A Case of Pyruvate Carboxylase Deficiency With Longer Survival and Normal Laboratory Findings

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Abstract- Pyruvate carboxylase deficiency (PCD) is a rare autosomal recessive defect in a biotin-containing enzyme, Pyruvate carboxylase, which is considered as an enzyme of TCA-cycle regulation, gluconeogenesis, lipogenesis, and biosynthesis of neurotransmitters. Increased lactate to pyruvate ratio and decreased three hydroxybutyrates to acetoacetate are the main biochemical features of PCD. The elevated level of Citrulline, Proline, and Lysine with a short life span has been reported previously. Patients' survival in almost all cases is below three months. Here, the authors aimed to report a girl with manifestations of Type B of PCD and longer survival (two-year and four-month-old). This patient did not have any changes in amino acid level, which was a unique case of Type B of PCD.

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Introduction

Pyruvate, the end product of glycolysis, turned to oxaloacetate in an ATP-dependent reaction performed by an enzyme so-called pyruvate carboxylase (1). The pyruvate carboxylase (PC) protein is encoded by *PC* genes on chromosome 11q13.2. It has one noncoding and 20 coding exons in humans. PC lies at the heart of human energy production getaway and the beginning of Krebs cycle as the roots of the human metabolic hub (2). The predominant expression of this protein in humans occurs in the liver, adipose tissues, followed by kidney, lactating mammary gland as well as pancreatic islets tissue (3,4). Pathogenic mutations in the *PC* gene, which lead to depletion of Oxaloacetate, have profound effects on biological processes such as synthesis of amino acids and glycogen, gluconeogenesis, lipogenesis, glycerogenesis, and neurotransmitters (5).

Pyruvate carboxylase deficiency (PCD; MIM#266150) is an autosomal recessive disorder. It occurs in 1 in 250.000 births (6). Based on onset age and symptoms' severity, PCDs are divided into three forms; A (American type), B (French type), and C (benign type). Laboratory test results and clinical manifestations exhibit remarkable similarities among different types (7).

Type B is an early-onset progressive disorder with diverse symptoms such as vomiting, hypothermia, hypotonia, lethargy, and abnormal ocular movements. Patients' survival in almost all cases is below three months. In this case report, the authors aimed to report a girl with manifestations of Type B of PCD and longer survival.

Case Report

A two-year and four-month-old girl was admitted to 17 Shahrivar children's hospital with tachypnea and vomiting. She was the second child and was born full-term through natural vaginal delivery (Figure 1). Her parents were healthy and had a consanguineous marriage.

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The first child of the family was a full-term girl with normal growth and asymptomatic until four months who had sudden metabolic acidosis and died at eleven months.

Figure 1. The patient's picture

After first breastfeeding, the patient experienced respiratory distress and vomiting and also showed an upward gaze. She also had a five-second seizure after vaccination at two months without a post-ictal phase. She was hospitalized six times because of recurrent seizures, hypoglycemia, respiratory distress, and metabolic acidosis that needed dialysis. She had poor gross motor development, fine motor skills delay, and blurry vision immediately after the attack. Although she had poor motor development compared to her same-age children, it improved gradually. However, general biochemical tests, evaluation of blood and urine amino acids, and organic acids were performed to evaluate her metabolic status. Biochemical analysis revealed hypoglycemia and lactic aciduria. Blood and urine amino acids, urine ketone, and organic acids were in the normal range. Ultrasonography showed hepatomegaly (Table 1).

Table1. Amino acid analysis in urine (mmol/mol) and blood (µmol/L)

		Birth	2 Month
Aspartic Acid	Urine	3	6
	Blood	6	16
Histidine	Urine	3	69
	Blood	65	33
Glutamine	Urine	9	21
	Blood	75	110
Arginine	Urine	4	5
	Blood	69	30
Citruline	Urine	1	7
	Blood	23	15
Glycin	Urine	64	41
	Blood	380	247
Thereonine	Urine	8	223
	Blood	248	198
Alanine	Urine	18	166
	Blood	525	330
Tyrosin	Urine	3	12
	Blood	90	23
Tryptophan	Urine	1	4
	Blood	41	19
Methionine	Urine	2	5
	Blood	35	22
Valine	Urine	32	38
	Blood	144	131
Phenylalanine	Urine	2	11
	Blood	52	20
Isolucin	Urine	3	6
	Blood	46	33
Leucine	Urine	8	6
	Blood	108	63
Ornithine	Urine	8	11
	Blood	80	85
Lysin	Urine	48	56
	Blood	319	192
Aspargine	Urine	3	36
	Blood	43	14
Glutamine Acid	Urine	9	9
	Blood	75	118
Serin	Urine	44	128
	Blood	176	88

Whole exome sequencing (WES) identified a likely pathogenic homozygous variant according to ACMG guideline in PC gene, c.806G>A presented in protein level as p.Arg269Gln. Sanger sequencing was performed for the girl and her parents, and maternal and paternal grandmothers and grandfathers and confirmed the result of WES in the patient (homozygous form) and her parents (heterozygous form) (Figure 2). Finally, PCD type B was reported. DNA was extracted using the salting-out method. Direct sequencing of the target region surrounding position c.806 G>A in the PC gene is performed by the cardiogenetic research center. Using the PC gene NCBI reference sequence, the mutations were named NG_008319.t, NM_001040716, and NP_ 001035806.1. The current description of mutation was recommended by HGVs. At the time, the patient was alive and had poor gross motor development, fine motor skills delay, and blurry vision.

