Macedonian Journal of Medical Sciences. 2009 Jun 15; 2(2):153-156.
doi:10.3889/MJMS.1857-5773.2009.0044
Case Report

Propionic Acidemia - Case Report With Fatal Outcome

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Key words:
Propionic acidemia; normochloremic acidosis; vomiting; cardiomyopathy; hypogammaglobulinemia.

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Received: 21-Jan-2009
Revised: 03-Mar-2009
Accepted: 16-Mar-2009
Online first: 23-Mar-2009

Abstract

Propionic acidemia is an inborn error of metabolism due to defective enzyme, propionyl-coenzyme A (CoA) carboxylase, which results in an accumulation of propionic acid. In this report we describe a 13 month old male infant who presented with protracted vomiting, psychomotoric delay and normochloremic acidosis. Metabolic decompensation resulted in multiorgan failure-severe anemia, osteopenia, cardiomyopathy, humoral immunodeficiency and coma. The diagnosis was established on the basis of elevated urinary concentration of 3 OH propionic acid. Thus in all children with normochloremic acidosis, neurodevelopmental delay and vomiting one should raise suspicion for organic acidemia. Urinary organic profile should be investigated immediately in order to establish correct diagnosis and administer appropriate treatment.

Introduction

Propionic acidemia is the most common acidemia due to defective enzyme, propionyl-coenzyme A (CoA) carboxylase, which results in an accumulation of propionic acid. Metabolism of isoleucine, valine, threonine, and methionine results in production of propionyl-CoA. The enzyme propionyl-CoA carboxylase catalyzes conversion of propionyl-CoA to methylmalonyl-CoA. This enzyme has 2 subunits and defects in genes encoding these units (*PCCA* and *PCCB*) result in insufficiency of the enzyme and accumulation of toxic metabolites. The clinical picture varies from patients presenting with mild psychomotor retardation to those with severe metabolic decompensation with vomiting, dehydration, encephalopathy and in rare instances fatal outcome (1-4).

In this report we present a 13 month old male infant, who presented with severe metabolic crisis and decompensation. The clinical course suggested organic acidemia; unfortunately the diagnosis or propionic acidemia was established postmortem.

Case Report

A 13 month old male infant was admitted to the Department of Gastroenterohepatology at the Children's Hospital Skopje with severe acidosis and dehydration. His past medical history was uneventful. He had been breast fed until the age of 11 months and afterwards he was given cow milk. The infant has had regular check ups by his pediatrician and normal

psychomotor and growth milestones. Since the age of 11 months he began to vomit and his motor development arrested. He has lost 2 kilograms for two months.

He has been constipated for seven days before this admission. His vomiting intensified in the last days and was referred to the local hospital. Besides parenteral hydration his general status did not improve and he was referred to our Institution. On admission he was severely dehydrated but alert. On the day of admission he had electrolyte determination at the local hospital (Na, K and Cl were within normal limits). His acid base status showed severe metabolic acidosis (HCO_3 lowest value 7.3 mmol/l). His urine showed pH 5 and ketones 3+, no glucose. There was hypercalciuria-calcium/creatinine ratio was 2.34 (normal < 2.0). Chest X-ray showed bilateral pneumonia. The bones showed osteoporosis (Figure 1). He was given intravenous fluids, glucose and bicarbonate and his general state improved. He started oral feedings, but he became again dehydrated and acidotic. His general state worsened and he presented with weakness, hypotonia, sopor, tachypnea and dyspnea. The laboratory investigation revealed severe metabolic acidosis, mildly increased serum anion gap at 18 mmol/l, with normal chloride 105 mmol/l. Urine pH was 5 (with dipstick). His kidney ultrasound was normal. There was mild hypokalemia (3.1 mmol/l) hypophosphatemia (0.91 mmol/l) and hypouricemia (136 micromol/l) suggesting tubular dysfunction. Chloride highest value 109 mmol/l during severe acidosis. Although his hematologic parameters were within normal range on admission he developed severe anemia (Hb 72 g/l) which required transfusion of packed red cells. His platelet count decreased to $46x10^{11}$/l. He revealed humoral immunodeficiency: IgG 1.3 g/l, IgM 0.7 g/l, IgA 0.2 g/l. Echocardiography showed poor kinetics of the left ventricle. Besides intensive treatment and mechanical support, his cardiac, pulmonary and neurologically status worsened and he died. Vomiting and loss of weight, neurodevelopmental delay, constipation, normochloremic acidosis, hypogammaglobulinemia, development of anemia and cardiopathy raised suspicion for organic acidemia and therefore biological material was obtained before exitus. The assay of the urinary organic acids revealed increased concentration of 3 OH propionioc acid (55 umol/mol creatinine; normal <10), with normal values for methylmalonic acid suggesting the diagnosis of propionic acidemia. Mutational analysis of the both genes responsible for PA is in progress.

