (PCCB) (2). Many genetic mutations may exist in the two subunits of the carboxylase gene, and these mutations may affect the functions of PCC to various degrees (3,4,5). A prenatal diagnosis of PA is possible. The diagnosis must be verified to provide genetic counselling to the family regarding future pregnancies. The definite diagnosis of PA is based on the demonstration of enzyme deficiency in the peripheral leukocytes or skin fibroblast culture, or the indication of mutant variants in PCCA-PCCB by genetic mutation analysis. Eighty percent of mutations in the PCCA gene and 99% of those in the PCCB gene can be determined by sequence analysis; however, only 20% of mutations can be determined by the deletion-duplication analysis (6). Our case underwent genetic mutation analysis in order to verify the diagnosis of PA; however, no mutation related to the disease could be determined in the sequence analysis of the PCCA-PCCB gene. Deletion-duplication analysis has been planned in order to assess the presence of mutations.

Discussion

The worldwide incidence of PA is not known; however, it is estimated that it has a general incidence of 1/100.000-1/150.000, and its incidence is assumed to be 1/2000-1/5000 in Saudi Arabia (6). Infants are generally brought to the hospital in the first days of their lives with signs of challenges with nutrition, vomiting, dehydration, lethargy, convulsions, and hypotonia. However, the disease, with a mild clinical course, may manifest at any time until adulthood (7).

Studies have demonstrated that hypoglycemia develops in both forms of the PA during the episodes of acute metabolic decompensation. The presence of hyperglycemia is an unexpected characteristic in these cases, and it has been associated with high mortality (8,9). The mechanism of hyperglycemia in organic acidemias has not been completely clarified, but it is assumed to be multifactorial (8).

The current case also had hyperglycemia, which was accompanied by ketoacidosis. When tachypnea, Kussmaul respiration and the signs of dehydration are taken into account, it is apparent that the case had great similarities with diabetic ketoacidosis.

The study of Rafique et al. investigated the demographic characteristic s and complications in 24 cases with propionic acidemia; hypoglycemi a, hyperglycemia and metabolic acidosis were determined in 25%, 8%, and 83% of the cases, respectively, and hyperammonemia was detected in all cases (10).

Dweikat et al. reported a 9-month-old case with respiratory distress, progressive loss of consciousness, metabolic acidosis, and hyperglycemia upon admittance, who were misdiagnosed with DKA. In this case, response to treatment was not good, and family history revealed unexplained infant death. Further analyses were conducted for these reasons, and an accurate diagnosis was made as PA (8).

The most common cause of hyperglycemia and metabolic ketoacidosis is diabetes mellitus; organic acidemias must be kept in mind if they are accompanied by hyperammonemia, if clinical improvement cannot be maintained despite proper treatment, and if the family history reveals parental consanguinity or unexplained infant death.

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