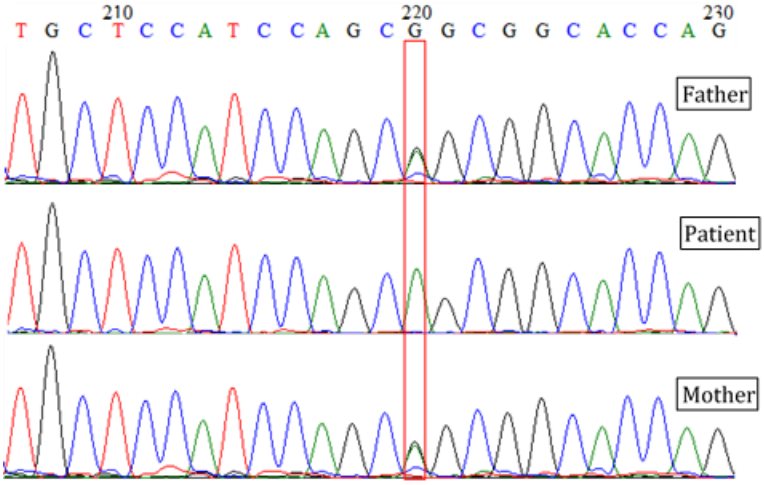

Figure 2. Electropherogram of the patient sequence and her parents

Discussion

Previous case reports revealed that the presentation of pyruvate carboxylic is different due to the time of early symptoms, clinical manifestations, laboratory findings, and life span. This case report also showed a girl with PCD who had normal laboratory findings and longer survival despite the expectation that PCD type B commonly presents with abnormal findings such as raised lactate/pyruvate ratio, reduced 3-hydroxybutyrate-to-acetoacetate ratio, changes in amino acid concentrations such as elevated levels of Citrulline, lysine, proline, and ammonia, and decreased concentration of glutamine (5).

Most of the neonates with the French type of PCD expires. In case of longer survival, the children remain severely hypotonic and unresponsive. They often die before the age of five months due to respiratory infection (5). Commonly death occurs in lower age groups (8-11), but a different case report mentioned that the life expectancy of these children increased to twenty years due to the probability of mosaicism. Based on Wang *et al.*, in 2008, it seems that patients with mosaicism have longer survival. They reported eight patients with PCD, of whom five were type B. Their results showed that among five patients with PCD type B, two were alive at nine and 20 years, respectively. Although they recommended that it would be valuable to check mosaicism in these patients, there is nothing about the patient's mosaicism status (12). Although the previous report mentioned more than a year as a unique case of pyruvate carboxylase deficiency (13), this patient is now three years old and has been hospitalized many times due to acute attacks, but it is interesting that, unlike the reported patients (10-14), patients gradually got better with occupational therapy.

Unlike other reports, this patient didn't have specific findings in MRI and lab tests. Hommes *et al.*, in 1968, presented the first case of PCD in a one-year-old patient after hepatic biopsy. They had neuropathological lesions' hallmark of subacute necrotizing encephalomyelopathy (SNE) (8).

Inconsistent with this study, Bartlett *et al.*, described a neonate with elevated urinary levels of citrulline, arginine, and lysine. Elevated levels of glycine, citrulline, alanine, leucine, tyrosine, lysine, and arginine were also reported. Urinary organic acid screening showed an

increased level of lactate and 3-hydroxybutyrate. The death occurred at about three months of age (9).

Moreover, Darryl *et al*., in 1977, reported a ten-month-old infant with severe lactic acidosis, increased blood lactate, pyruvate, 3-hydroxybutyrate, acetoacetate, alanine, proline, and glycine, decreased blood concentrations of glutamine, aspartate, valine, and citrate (10). Mochela *et al*., in 2005, reported a six-day-old girl with PCD type B who had presented with severe hepatic failure, dehydration, axial hypotonia, lactic acidosis, and ketoacidosis (11).

Age of presentation PC type B is different, but it almost always began in the early neonatal period, but even in the prenatal period was reported (15). In patients with PC there is a moderate increase of ammonia but it usually does not interfere in the management of these patients nevertheless ignored cause of hyperammonemia encephalopathy in pyruvate carboxylase deficiency was reported (15).

This patient had normal blood and urine organic acid and amino acids but she had hypoglycemia, ketone in the urine, elevated ammonia, and lactic acidosis. The authors assumed that probably the patient had normal amino acid and organic acids because of variable expressivity, but this hypothesis can be confirmed with further evaluation and studies.

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