**DGAT1 mutation in two sisters with failure to thrive: a case report**

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**ABSTRACT**

Congenital diarrhea and enteropathies (CODEs) are a group of monogenic disorders that have been described in recent years. Within the CODEs, the mutation in the diacylglycerol O-acyltransferase 1 (DGAT1) gene is a rare enzyme disorder associated with severe, early-onset chronic diarrhea.

Our objective is to describe the case of 2 sisters who consulted for chronic diarrhea, growth retardation, vomiting, and hypoalbuminemia in early childhood. A compound heterozygous DGAT1 mutation was found in both patients. This mutation was previously described in the Asian population; however, these are the first 2 patients to show this mutation in the Latin American population. These 2 cases may expand our knowledge about congenital diarrhea in general and the clinical characteristics of patients with DGAT1 mutations in particular.

**Keywords:** mutation, diacylglycerol O-acyltransferase/genetics, diarrhea/congenital, malnutrition, growth failure.

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INTRODUCTION

Diarrhea is one of the main reasons for consultation in pediatrics. In recent years, with the advent of genome sequencing, a new group of chronic diarrheas has been identified: congenital diarrhea and enteropathies (CODEs). They are classified into 5 groups (Table 1). Group 2 includes an enzyme called diacylglycerol O-acyltransferase 1 (DGAT1). The mutation in the DGAT1 gene causes severe chronic diarrhea, which develops mainly in the neonatal period or within 2 months after birth. The objective of this study is to describe the case of 2 sisters who consulted for chronic diarrhea and growth retardation, in whom a mutation in the gene encoding for the DGAT1 enzyme was diagnosed. These are the first 2 patients found to have this mutation in Latin America.

CASE REPORT 1

Female term newborn infant born at 38 weeks of gestation with a birth weight of 3410 g and a height of 50 cm seen at 4 months old due to growth retardation. She was not vomiting, but although she had only 1 bowel movement per day, her stools were very liquid. She was fed with baby formula and had an adequate calorie intake, but she was not gaining weight. Her physical examination showed that she was severely malnourished: weight of 4.340 kg (Z-score: -2.9), height of 59.5 cm (3rd percentile, Z-score: -2), and normal head circumference for age.

The initial laboratory tests indicated anemia, thrombocytosis, hypoalbuminemia, and hypogammaglobulinemia.

The initial studies, which included abdominal ultrasound, echocardiogram, 2 sweat tests, and a molecular test for mutation in the cystic fibrosis

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Table 1. Congenital diarrhea and enteropathies (CODEs)

| Group 1. Epithelial nutrient/electrolyte transport | Congenital chloride diarrhea | Congenital sodium diarrhea | Glucose-galactose malabsorption | Bile acid diarrhea | Acrodermatitis enteropathica |
| Group 2. Epithelial enzymes and metabolism | Congenital lactase deficiency | Sucrase-isomaltase deficiency | Disaccharidase deficiency | Trehalase deficiency | Enterokinase deficiency | DGAT1 deficiency | PLVAP deficiency | Abetalipoproteinemia | Hypobetalipoproteinemia | Chylomicron retention disease | Dyskeratosis congenita | Kabuki syndrome |
| Group 3. Epithelial trafficking and polarity | Microvillus inclusion disease | Congenital tufting enteropathy | Congenital sodium diarrhea | Trichohepatoenteric syndrome 1 | Trichohepatoenteric syndrome 2 | Familial hemaphagocytic lymphohistiocytosis | TTC7A deficiency |
| Group 4. Enteroendocrine cell dysfunction | Enteric anendocrinosis | X-linked lissencephaly | Proprotein convertase 1/3 deficiency | Mitchell-Riley syndrome |
| Group 5. Immune dysregulation | IPEX syndrome | ICOS deficiency |

transmembrane conductance regulator gene, did not reveal any positive findings. The stool tests were negative for viruses, bacteria, and parasites; an increased alpha-1-antitrypsin clearance level suggested protein-losing enteropathy.

An immunological evaluation showed decreased immunoglobulin G and a normal lymphocyte count (secondary to protein-losing enteropathy).

Based on previous findings, an upper endoscopy and a colonoscopy with biopsy were performed, which showed moderate grade II enteropathy, mild chronic inactive gastritis, and non-specific colitis with increased eosinophil levels.

Due to poor weight gain with extensively hydrolyzed formula and suspected eosinophilic colitis, the patient was started on methylprednisolone at 2 mg/kg/day. She did not respond to treatment, so a second upper endoscopy was performed, which was suggestive of congenital tufting enteropathy. However, the molecular tests for the EPCAM gene associated with this disease did not show any mutation.

The patient was fed with extensively hydrolyzed formula but did not gain weight despite adequate calorie intake, so she was started on parenteral nutrition. She remained hospitalized for a year with slow nutritional recovery and was discharged without a clear diagnosis.

