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Neonatal Propionic Acidemia with Dyspnea as the First Manifestation: A Case Report

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Abstract

Propionic Acidemia (PA) is a disorder in organic acid metabolism resulting from a genetic defect in propionyl CoA carboxylase. Due to its inconspicuous clinical manifestations, misdiagnosis, missed diagnoses, and delayed treatment are prone to occur. Here, we present a case of a newborn infant with PA admitted to our hospital, exhibiting dyspnea as the initial manifestation. A 2-day-old newborn was admitted due to dyspnea and nasal congestion, presenting with physical examination findings of a high respiratory rate, lower blood oxygen saturation, and shortness of breath. Laboratory findings corroborated the presence of metabolic acidosis and increased ketone bodies in the urine. Additionally, blood tandem mass spectrometry showed raised levels of propionyl Carnitine (C3), while the urine organic acid test revealed a more than tenfold increase in the levels of 3-hydroxypropionic acid-2 and methyl citrate-4. Genetic analysis revealed compound heterozygous mutations in the *PCCB* gene: c.733G>A (p.G245S) and c.181C>T (p.R61X), which were inherited from the father and mother, respectively. Following several days of treatment, the baby was discharged from the hospital and exhibited normal growth and development until the age of 1 year. Clinicians should consider propionic acidemia in newborns presenting with unexplained shortness of breath, difficulty feeding, and uncorrectable metabolic acidosis. This report identifies new heterozygous mutations in the *PCCB* gene: c.733G>A (p.G245S) and c.181C>T (p.R61X).

Keywords: Propionic acidemia; Neonatal; Dyspnea; *PCCB* gene

Background

Propionic acidemia is an inherited disorder of organic acid metabolism resulting from a genetic defect in propionyl CoA carboxylase [1]. Due to its hidden clinical manifestations, it can easily lead to misdiagnosis, missed diagnosis, and delayed treatment. Disease progression can result in fatal outcomes or significant sequelae. In this case report, we present the admission of a newborn infant with propionic acidemia who initially exhibited dyspnea.

Case Presentation

A two-day-old infant girl presented to our hospital with respiratory distress and nasal congestion.

The newborn's medical history revealed a birth weight of 3,450 g, length of 51 cm, and head circumference of 42 cm. The gestational age was confirmed as 40 weeks. No family history of genetic conditions was reported.

In the physical examination, the patient presented with a respiratory rate of 66 breaths per minute. Additionally, the blood oxygen saturation level was found to be 88%. The lips exhibited cyanosis, and there was evidence of shortness of breath. Moreover, the patient displayed the inspiratory triple concave sign. No dry or wet rales were detected in the lungs during the examination. All other findings from the system examination were within normal limits.

In the laboratory evaluation, the Chest X-ray reveals a slight increase in bilateral lung markings. The routine blood test, CRP, liver and kidney functions, and electrolytes were all found to be within the normal range. However, the arterial blood gas analysis (samples was drawn after the patient was given oxygen) detected an abnormality, specifically metabolic acidosis (Table 1). Moreover, the urine analysis indicated an increase in ketone bodies.

During the clinical follow-up, sodium bicarbonate was administered to treat metabolic acidosis. This intervention temporarily relieved the patient's dyspnea, but the symptoms recurred

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Table 1: Result of arterial blood gas analysis.

	pH	PaO_2 (mmHg)	$PaCO_2$ (mmHg)	HCO_3^- (mmol/L)	BE (mmol/L)	AG (mmol/L)	Lac (mmol/L)
On admission	7.24	135	16	6.9	-20.5	34	1.2
Treated with sodium bicarbonate	7.20~7.38	84~106	16~19	7.4~9.5	-15.6~-20.6	24~27	1.0~1.9
Treated with low dose insulin	7.39~7.46	83~90	18~30	12.8~19	-5.5~-9.3	17~19	1.3~2.9
Before discharge	7.39	94	35	19.4	-5.6	12	1.2

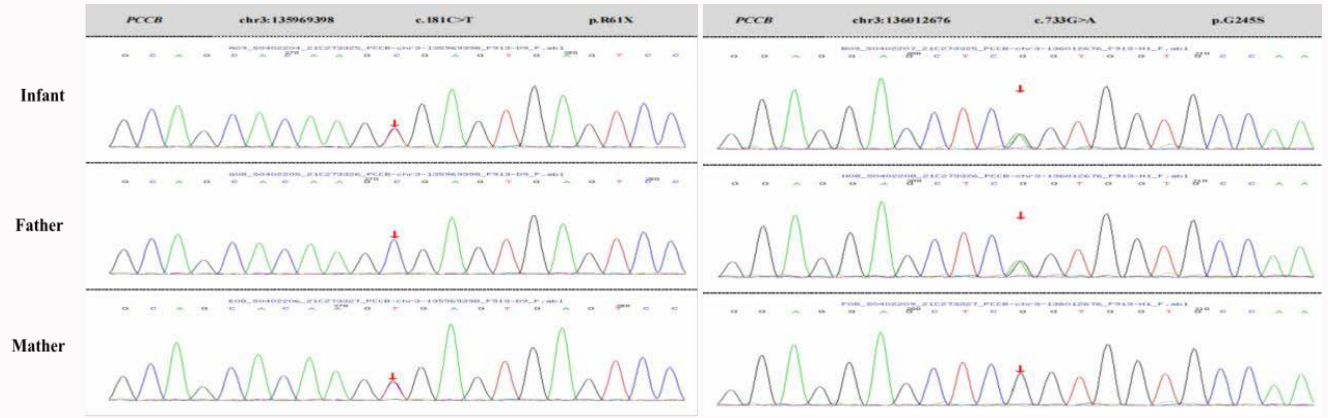

Figure 1: The DNA sequencing results from PCCB.

