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Case Report-Medical Sciences

A case report of pyruvate carboxylase deficiency with long-term survival

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ABSTRACT:
Pyruvate carboxylase deficiency is a rare metabolic disorder with autosomal recessive inheritance. This biotin-dependent enzyme is involved in the tricarboxylic acid cycle, gluconeogenesis, lipogenesis, and the synthesis of the brain neurotransmitters nicotinamide adenine dinucleotide phosphate. The severity of symptoms and survival rates vary depending on the type of enzyme deficiency. In this article, we introduce a 3-year-old boy with the onset of symptoms (hypoglycemia) and lactic acidosis from the first 24 hours of life. In a genetic study, genetic inheritance in favor of pyruvate carboxylase deficiency was reported.

Keywords: Lactic acidosis, pyruvate carboxylase deficiency disease, hypoglycemia

INTRODUCTION:

Pyruvate carboxylase is involved in the TCA cycle of tricarboxylic acid and the conversion of pyruvate to oxaloacetate. Gene mutations in this enzyme cause oxaloacetate deficiency. It is involved in lipogenesis, gluconeogenesis, and brain neurotransmitters such as glutamine (2). It is an autosomal recessive disorder that occurs in 1/250000 births (3).

Symptoms vary depending on the type of enzyme deficiency:

1) Type A is the infantile form, which is common in North America and is associated with developmental delay, severe acidosis, vomiting, abdominal pain, and growth failure. These patients mostly die in infancy or early childhood.

2) Type B is the French form with onset of symptoms in infancy and the most severe type of pyruvate carboxylase deficiency, with lactic acidosis, hyperammonemia, hypercitrullinemia, hypotonia, motor disorders, and seizures. It mostly leads to death in the child under 3 months.

3) Type C is the benign form, which is mostly associated with intermittent lactic acidosis and mild developmental delay in stress and disease (3 and 4). These 3 types are mostly differentiated according to laboratory findings and clinical symptoms. High levels of lactate >10 mmol/Lit, citrulline and lysine, and high protein are seen in type B, while citrulline levels are normal in type A and type C (5).

Case study introduction: This article presents a 3_12m^5m male child who suffered from respiratory distress, tachypnea, and cyanosis in the first 24 hours of birth. He was transferred from the women's ward to the ICU of Hakim Hospital in Neyshabur after breastfeeding began. Initial tests revealed severe metabolic acidosis and increased liver enzymes. The patient was initially diagnosed with a neonatal infection and was treated with antibiotics. He was intubated due to severe acidosis and apnea, and supportive measures were taken. The patient was re-examined due to lack of proper recovery and frequent hypoglycemia. He was metabolically evaluated with suspicion of metabolic disorders due to liver enzymes and frequent hypoglycemia despite serum therapy. Moreover, in the patient's history, the parents were cousins, the child was the second child in the family, and there was no history of metabolic disorders in the family. In the metabolic study, ammonia was slightly higher than normal, lactate was higher than 80 mg/dl, pyruvate was low, and lactate-pyruvate ratio was above 20. Additionally, glutamine, aspartic acid, and citrulline levels were low in the chromatography of serum amino acids at 4 days of age. In addition, in the study of urine organic acids at 3 days of age, 4-hydroxyphenyllactic acid (159 times) and 4-hydroxyphenylpyruvic acid (6.8 times) were reported.

Based on the initial tests, the possibility of organic acidemia was raised for the patient. The patient underwent initial treatment and was discharged in an almost good general condition. The child was again admitted to the ICU at 4 months of age with similar attacks, respiratory distress, hypoglycemia, and high lactate. The patient recovered after receiving 10% glucose serum and bicarbonate and was discharged with Schulze solution and the administration of vitamins B1, B6, B12, and biotin.

He also experienced several episodes of hypoglycemia, metabolic acidosis, and elevated lactate following viral infections during this period. He recovered with supportive treatments. Finally, a WGS genetic test was requested due to the lack of a definitive diagnosis for the patient, and a homozygous pathogenic variant in the pyruvate carboxylase gene was identified. Finally, genetic testing of the parents and Sanger sequencing

were recommended for the patient and parents, but it was not performed due to the parent's lack of consent.
Finally, the diagnosis of pyruvate carboxylase type B is most likely for the patient given the onset of our patient's symptoms from birth, frequent attacks of lactic acidosis and hypoglycemia, and positive laboratory signs. Although the patient has had a long-term survival during this period and started walking at 18 months of age, and fine motor movements are slightly impaired, speech movements and completion also started with a delay. However, he is almost normal regarding speech development. Growth criteria are normal and the patient was treated with Schulze, vitamin B1, and biotin. In other words, our patient's course is inconsistent with type B pyruvate carboxylase deficiency.

