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CASE REPORT – OPEN ACCESS



# Diarrhea Triggered by Breastfeeding: A Novel Variant Causing Congenital Lactase Deficiency

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ABSTRACT

**Background:** Congenital lactase deficiency (CLD) is a rare disorder that is characterized by severe osmotic diarrhea and malnutrition on the first day of birth. Clinical findings occur due to the defective digestion of the main carbohydrate, lactose, in breast milk. This autosomal recessive disorder is caused by variants in lactase-phlorizin hydrolase (LCT).

**Case Report:** We report the first genetically confirmed case of CLD in Türkiye. The patient suffered from watery diarrhea after breastfeeding, which ceased after feeding the formula containing lactose-free hydrolyzed cow's milk. The lactose challenge test demonstrated a lactose intolerance pattern. A novel homozygous variant was detected in LCT.

**Conclusion:** Although genetic analyses are important to highlight underlying etiologies of congenital diarrhea, it should be remembered that clinical findings of patients, fecal characteristics, and the effects of dietary treatment are the primary and most important steps that lead to an accurate diagnosis.

**Keywords:** Congenital osmotic diarrhea, lactase deficiency, lactase-phlorizin hydrolase

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## INTRODUCTION

The major carbohydrate in breast milk is lactose (1). The lactase enzyme is present in the intestinal brush border and is required for the hydrolysis of lactose (1). The lactase-phlorizin hydrolase gene (LPH/LCT) is located on chromosome 2q21 (2). In patients with congenital lactase deficiency (CLD) (OMIM 223000), watery diarrhea and meteorism are seen in the first days of life after breastfeeding or consuming formula containing lactose (3). Diarrhea has osmotic characteristics and causes dehydration, acidosis, and malnutrition (4). Symptoms rapidly improve but patients grow and develop normally after the elimination of lactose from the diet (5). We report the first molecularly confirmed case of CLD in Türkiye.

## CASE REPORT

The patient was born at term with a birth weight of 3300 g from consanguineous parents. She was fed with breast milk after birth. At the age of 1 month, she was referred to our hospital due to diarrhea and failure to thrive. She had diarrhea without blood and mucus, which started on the third postnatal day and occurred 5–6 times a day. Physical examination revealed body weight to be 2800 g (-2.26 SDS), height 49.5 cm (-1.98 SDS), and head circumference 35 cm (-2.25 SDS). Her general condition was moderate. Skin turgor was reduced, and she looked cachectic and pale. Laboratory analyses at admission revealed metabolic acidosis. The patient's BUN was 34 mg/dL (0–10) and creatinine was 0.5 mg/dL (0.2–0.4 mg/dL). After treatment with intravenous fluids, metabolic acidosis and dehydration resolved but diarrhea continued. The sweat chloride level was normal. Stool microscopy and electrolyte concentrations were normal; stool adenovirus and rotavirus antigens were negative. Fecal pH was 5, osmotic gap was 222 mOsm/kg, and there was a high positive level of fecal reducing bodies. She was kept on a complete fast, and her diarrhea was dramatically resolved. A stool chromatogram detected a lactose stain. A diet consisting of lactose-free formula was initiated after which diarrhea did not reoccur. The patient was discharged with lactose-free formula. At the time of the sixth-month follow-up, her weight was 7 kg (-0.29 SDS), height 66 cm (0.08 SDS), and head circumference 42 cm (-0.48 SDS). At this time, a lactose-containing formula was given to the patient to identify whether lactose intolerance was primary or secondary. After the formula, the patient's diarrhea started again and became severe, and she developed metabolic acidosis. Genetic studies were performed after obtaining written informed consent from the parents. Sequencing analysis revealed a homozygous novel missense variant c.1729G>C (p.Ala577Pro) in LCT (NM_002299). The patient remained asymptomatic without any clinical findings and showed normal growth and development during the follow-ups while on a lactose-free diet.

## DISCUSSION

Diarrhea that starts in the neonatal period could rapidly lead to life-threatening dehydration and malnutrition. Therefore, early diagnosis and management of neonatal diarrhea are highly important (6). In neonatal osmotic diarrhea, nonabsorbable or poorly absorbed food results in fluid accumulation in the intestinal lumen, and diarrhea resolves significantly during fasting periods (6). In addition, the stool osmotic gap is high (>50 mOsm/kg), which indicates the presence of nonabsorbable substances. In this patient, the stool osmotic gap was high and diarrhea improved rapidly after oral intake was discontinued. For this reason, we thought that the present patient suffered from osmotic diarrhea. The most common cause of osmotic diarrhea is carbohydrate malabsorption characterized by positive reducing substances and acidic pH (5, 6) of the stool (7). The acidic pH observed in this patient supports the diagnosis of carbohydrate malabsorption. The patient was diagnosed with CLD because the main carbohydrate in the diet during infancy was lactose, and a lactose stain was detected in her stool chromatography. When lactose was added to her diet, diarrhea occurred, leading to metabolic acidosis and dehydration. Recurrence of diarrhea confirms the diagnosis of CLD.

A novel homozygous c.1729G>C (p.Ala577Pro) variant was identified in this study. This variant is located in the second domain of the protein, in the profragment, that plays a major role as an intramolecular chaperone in the initial folding of pro-LPH, such as the reported variants p.Gln268His and p.Ser688Pro (8). Identified p.Ala577Pro variant in LCT was considered to be responsible for the clinical findings of the present patient for several reasons. First, this variant was not reported in the GnomAD or G1000 databases and was predicted as damaging by several in silico prediction tools including SIFT, REVEL, and MutationTaster. Second, this variant affects a position highly conserved in other organisms and replaces alanine for a proline which would significantly change the secondary structure and the stability of the protein (9). Nevertheless, determining the precise role of the identified p.Ala577Pro substitution will require further functional analyses. CLD cases have been previously reported in Turkish patients residing in Europe (10). When the literature was searched for CLD cases (via PubMed or OMIM), it was seen that no previous cases were reported in Türkiye. For this reason, we believe our case is the first genetically confirmed CLD patient reported in Türkiye.

## CONCLUSION

Although genetic analyses are important to highlight underlying etiologies of congenital diarrhea, it should be remembered that clinical findings of patients, fecal characteristics, and the effects of dietary treatment are the primary and most important steps that lead to an accurate diagnosis.

**Informed Consent:** Written, informed consent was obtained from the patient's family for the publication of this case report and the accompanying images.

**Peer-review:** Externally peer-reviewed.

**Author Contributions:** Concept – FÖH; Design – FÖH, GŞ; Data Collection and/or Processing – FÖH; Analysis and/or Interpretation – FÖH, GŞ; Literature Search – FÖH, GŞ; Writing – FÖH; Critical Reviews – FÖH, GŞ.

**Conflict of Interest:** The authors have no conflict of interest to declare.

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