Table 2: Result of blood tandem mass spectrometry and urine organic acid.

Specimen	Items	Result	Normal range	
Blood	propionyl carnitine (C3)	7.91	0.40-5.00	↑
	acetylcarnitine (C2)	7.54	5.00-55.00	
	C3/C2	1.05	0.03-0.20	↑
Urine	3-hydroxypropionic acid-2	43.5	0.0-4.0	↑
	methylcitrate - 4(1)	63.1	0.0-0.7	↑
	methylcitrate-4(2)	27.7	0.0-0.8	↑

later. Based on these observations, a congenital abnormality in organic acid metabolism was suspected. Low-dose insulin (0.1 U/kg/h) was then initiated along with continuous infusion of glucose solution. After an additional 12 h of treatment, the patient's dyspnea resolved, and arterial blood gas analysis and urine ketone levels returned to normal. Tandem mass spectrometry of the serum (the sample drawn on admission) revealed an increase in propionyl Carnitine (C3), while the urine organic acid test indicated a more than tenfold increase in 3-hydroxypropionic acid and methyl citrate [1] (Table 2). Furthermore, whole exome sequencing of the patient's blood (KingMed Diagnostics Group, Guangzhou, China) identified compound heterozygous mutations in the *PCCB* gene: c.733G>A (p.G245S) inherited from the father and c.181C>T (p.R61X) inherited from the mother (Figure 1). Importantly, the c.733G>A mutation has been previously reported as pathogenic [2], while the c.181C>T mutation is being reported for the first time in this study. These results indicate that the proband's healthy parents are carriers of the mutated gene. After several days of treatment, the baby was discharged from the hospital and has since shown normal growth and development up to 1 year of age.

Discussion

Propionic acidemia is an inherited metabolic disorder caused by a deficiency of the mitochondrial enzyme Propionyl-CoA Carboxylase (PCC), which hinders the conversion of propionic acid into methylpropionyl CoA. Dysfunctions of PCC cause propionyl-CoA accumulation in the body and produce abnormal precursors by activating the bypass metabolic pathway. Abnormal metabolites can cause clinical symptoms and eventually lead to organ damage. Therefore, early diagnosis and treatment are particularly important for genetic diseases.

The clinical presentation of propionic acidemia varies from neonatal-onset to late-onset disease, depending on when the initial symptoms manifest [3,4]. Neonatal-onset propionic acidemia is the most common form and is characterized by poor feeding, vomiting, lethargy, and hypotonia, accompanied by metabolic acidosis. In this particular case, the first symptoms appeared two days after birth, presenting as dyspnea. Dyspnea often occurs in respiratory diseases, making it easy to misdiagnose. However, considering the course of the disease, dyspnea can be seen as a respiratory compensation for severe metabolic acidosis in the body. Therefore, if a patient exhibits unexplained shortness of breath, difficulty feeding, and uncorrectable metabolic acidosis, clinicians should be alert to the possibility of propionic acidemia.

Currently, the management of PA primarily emphasizes symptomatic support. Clinical recommendations involve limiting protein intake, supplementing biotin and carbohydrates, as well as administering fluid infusion to correct acidosis [5]. It is worth noting that patients with PA exhibit non-diabetic ketoacidosis. The infant was treated with a combination of low-dose insulin and a continuous infusion of 5% glucose solution. The treatment effect is significant since the combination of sugar and insulin reduces the concentration of free fatty acids in the blood, promotes amino acid intake, protein synthesis, and sugar utilization. However, it is crucial to carefully adjust the optimal ratio of sugar and insulin considering individual differences and to avoid iatrogenic hypoglycemic brain damage.

PCC is composed of α and β subunits, which form an α6β6

structure [6]. The α and β subunits are encoded by the PCCA and *PCCB* genes. Over 200 mutations have been reported in both the PCCA and *PCCB* genes [7]. In this study, two different mutations were identified in the *PCCB* gene: c.733G>A (p.G245S) and c.181C>T (p.R61X). The c.733G>A (p.G245S) mutation has been previously reported [2], while the c.181C>T (p.R61X) mutation is reported for the first time in this study. According to the American College of Medical Genetics and Genomics (ACMG), the c.181C>T (p.R61X) mutation is classified as pathogenic. A study cohort showed that PCCB was the main variant associated with neonatal screening-detected PA in Japan. Moreover, the study showed that 24% of the patients with PA exhibited symptoms within the first 2 days of life. The newborn with PA in this report also exhibited dyspnea as the initial symptom on the second day of life. Further verification is required to determine the pathogenicity of the c.181C>T (p.R61X) mutation and to explore genotype-phenotype correlations.

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