

Case Report

## A case of propionic acidemia during late infancy presenting with metabolic acidosis

### Geç infantil dönemde metabolik asidoz ile başvuran bir propiyonik asidemi olgusu

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#### ABSTRACT

Propionic acidemia is a disorder of amino acid metabolism caused by propionyl-CoA carboxylase deficiency, which results in the accumulation of propionic acid. It is inherited in an autosomal recessive manner, and its incidence has increased in areas like our country, Türkiye, where consanguineous marriages are common. During exacerbations, patients may demonstrate hyperammonemia, metabolic acidosis, and hyperglycinemia, as well as increased levels of methyl citrate, 3-OH propionate, and propionylglycine. While the disease may have an asymptomatic course, it may present with poor feeding, failure to thrive, lethargy, and seizures. A sixteen-month-old male patient had been admitted to the emergency department with vomiting, hyperpnea, and impaired consciousness and was then referred to us after the detection of severe metabolic acidosis with the suspicion of metabolic diseases. He had a Glasgow coma scale of five and was intubated. He was taught to be fed eggs on his last meal for the first time two hours before the onset of complaints. His parents were fourth-degree relatives. On-admission blood gas analysis revealed the following: pH: 6.88, pCO<sub>2</sub>: 20.2 mmHg, HCO<sub>3</sub>: 3.8 mmol/L, cBE: -29.4 mmol/L, lactate: 1.3 mmol/L, with urinary ketone: +++, ammonia: 130 umol/L. With the detection of metabolic acidosis with an increased anion gap, ketonuria, and mild hyperammonemia, a preliminary diagnosis of metabolic disorder was considered, and oral nutrition was discontinued. He was consulted by the Department of Pediatric Metabolic Diseases, and treatment with carnitine, biotin, hydroxycobalamin, high-dose dextrose, insulin, and sodium benzoate was initiated. Since the patient's acidosis was refractory, hemodialysis was initiated. Work-ups obtained at 24 hours of hemodialysis were as follows: pH: 7.35, pO<sub>2</sub>: 29.6 mmHg, pCO<sub>2</sub>: 37.5 mmHg, HCO<sub>3</sub>: 20.9 mmol/L, and ammonia: 22 umol/L. The patient's metabolic testing was consistent with propionic acidemia. Treatment with a protein-restricted diet (1 g/kg/day), L-carnitine (100 mg/kg/day), and biotin (10 mg/day) was recommended. Metabolic disorders should be considered in the differential diagnosis of patients with refractory metabolic acidosis.

**Keywords:** Hemodialysis, infant, metabolic acidosis, propionic acidemia

#### ÖZET

Propiyonik asidemi propiyonil KoA karboksilaz enzim eksikliği sonucu propiyonik asit birikimine sebep olan aminoasit metabolizma hastalığıdır. Otozomal resesif geçişli olup ülkemiz gibi akraba evliliğin sık görüldüğü bölgelerde insidansı artmıştır. Hastaların atak esnasındaki tahlillerinde hiperamonyemi, metabolik asidoz, hiperglisinemi, metil sitrat, 3-OH propionat ve propionil glisin artmış görülebilir. Hastalık asemptomatik olabileceği gibi kötü beslenme, büyüme gelişme geriliği, letarji ve konvülsiyon ile kendini gösterebilir. On altı aylık erkek

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hasta kusma, derin nefes alıp verme, şuur bulanıklığı şikayetleri ile acil servise başvurmuş ve tetkiklerinde ağır metabolik asidoz saptanması üzerine tarafımıza sevk edildi. Glasgow koma skalası beş olan hasta entübe edildi. Şikayetlerinin başlamasından iki saat önce ilk kez son öğününde yumurta ile beslendiği öğrenildi. Anne baba ile dördüncü dereceden akrabaydı. Başvuru sırasında bakılan kan gazı incelemesinde şunlar saptandı: pH: 6.88 pCO<sub>2</sub>: 20.2 mmHg HCO<sub>3</sub>: 3.8 mmol/L, cBE: -29.4 mmol/l, laktat: 1.3mmol/l, idrar ketonu: +++ , amonyak: 130 umol/L idi. Artmış anyon açıklı metabolik asidoz, ketonüri, hafif hiperamonyemi olması üzerine metabolik hastalık ön tanısı düşünüldü ve hastanın beslenmesi kesildi. Çocuk Metabolizma Hastalıkları uzmanına danışılarak karnitin, biyotin, hidroksikobalamin, yüksek dekstroz ve insülin tedavisi ve sodyum benzoat tedavileri başlandı. Hastanın asidozu dirençli seyredince, hemodiyalize uygulandı. Hemodiyaliz yirmi dördüncü saatinde pH: 7.35 pO<sub>2</sub>: 29.6 mmHg pCO<sub>2</sub>: 37.5 mmHg HCO<sub>3</sub>:20.9 mmol/L, amonyak: 22 umol/L izlendi. Hastanın metabolik tetkikleri propiyonik asidemi ile uyumlu bulundu. Proteinden fakir diyet (1g/kg/gün), L-karnitin (100 mg/kg/gün), biyotin (10 mg/gün) tedavileri önerildi. Dirençli metabolik asidozu olan hastaların ayırıcı tanısında metabolik bozukluklar göz önünde bulundurulmalıdır.