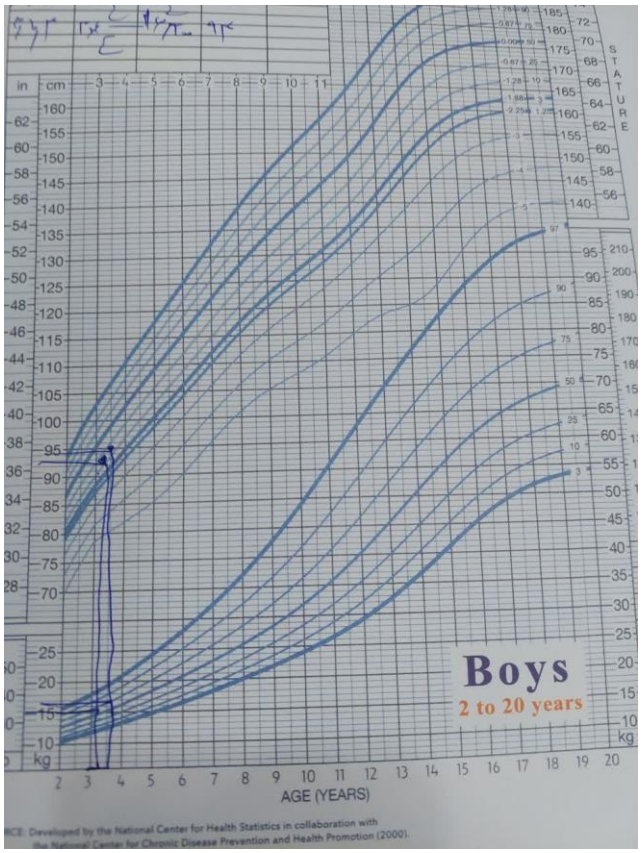
Table 1) Laboratory signs

	4-day	4-month
Alanine Citrulline Tyrosine Lysine	)195-56 (270 56 (10-45))345-385 (128 80-240) (236	477 (590- 195) 7 (45- 10) 256 (225-685) 43 (10-145) (186 (80-240)

	One-day	4-day
Bs Alt Ast Lactate Ammonia pyruvate lactate/pyrovate Pt PTT Initial CBC VBG initial	33 mg⁄dl 55 36 80 130 ug⁄dl 2 20< 14 36 Normal PH=6.99 HC= 5	45 82 36 72 100 ug⁄dl --- --- --- --- normal PH= 7.02 HC=13

Clinical history

Age at diagnosis	In the first 3 hours after birth
Gender Parental relationship Pregnancy complications Maturation at birth Birth weight Current weight Current height	Male Relative (cousin) No Term Kg 3200 15.90 92



DISCUSSION:

This article presents a case of pyruvate carboxylase deficiency starting within the first 72 hours of birth. Pyruvate carboxylase is a biotin-dependent enzyme converting pyruvate to oxaloacetate. This metabolic disorder has an autosomal recessive inheritance. It can be divided into 3 types depending on the time of onset of symptoms and clinical manifestations (6). In this article, the onset of symptoms was from birth. The disease duration was prolonged. The laboratory signs were in favor of pyruvate carboxylase deficiency, which was not determined in the initial genetic test of the disease type. In any patient with hypoglycemia and high lactate (after excluding secondary causes), respiratory chain disorders and pyruvate carboxylase and pyruvate dehydrogenase deficiency are considered if the increase in lactate in the fasting state is accompanied by neurological symptoms. To differentiate these cases, the lactate-to-pyruvate ratio and the 3-hydroxybutyrate to acetoacetate ratio should be examined. Laboratory changes were experienced in pyruvate carboxylase deficiency, especially in type B.

* Pyruvate carboxylase deficiency is suspected if the lactate to pyruvate ratio is above 20 and the 3-hydroxybutyrate to acetoacetate ratio is high.
* Respiratory chain disorders are suspected if the lactate-to-pyruvate ratio is high and the hydroxybutyrate-to-acetoacetate ratio is low.
* Pyruvate dehydrogenase deficiency disorders are suspected if the lactate-to-pyruvate ratio is low or normal (7).

