Case Report

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A Case Report of a Patient with Pyruvate Carboxylase Deficiency

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ABSTRACT

Background: Pyruvate carboxylase catalyzes the carboxylation of pyruvate to oxaloacetate, a crucial intermediate of the tricarboxylic acid (TCA) cycle and the initial step in converting pyruvate to glucose (gluconeogenesis). Pyruvate carboxylase deficiency is a rare metabolic disorder characterized by lactic acidosis, failure to thrive, development delay, and recurrent seizures at an early age in severely affected patients. The onset and severity of pyruvate carboxylase deficiency have been classified as severe neonatal (type B), usually fatal, less severe infantile (type A), compatible with survival but with impaired neurologic development, and milder, later onset (type C) with some residual impairment. Clinical manifestations include hypotonia, mixed hypertonia, ataxia, choreoathetosis, microcephaly, and other signs of impaired white matter development.

Case Report: A 7-day-old baby with a birth weight of 3kg, born to related parents, presented with clinical symptoms such as lethargy, poor feeding, and grunting since birth. Additionally, he experienced a drop in O_2 saturation and cyanosis during his hospitalization. Test results revealed lactic acidosis and hyperammonemia. Furthermore, serum amino acids chromatography- HPLC indicated an increase in lysine and citrulline. The patient succumbed after 16 days due to multi-organ damage. Genetic analysis identified pyruvate carboxylase enzyme deficiency.

Conclusion: Pyruvate carboxylase deficiency is a rare inborn error of metabolism that can lead to developmental delay and failure to thrive, typically beginning in the neonatal or early infantile period. The possibility of pyruvate carboxylase deficiency should be considered in any child presenting with lactic acidosis and neurological abnormalities, particularly if associated with hypoglycemia, hyperammonemia, or ketosis.

Introduction

Pyruvate carboxylase is a mitochondrial, biotin-containing enzyme that is essential in the process of gluconeogenesis.[1] It catalyzes the conversion of pyruvate to oxaloacetate. The enzyme is essential for the Krebs cycle function as a provider of oxaloacetate and is also involved in lipogenesis and the formation of non-essential amino acids.[2] Pyruvate carboxylase deficiency is a rare autosomal recessive metabolic disease. Its estimated incidence is one in 250,000 births, and results in abnormally high pyruvate, lactic acid, and alanine levels.[3]

Pyruvate carboxylase deficiency is associated with three phenotypes, each varying in clinical severity based on residual enzyme activity.[4] The French phenotype (type B) manifests within 3-48 hours after birth with hypothermia, hypotonia, lethargy, vomiting, severe lactic acidosis, hyperammonemia, citrullinemia, and hyperlysinemia. The North American phenotype (type A) appears between 2 and 5 months of age, typically with mild to moderate lactic acidosis and developmental delay. In both types, surviving patients often experience severe psychomotor retardation with seizures, spasticity, and microcephaly. Some patients have pathologic changes in the brain stem and basal ganglion that resemble Leigh's disease. Neuro-radiological findings include specific brain lesions, periventricular hemorrhagic cysts, cerebral atrophy, and delayed myelination. The disease typically leads to death in infancy, but a benign form characterized by recurrent lactic acidosis and mild neurologic deficit also exists.[4,5] The gene responsible for pyruvate carboxylase is located on chromosome 11q13.4-q13.5.[6,7]

Treatment involves avoiding fasting, consuming carbohydrates before bedtime, and administering continuous IV glucose during acute lactic acidosis episodes.[8-10] All forms of pyruvate carboxylase deficiency are inherited in an autosomal recessive manner, and diagnosis is made by measuring enzyme activity in liver or cultured skin fibroblasts.[5]

Materials and Methods

A 7-day-old infant was admitted to the NICU due to jaundice and lethargy. The patient had NVD term with BW = 3 KG from the related parents. His clinical symptoms included lethargy, poor feeding, grunting since birth, and a decrease in urine volume. The infant underwent a sepsis work-up, intravenous fluid therapy, antibiotics, and phototherapy. In the course of hospitalization, the patient's lethargy worsened. He experienced a decrease in O_2 saturation and cyanosis, which led to intubation and connection to a ventilator. The results of the tests and serum amino acids chromatography are given in the Table 1.

Table 1. Laboratory results

Variable	Patient's Value	Reference Value
pH	6.93	7.35-7.45
HCO_3^-	3.6	20-28 mmol/L
PCO2	16.8	40 mmHg
SGOT	92	5-42 mg/dL
SGPT	41	5-38 mg/dL
Alkp	1192	Up to 1100
pT	>30	12-14 (sec)
PTT	112	25-39 (sec)
INR	>5.4	Up to 1
BS	78	70-115 mg/dL
Ammonia	1117	Up to 175 µg/dL
Lactate	41	10-22 mg/dl
Citrulline	276	5-50 µmol/lit
Lysine	411	60-300 µmol/lit

The patient was treated with intravenous bicarbonate due to severe acidosis and died in 16 days with multi-organ damage. In the genetic study, pyruvate carboxylase enzyme deficiency was considered (which was expected due to clinical symptoms, pyruvate carboxylase deficiency Type B).

Discussion

Pyruvate carboxylase is a biotin-containing mitochondrial enzyme that accelerates the conversion of pyruvate to oxaloacetate by CO_2 fixation.[11] Pyruvate carboxylase deficiency is a rare neurometabolic disorder with less than

40 cases reported.[3] Our patient's symptoms started from birth, with presentation consistent with pyruvate carboxylase deficiency Type B. French form (Type B), is identified by severe neonatal lactic acidosis, hyperammonemia, truncal hypotonia, coma, and liver failure. The initial acidosis may be fatal, and many patients die within the first six months of life.[3] Most of them have hepatomegaly and metabolic acidosis that may lead to dehydration, coma, shock, and apnea. Biochemical findings, including hyperammonemia, citrullinemia, and hyperlysinemia are characteristic.[12] The prognosis for pyruvate carboxylase deficiency is poor. Our patient died in 16 days with multi-organ damage.

Conclusion

The possibility of pyruvate carboxylase deficiency should be considered in any child presenting lactic acidosis and neurological abnormalities, especially if associated with hypoglycemia, hyperammonemia, or ketosis. In neonates, a high lactate/pyruvate ratio is associated with a low 3-OH butyrate/acetoacetate ratio, and hyper citrullinemia with low glutamate/glutamine is nearly pathognomonic. The discovery of cystic periventricular leukomalacia at birth associated with lactic acidosis is also highly suggestive. Typically, blood lactate increases in the fasting state and decreases after the ingestion of carbohydrates.[13]

Conflict of Interest

The authors declare no conflicts of interest.

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Ethical Considerations

The present study was approved by the Ethics Committee of Shahid Sadoughi University of Medical Sciences (IR.SSU.REC.1403.021).

Author's Contribution

Performing the examination of the patients, N.M. & M.G.T; writing and editing the manuscript, S.M. All authors read and approved the final manuscript.

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