**Keywords:** Hemodiyaliz, Infant, Metabolik asidoz, Propiyonik asidemi

## INTRODUCTION

Propionic acid is an intermediate metabolite of isoleucine, valine, threonine, methionine, single-chain fatty acids, and cholesterol metabolisms. It is also synthesized by intestinal bacteria. At a biotin-dependent step, propionic acid is carboxylated to methylmalonic acid by propionyl-CoA carboxylase. This enzyme has two components: alpha and beta. The alpha component is biotin-dependent. There may be mutations in chromosomes where these two chains are mapped. The severity of the clinical presentation is determined by these mutations. While the disease becomes symptomatic more commonly during the neonatal period, it may also exhibit an asymptomatic course for a long time. The disease presents with difficulty feeding, vomiting, lethargy, hypotonia, seizures, and encephalopathy during the neonatal period, whereas it presents with poor feeding, failure to thrive, loss of percentile, and retarded neuromotor development. Symptoms may occur with intercurrent infections, switching to supplementary foods, or the integration of new food into nutrition (1). Herein, we report a sixteen-month-old infant admitted to the emergency department with tachypnea and somnolence, severe metabolic acidosis, and a diagnosis of propionic acidemia.

## CASE REPORT

A sixteen-month-old male patient without known disease had been admitted to the emergency department with vomiting, tachypnea, and impaired consciousness and was then referred to us after the detection of severe metabolic acidosis. Due to metabolic acidosis and respiratory failure, the patient was intubated and then admitted to the pediatric intensive care unit. His physical examination revealed a capillary refilling time of 3–4 seconds. The lung auscultation was normal. The apical heart rate was 120 bpm, rhythmic, with no additional sounds or murmurs. Abdominal examination re-

vealed no organomegaly. The patient's blood gas analysis showed severe metabolic acidosis (pH: 6.88, pCO<sub>2</sub>: 20.2 mmHg, HCO<sub>3</sub>: 3.8 mmol/L, cBase: -29.4 mmol/l, and lactate: 1.3 mmol/l). A complete blood count and liver and kidney function tests were normal. Urinary ketone was 3+, and ammonia was found to be 130 umol/L.

The patient infant had been breastfeeding, and vegetable soups were given as supplementary foods. He was given eggs for the first time in the morning. The parents were fourth-degree relatives, and the patient's neurological development was appropriate for his age. He had no history of deceased siblings. Due to the presence of parental consanguinity and the development of severe metabolic acidosis, ketonuria, and hyperammonemia following egg ingestion, a metabolic disease was suspected, and blood amino acid, urinary amino acid, organic acid panel, and tandem mass spectrometry testing were performed.

The patient was consulted by the department of pediatric metabolic diseases, after which treatment with carnitine, biotin, hydroxycobalamine, intravenous fluids with a high glucose infusion rate, insulin, and sodium benzoate was initiated. Since the metabolic acidosis was refractory, hemodialysis was performed. Metabolic acidosis and elevated ammonia levels were observed to regress after 36 hours of hemodialysis. Urinary organic acid results were as follows: methylmalonic acid 46 mg/g/creatinine (<15), lactic acid 2358 mg/g/creatinine (0-227), 3-Hydroxyisovaleric acid 647.8 mg/g/creatinine (0-69.9), tiglylglycine 9.7 mg/g/creatinine (<5), 3-Hydroxypropionic acid 346.5 mg/g/creatinine (0.79-28.67), and methylcitric acid 150.1 mg/g/creatinine (0-21.9). Tandem filter papers revealed the following: C3/C0 0.22 (n: 0-0.19), C5-DC (glutaryl) carnitine 0.41 umol/l (n: 0-0.21), and C4-OH (3-OH butyryl) carni-

tine 2.21  $\mu\text{mol/l}$  (0-0.48). The blood amino acid panel revealed the following: valine 541  $\mu\text{mol/L}$  (64–294), isoleucine 171  $\mu\text{mol/L}$  (31–86), and leucine 294  $\mu\text{mol/L}$  (47–155). According to these results, the patient had a diagnosis of propionic acidemia. He was extubated on post-admission day 3 and referred to a level-three hospital with a metabolic diseases service.