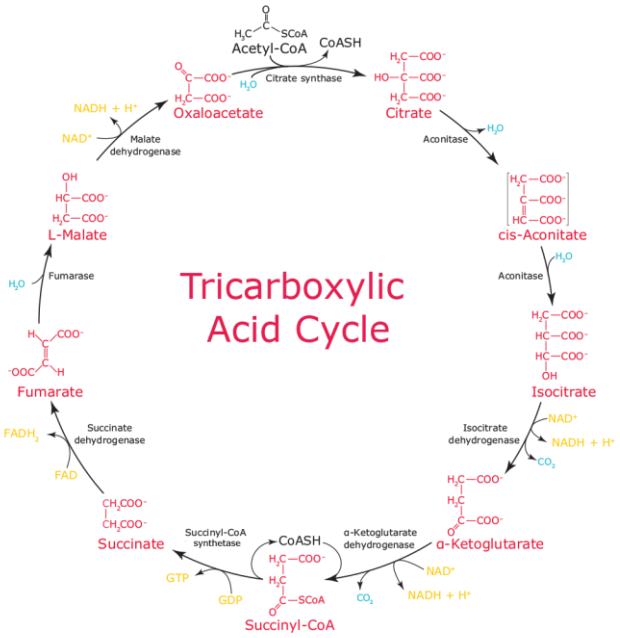
In addition, in pyruvate carboxylase type B deficiency, serum lysine-proline-citrulline levels are high and

ammonia is slightly increased in chromatographic acid levels.

Increased citrulline is a particularly significant result in pyruvate carboxylase deficiency type B. The increase in citrulline in this case is due to the deficiency of oxaloacetate, involved in the production of aspartate. Aspartate is involved in the conversion of citrulline to argininosuccinic acid in the urea cycle. It increases due to the disorder in the urea cycle (8 and 9). In examining urinary organic acids in pyruvate carboxylase type B deficiency, 3-hydroxybutyrate-lactate-acetoacetate-4-hydroxyphenyllactate, and 2-oxoglutarate are high. Given the above laboratory signs, the diagnosis of pyruvate carboxylase type B deficiency with long-term survival is considered for our patient, which is generally one of the rare cases with clinical manifestations of pyruvate carboxylase type B deficiency.

Dalili et al. (2021) reported a 26 and 7-month-old girl at the University of Gilan with clinical manifestations consistent with pyruvate carboxylase type B deficiency but without laboratory symptoms and with long-term survival in some cases with pyruvate carboxylase type B deficiency. This was mostly due to heterozygous mutations and mosaicism (10). WangeTal. (2008) reported five patients with pyruvate carboxylase deficiency type B. In this study, two of these patients survived to the ages of 9 and 20 years. However, mosaicism was not examined in these patients (11). Daryletal. (1977) reported a 10-month-old infant with severe lactic acidosis and elevated pyruvate lactate, 3-hydroxybutyrate, acetoacetate, and increased proline and alanine, which were in favor of pyruvate carboxylase type B deficiency (12).

A case of pyruvate carboxylase type B deficiency with neurological manifestations on fetal ultrasound in the form of subependymal cysts and dilation of the lateral ventricles was reported in Wuhan Hospital, China in 2023. Genetic examination of ammonia fluid was performed and pyruvate carboxylase type B deficiency was reported. Finally, this infant died at 26 days of age (13). This result highlights the importance of the pyruvate carboxylase enzyme in the brain in the synthesis of neurotransmitters and brain development. Regarding MRT symptoms, it is more consistent with Leiqh syndrome and subacute necrotizing encephalomyelopathy. Moreover, radiological signs in the form of periventricular leukomalacia on MRI in infancy with lactic acidosis are in favor of this disorder (14). Therapeutically, these patients should be treated with supportive measures of hydration and correction of acidosis along with administration of thiamine cofactor for pyruvate carboxylase type B deficiency, biotin, and Bicitra and Schulze solution, and treatment of hyperammonemia with sodium benzoate and arginine.



CONCLUSION:

The possibility of pyruvate carboxylase deficiency should be considered in any infant with severe respiratory and lactic acidosis symptoms, hypoglycemia, and high ammonia.

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