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Propionic aciduria in a 5-month-old child

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Propionic aciduria is a rare hereditary metabolic disease with autosomal-recessive inheritance mode associated with organic acid metabolic disorder. Early diagnostics is difficult as clinical symptoms caused by metabolic defects are often observed at hypoxicischemic central nervous system lesion, brain malformations and intrauterine infections. Laboratory examination reveals increased concentration of organic acids in blood and urine. The article presents observation of propionic aciduria in a 5-month-old child.

Key words: hereditary metabolic diseases, propionic aciduria, children, diagnostics.

CASE STUDY

A 5-month-old child was referred to the advisory polyclinic of the Kirov children's regional hospital due to slight idiopathic anemia. Fainting fit followed by diffuse hypotonia and general cyanosis up to 1 minute developed during pediatric examination, therefore, the child was urgently hospitalized.

Medical history: first-pregnancy child; pregnancy complications: chronic calculous cholecystitis, gestational pyelonephritis, anemia, chronic intrauterine fetal hypoxia and threatened miscarriage in week 33. Term birth, elective caesarean section, APGAR score – 8/9; birth weight – 3,380 g, body length – 51 cm. Hemoglobin decrease detected at 3 months of age; Maltofer intake. No psychomotor development delay. According to the mother, hereditary background – not burdened. Condition at admission to inpatient hospital – moderate (due to post-fit period). Somatic status: skin pallor, liver enlargement up to 2 cm below the costal margin (midclavicular line); no respiratory and cardiovascular deviations detected. The child's phenotype: high forehead, epicanthic fold, short filter, full lips, low nasal bridge. Neurological status: cranial circumference – 43 cm, no focal neurological symptoms, marked diffuse muscular hypotonia secondary to intact tendon reflexes. The child's condition was considered satisfactory in the setting of Convulex intake (9 days); no fits. After a “promising period” – abrupt development of metabolic crisis: marked asthenia, hypothermia, food refusal, marked dyspnea, increase in muscular hypotonia, generalized tonicoclonic spasms. Due to severe condition, the child was transferred to the intensive care unit, where the child's condition progressively aggravated despite the provided treatment: progressive impairment of consciousness to the third-order coma, persisting spasms, increasing respiratory failure requiring artificial pulmonary ventilation, cardiovascular and renal insufficiency. Fatal outcome after 4 days due to development of multiple organ failure.

The child was consulted by a neurologist, an ophthalmologist and a geneticist throughout the treatment period and underwent laboratory tests and instrumental examinations for diagnostic purposes.

Clinical blood analysis: hemoglobin and erythrocyte decrease down to 99 g/l and $3.42 \times 10^{12}/l$, respectively, over time – increase in anemia, leukopenia (up to $1.7 \times 10^9/l$) and thrombocytopenia (up to $79 \times 10^9/l$).

Biochemical blood analysis: glucose – 5.18 mmol/l, in the event of condition aggravation – up to hypoglycemia (0.85 mmol/l); urea – 22.85 mmol/l, creatinine – 173.2 mmol/l, lactate – 0.7 mmol/l, phenylalanine (selectively) – 0.58 mg/dl.

Urine screening: Fehling's solution – yellow, homogentisic acid test – negative, Sulkowitch test – positive, Benedict's reagent – blue, magnesium reagent test – yellow.

At transfer to the intensive care unit:

Blood acid-base balance: pH – 6.983, BE – 25.6 mmol/l, over time – pH 7.260-7.137, electrolyte decrease: potassium – down to 2.64 mmol/l, ionized calcium – down to 0.419 mmol/l.

Chest X-ray examination: thymomegaly (class I).

Ultrasound of abdominal cavity organs: slight and moderate liver alterations, hepatomegaly.

Neurosonography: focal alterations in anterior thalami (both sides).

Electrocardiogram: within the age norm.

Electroencephalography was performed during physiological sleep: sleep spindles, occasional delta wave activity with peak amplitude in the right temporal-occipital area; no typical forms of paroxysmal and epileptic activity detected.

Brain computed tomography: symmetrical regions of decreased density in basal ganglia (both sides), hypodense at staining.

DIAGNOSIS AND DISCUSSION

Analysis of clinical and laboratory-instrumental data allowed suspecting a hereditary metabolic disease (a mitochondrial disease or an organic aciduria). Content of organic acids in urine was measured at the laboratory of hereditary metabolic diseases of the Medical Genetic Scientific Center (Federal State Budgetary Institution) (tb.).

The revealed significant increase in content of organic acids in urine and distinctive clinical manifestations allowed diagnosing the child with propionic aciduria. Despite the provided intensive care, the child died of multiple organ failure and toxic encephalopathy caused by severe metabolic acidosis. Established diagnosis – “Infantile propionic aciduria”.

Hereditary metabolic diseases have a high specific weight among hereditary diseases; they are present in 1:1000 [1] - 1:500 [2] neonates. The diseases are characterized by high mortality, especially in infancy, and often cause sudden infant death. According to the data as of 01.01.2013, autosomal-dominant congenital connective tissue dysplasias are the most widespread in the structure of the register of hereditary diseases (Kirov Region) (28%); rare monogenic syndromes with different modes of inheritance are the 2nd most widespread (22%), chromosome pathology (15%) and a wide range of hereditary metabolic diseases (9%) are the 3rd most widespread. 85-95 cases of hereditary pathology are diagnosed for the first time annually, 70% of them being genetic hereditary diseases and syndromes, 30% - chromosome pathology [3].