## DISCUSSION

Propionic acidemia is an autosomal recessive disorder of amino acid metabolism that leads to the accumulation of propionic acid due to a deficiency of propionyl-CoA carboxylase (4). The incidence of the disease is 1:100.000–150.000, and as the disease is inherited in an autosomal recessive manner, its incidence has increased in geographic areas where consanguineous marriages are common, like in our country (6–9). Propionic acidemia may be early-onset or late-onset. Early-onset cases become symptomatic within the first three months of life. About 80% of the patients become symptomatic during the neonatal period. During the neonatal period, patients have difficulty feeding, vomiting, lethargy, and seizures. Workups reveal severe metabolic acidosis, hyperammonemia, ketonuria, and lactic acidosis (8). The symptoms of late-onset disease vary; patients may present with neuromotor retardation, movement disorders, hypotonicity, intercurrent infections, and episodes of metabolic acidosis following nutritional changes (3). A case presenting with isolated cardiomyopathy without metabolic decompensation has been reported (5). Our case was admitted in the late-term with severe metabolic acidosis, hyperammonemia, and ketonuria following nutritional changes and was diagnosed with a urinary organic acid panel and tandem mass spectrometry. Laboratory testing reveals concurrent metabolic acidosis with an increased anion gap, ketosis, hyperammonemia, and elevated lactate levels. Urinary organic acid analysis demonstrates a characteristic metabolic excretion pattern, including 3-hydroxypropionic acid, propionylglycine, methylcitrate, and tiglylglycine. Lactic acid levels may be extremely elevated in samples obtained during an acute episode. A definitive diagnosis is made by demonstrating the enzyme deficiency and/or molecular analysis. Propionyl-CoA carboxylase activity in cultured fibroblasts and measurements of other carboxylases like 3-methylcrotonyl-CoA carboxylase and pyruvate carboxylase are used to exclude multiple carboxylase deficiency (2). Laboratory testing of our case revealed ketonuria in urinalysis and severe metabolic acidosis in blood gas analysis. Tandem mass spectrometry demon-

strated elevated C3 (propionyl)/C2 (acetyl) and C3 (propionyl)/C0 (free carnitine) ratios. Urinary organic acid analysis revealed above-normal levels of 3-hydroxypropionic acid, methylcitric acid, and lactic acid.

Treatment of acute episodes relies on the correction of hyperammonemia and acidosis, limiting the metabolism of propionate precursors by protein restriction, and fluid and glucose resuscitation. Biotin and carnitine are added to the treatment. Dialysis may be needed when hyperammonemia and metabolic acidosis are severe. Our case was hemodialyzed since he had metabolic acidosis that was refractory to medical treatment. Long-term treatment includes a protein-restricted diet fortified with a special formula. Treatment of our cases was ordered as follows: protein-restricted diet (1-2 g/kg/day), L-carnitine (100 mg/kg/day), and biotin (10 mg/day).

## CONCLUSION

Metabolic diseases should be considered in patients with refractory metabolic acidosis in countries like Türkiye, where the rate of consanguineous marriages is high.

### Patient Consent Form / Hasta Onam Formu

The parents' of this patient consent was obtained for this study.

### Conflict of Interest / Çıkar Çatışması

The authors declared no conflicts of interest with respect to authorship and/or publication of the article.

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## REFERENCES

1. aumgartner MR, Hörster F, Dionisi-Vici C, et al. Proposed guidelines for the diagnosis and management of methylmalonic and propionic acidemia. *Orphanet J Rare Dis* 2014; 9: 130.
2. Chalmers RA, Lawson AM. Disorders of propionate and methylmalonate metabolism. In: *Organic Acids in Man*. Springer, Dordrecht. 1982; 296–331.
3. Delgado C, Macías C, de la Sierra García-Valdecasas M, Pérez M, del Portal LR, Jiménez LM. Subacute presentation of propionic acidemia. *J Child Neurol*. 2007 Dec;22(12):1405-7.
4. Fenton WA, Gravel RA, Rosenblatt DS 2001. "Disorders of Propionate and Methylmalonate Metabolism. Scriver, CR, Beaudet, AL, Sly, WS, y Valle, D (Eds)." *The metabolic and molecular bases of inherited disease*.
5. Lee TM, Addonizio LJ, Barshop BA, et al. Unusual presentation of propionic acidemia as isolated cardiomyopathy. *J Inher*

- Metab Dis. 2009 Dec;32 Suppl 1(0 1):S97-101.
6. Ozand PT, Rashed M, Gascon GG, Youssef NG, Harfi H, Rahbeni Z, al Garawi S, al Aqeel A. Unusual presentations of propionic acidemia. *Brain Dev.* 1994 Nov;16 Suppl:46-57.
  7. Selim LA, Hassan SA, Salem F, et al. Selective screening for in-born errors of metabolism by tandem mass spectrometry in Egyptian children: a 5 year report. *Clin Biochem.* 2014 Jun;47(9):823-8.
  8. Shchelochkov OA, Carrillo N, Venditti C. Propionic Acidemia. 2012 May 17 [Updated 2016 Oct 6]. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. *GeneReviews*® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2024. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK92946/>
  9. Zayed H. Propionic acidemia in the Arab World. *Gene.* 2015 Jun 15;564(2):119-24.