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Title: Diarrhea triggered by breastfeeding; a novel variant causing congenital lactase deficiency

Running Title: Diarrhea triggered by breastfeeding due to 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 life. 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 LCT (Lactase phlorizin hydrolase).

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

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

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

Introduction

The major carbohydrate in breast milk is lactose (1). Lactase enzyme is present in the intestinal brush border and is required for the hydrolysis of lactose (1). Lactase phlorizin hydrolase gene (LPH/LCT) is located on chromosome 2q21 (2). In patients with 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 an osmotic character and causes dehydration, acidosis, and malnutrition (4). Symptoms rapidly improve and patients grow and develop normally after the elimination of lactose from the diet (5). We report the first molecularly confirmed case of CLD from Turkey.

Case Report

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The patient was born at term with a birth weight of 3300g from consanguineous parents. She was started to feed with breast milk after birth. At the age of one month, she was referred to our hospital due to diarrhea and failure to thrive. She had diarrhea without blood and mucus, that started at the third postnatal day, and occurred 5 to 6 times a day. Physical examination revealed body weight to be 2800 grams (-2.26 SDS), height 49.5 cm (-1.98 SDS), and head circumference to be 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. Patients’s BUN was 34 mg/ dL (0-10), creatinine was 0.5 mg/dL (0.2-0.4 mg/dL). After treatment with intravenous fluids, metabolic acidosis and dehydration were resolved while diarrhea continued. Sweat chloride level was normal. Stool microscopy and electrolyte concentrations were normal; stool adeno virüs 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. Stool chromatogram detected a lactose stain. A diet consisting of lactose-free formula was initiated and diarrhea did not reoccur. Patient was discharged with lactose-free formula. At the time of the 6th 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 define whether lactose intolerance was primary or secondary. After the formula, the patient’s diarrhea started again, so severe that she had 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 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 the neonatal osmotic diarrhea, nonabsorbable or poorly absorbed food results in fluid accumulation in the intestinal lumen, and diarrhea resolves significantly during fasting periods (6). Additionally, the stool osmotic gap is high (>50mOsm/kg) which indicates...
presence of non-absorbable substances. In this patient, 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 with positive reducing substances and acidic pH (5-6) of the stool (7). Acidic pH observed in this patient supports the diagnosis of a carbohydrate malabsorption. The present patient was diagnosed with CLD because the main carbohydrate in the diet during infancy is lactose and lactose stain was detected in her stool chromatography. Additionally, when lactose was added to her diet, diarrhea occurred leading to metabolic acidosis and dehydration. Recurrence of diarrhea supports 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 from Turkey. For this reason, we believe our case is the first genetically confirmed CLD patient reported from Turkey.

In conclusion, although genetic analyses are important to enlighten underlying etiologies of congenital diarrhea, it should be kept in mind that clinical findings of patients, fecal characteristics and the effects of dietary treatment is the primary and most important steps that lead to accurate diagnosis.

Consent: Informed consent was taken from the family to publish this case.

Conflict of Interest: There is no conflict of interest.

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