Propionic aciduria (acidemia) is a rare genetically heterogeneous hereditary disease caused by propionyl-CoA carboxylase deficiency resulting in propionate metabolism blocking on the level of propionyl-CoA conversion into methylmalonyl-CoA and impaired metabolism of a range of amino acids and fatty acids with odd amount of carbohydrate and cholesterol atoms.

Propionyl-CoA carboxylase has alpha and beta isozymes – PCCA and PCCB. The genes responsible for development of the disease are mapped: PCCA – 13q32, PCCB – 3q21-q22. Genetic mutations of isozymes of mitochondrial propionyl-CoA carboxylase are accompanied by its deficiency in liver, kidneys, heart, fibroblasts and leukocytes.

Pathogenesis of the disease is associated with accumulation of propionic acid, amino acids – propionate precursors (isoleucine, valine, methionine and threonine), ketones (butanone, hexanone, methanone), long-chain fatty acids with odd amount of carbohydrate atoms, methylcitrate, propionylglycine and tiglylglycine in the body [4].

Accumulated compounds cause severe metabolic ketoacidosis, secondary hyperammonemia, hypoglycemia and have toxic effect on various tissues resulting in fatty degeneration of liver,

degeneration and atrophy of various brain divisions and marrow function inhibition. High blood level and high renal excretion of propionylcarnitine deplete carnitine supply resulting in secondary carnitine deficiency [5].

Rate of propionic aciduria in neonates in the USA and European countries is 1:350,000 [6], in the Russian Federation – unknown.

Scientists distinguish between two variants of propionic aciduria: type I (gene *PCCA* mutations) and type II (gene *PCCB* mutations) (more frequent) – and two clinical forms depending on time and severity of manifestations: acute neonatal and infantile (late) [5].

The disease takes a crisis course in most cases: emesis, dehydration, food refusal, respiratory disorders, generalized muscular hypotonia, flaccidity, sleepiness, coma, i.e. clinical manifestations of toxic encephalopathy. Acute pancreatitis and cardiomyopathy may also develop. Mortality rate reaches 40%. Even if such children do not suffer from metabolic decompensation, they have physical and psychomotor development delay. Spasms, extrapyramidal disorders (rarely), cardiomyopathies, cardiac rhythm disturbance, erythematous dermatitis, atrophy of optic nerves (often) are observed in half of the patients. Computed tomography reveals cortical atrophy, ventricular enlargement, brain tissue density decrease; magnetic resonance imaging reveals increase in signal intensity in T2-weighted images in the area of basal ganglia. Severe metabolic ketoacidosis accompanied by hyperammonemia, hyperglycinemia, glucose level decrease, leukopenia and thrombocytopenia developed during metabolic crisis. Blood analysis reveals high content of propionic acid, glycine and lysine; high level of propionylcarnitine; low content of free carnitine. Urine analysis reveals high content of hydroxypropionic, methylcitric and other propionic acid derivatives.

The treatment is primarily aimed at decreasing propionate production, prevention of development of ketoacidosis, toxic brain and visceral lesion; this helps to establish conditions for a child's normal development. The treatment is based on diet therapy: restricted intake of isoleucine, valine, threonine, methionine (down to minimal need) and fatty acids with odd amount of carbohydrate atoms. Prescription: levocarnitine and glycine – to improve binding of the toxic propionyl-radical [5, 7].

We demonstrated this case to attract attention of pediatricians to the issue of hereditary metabolic diseases: despite objective difficulties in diagnosing propionic aciduria, such reference symptoms as early onset of the disease, distinctive crises caused by toxic encephalopathy, detection of severe metabolic ketoacidosis and specific blood and urine alterations with laboratory tests help not only to suspect propionic aciduria, but also to start specific treatment on time and thus save the child's life.

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Table. Urine concentration of organic acids

Name	Concentration, mM/M	Maximum normal concentration, mM/M
2-hydroxyisobutirate	5036.1	2.00
3-hydroxypropionic acid	2734.3	10.0
3-hydroxybutirate	4789.4	3.00
Acetoacetate	1212.2	2.00
Lactate	3947.6	25.00
Methylcitrate	722.04	12.00
Propionylglycine	302.9	2.00
Tiglylglycine	1882.5	2.00

Expert Opinion (N.V. Zhurkova, MD, physician-geneticist SCCH): Indeed, propionic aciduria - a rare hereditary disease from the group of inherited metabolic diseases. The disease is caused by deficiency of the enzyme propionyl-CoA carboxylase, which results in accumulation of propionic acid and its metabolites in the organs and tissues. Diagnosis is based on the increase of propionic acid and its metabolites in the blood, as well as increasing of isoleucine, valine, methionine and threonine levels. This article is certainly of great interest to pediatricians, child neurologists and other doctors. However, it should be noted that for accurate verification of the diagnosis molecular genetic testing - search for mutations in the genes PCCA and PCCV – is required. Reaffirmation of the diagnosis is necessary not only to the management of the sick child, but also necessary in the planning of subsequent births in the family.