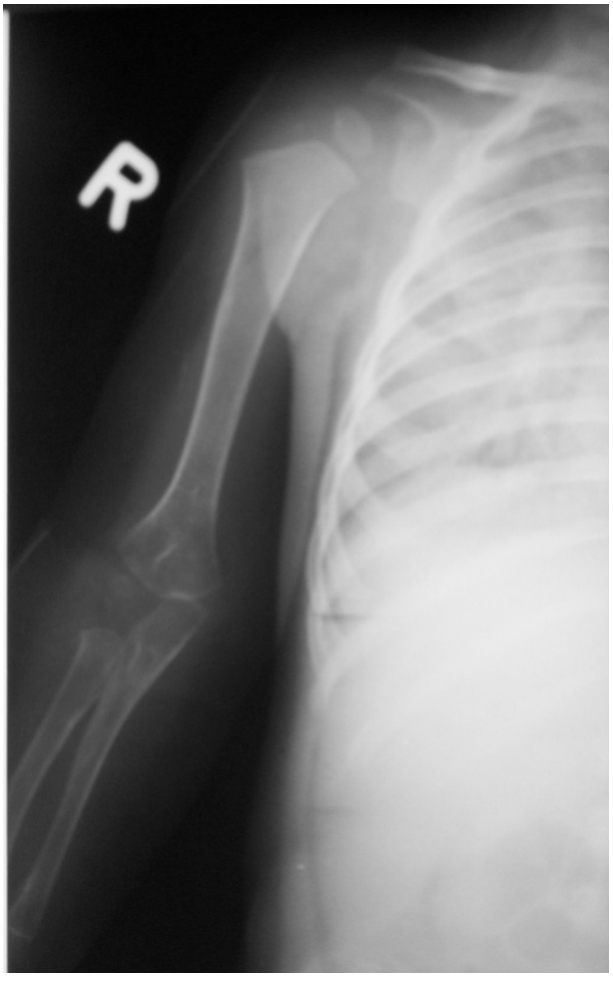

Figure 1: Osteoporosis of upper forehand.

The autopsy shows that in the part of the brain where there are degenerative changes in the nerv-fibers with homogenisation of the nuclei (Figure 2), lost of the nucleus inside and sponge tissue inside (spongiosis) and focal lost of Purkinje cells in the small brain.

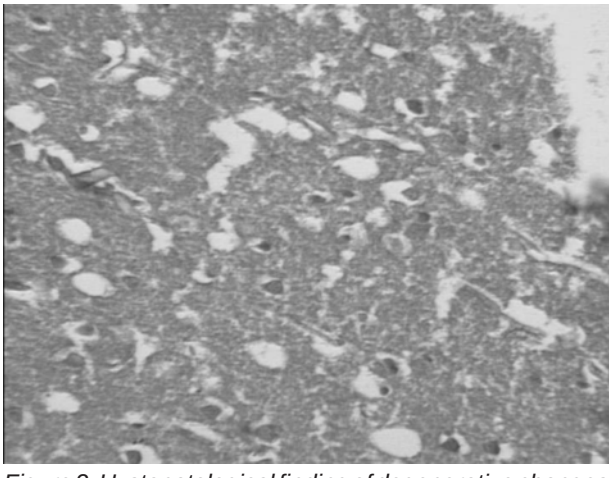

Figure 2: Hystopatological finding of degenerative changes in the brain.

Discussion

Propionic acidemia is the most common organic acidemia with the estimated prevalence between 1:35,000-75,000/population. The true prevalence is not known since the patients with the early onset form die in the neonatal period often misdiagnosed as sepsis. With the neonatal screening more cases are diagnosed and with appropriate medical measures these babies survive (5). The patients with late form may present with neurological symptoms characterized with severe movement disorders and dystonia (4).

The disease has relapsing course of severe metabolic ketoacidosis, often precipitated by excessive protein intake, constipation, or intercurrent infection. Ketoacidosis develops because propionic acid inhibits citric acid cycle enzymes. Along with the acidosis, manifestations of the disease may include seizures, neurodevelopmental retardation, hypotonia, coma, episodic vomiting/gastroesophageal reflux, protein intolerance, hyperammonemia, hypogammaglobulinemia, bone marrow dysfunction, osteopenia, pancreatitis, and cardiomyopathy (1, 3, 4, 6-8). The initial treatment in metabolic crisis includes intravenous fluids, glucose and bicarbonate; after improvement oral feeding consists of diet that is low in proteins with supplements of carnitine, and biotin (2).

It is an autosomal recessive disorder caused by mutations in PCCA and PCCB genes which encode a and b subunits of PCC, respectively. Prenatal diagnosis is possible with measurement of the abnormal metabolites in the amniotic fluid (9-11). If the gene defect is known in the family than molecular diagnosis is more acceptable. Recently a group form Spain demonstrated that non-invasive prenatal diagnosis is possible by studying maternal plasma from a pregnant woman at risk of having a fetus affected with propionic acidemia (9). It is known that 3-6% of the total plasma DNA in pregnant women has fetal origin. Propionic acidemia is a recessive disorder in which about 80% of patients are compound heterozygotes. If paternal mutation in not detected in the plasma than the fetus is not affected by the disease and there is no need for amniocenthesis.

Our patient presented with very unusual features: slight neurodevelopmental delay, constipation, vomiting, acidosis, anemia, cardiopathy and hypogammaglobulinemia. These features are result of the toxic effect of the organic acids particularly on bone marrow, heart, B cells and brain tissue. Long lasting acidosis leads to osteopenia and release of buffering calcium salts and hypercalcirua which may produce confusion with renal tubular acidosis. Although serum anion gap was mildly increased in our patient, normal chloride during severe systemic acidosis alerted us towards organic acidemia. Thus in all children with normochloremic acidosis, neurodevelopmental delay and vomiting one should raise suspicion for organic acidemia. Urinary organic acids should be investigated immediately in order to establish correct diagnosis and administer appropriate treatment.

Acknowledgments

The authors would like to gratefully acknowledge Prof. A. Das and Priv. Doc. T. Lucke, Medizinische Hoch Schule Hannover for performing urinary organic profile.

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