CASE REPORT 2

Two years later, her younger sister consulted due to similar symptoms. She was a term newborn infant born at 38 weeks of gestation with a birth weight of 3200 g and a height of 49 cm. At 2 months of age, she started with vomiting, watery diarrhea (1 bowel movement per day), and growth retardation. Her physical examination showed that she had mild dehydration and was severely malnourished: weight upon admission of 3.580 kg (Z-score: -3.3), height of 56 cm (3rd percentile, -10), and normal head circumference for age.

Like her sister, she had anemia, thrombocytosis, hypoalbuminemia, and hypogammaglobulinemia. The same ancillary tests were performed; all results were normal. The results of an upper endoscopy and a colonoscopy were non-specific (mild enteropathy, chronic inactive gastritis, and colonic mucosa with edema).

The patient did not gain weight despite adequate calorie intake with extensively hydrolyzed formula, which she received from the beginning of hospitalization, so parenteral nutrition was started.

Since the patient had the same symptoms as her elder sister, a full congenital diarrhea panel was requested. The analysis showed 2 heterozygous mutations in the gene encoding the DGAT1 enzyme: c.838C>T (p.Arg280*), classified as pathogenic, and c.1162C>T (p.His388Tyr), classified as probably pathogenic according to the American College of Medical Genetics and Genomics.

Based on these findings, direct sequencing of exomes 9 and 15 of the DGAT1 gene from both parents and the elder sister was performed, with the following results:

- Mother: heterozygous variant c.1162C>T (p.His388Tyr) and absence of variant c.838C>T (p.Arg280*).
- Father: heterozygous variant c.838C>T (p.Arg280*) and absence of variant c.1162C>T (p.His388Tyr).

Based on these findings, a diagnosis of congenital diarrhea secondary to DGAT1 deficiency was made and genetic counseling was provided to the parents. As a result, both girls received a fat-restricted diet (carbohydrates, such as rice, lean meat, and vegetables), and their nutritional status improved.

Parenteral nutrition was subsequently discontinued in both patients and they maintained an adequate weight gain. The elder sister is currently 3 years and 7 months old, with a weight of 15.1 kg (25th–50th percentile), a height of 100.5 cm (70th percentile), and a weight for height of 92%; while the younger sister is 1 year and 6 months old, with a weight of 9.530 kg (50th–75th percentile), a height of 80.5 cm (25th–50th percentile), and a weight for height of 92.6% (Figure 1).

DISCUSSION

CODEs are rare but severe causes of chronic diarrhea in children. In recent years, due to advances in genome sequencing, many monogenic disorders have been identified, including DGAT1 deficiency. The gene is on human chromosome 8 and encodes for the DGAT enzyme. It is responsible for catalyzing the final step in triglyceride synthesis, using diacylglycerol and fatty acyl-CoA. Despite several studies suggest that DGAT1 deficiency increases sensitivity to lipid-induced toxicity and apoptosis of the intestinal epithelial cells resulting
in protein-losing enteropathy, the cause of diarrhea remains unknown.

To date, no genotype-phenotype correlation has been identified, as the outcome varies from complete resolution of gastrointestinal symptoms to a lethal disease course. Patients with DGAT1 deficiency may have different clinical manifestations: protein-losing enteropathy, vomiting and/or diarrhea, fat intolerance, and growth retardation. In addition, according to previous reports, it may cause early-onset, chronic, intractable diarrhea leading to intestinal failure.

Vomiting is another important symptom, reported in most patients. A probable explanation for this symptom would be that DGAT1 deficiency inhibits chylomicron secretion and delays gastric emptying.

As mentioned above, our patients had hypoalbuminemia and hypogammaglobulinemia; however, unlike previous reports, their triglyceride levels were normal.

Different mutations in the DGAT1 gene have been described, mostly homozygous and in individuals of Asian or Ashkenazi Jewish ancestry.

**Figure 1.** Girls chart for weight-for-age from birth to 5 years. Child growth standards published by the World Health Organization (WHO)

![Patient 1](https://www.who.int/tools/child-growth-standards/standards/weight-for-age)

![Patient 2](https://www.who.int/tools/child-growth-standards/standards/weight-for-age)

Source: [https://www.who.int/tools/child-growth-standards/standards/weight-for-age](https://www.who.int/tools/child-growth-standards/standards/weight-for-age)
Two variants were found in different coding regions (exons 5 and 9), one of which had not been previously reported. The first variant, NM_012079.6:c.838C>T, results in a stop codon leading to loss of function, a known disease mechanism for this gene. This variant was reported as a disease-causing mutation in ClinVar (last accessed on August 19th, 2021).

The second variant, c.1162C>T in DGAT1, is a missense mutation that produces an amino acid change in the region of the MBOAT family where other mutations have previously been reported. Although this mutation has not been reported in other patients, correlation and segregation clinical trials support its pathogenicity.

The management of this disease consists of a fat-restricted diet, along with the administration of short-chain fatty acids, which has proven to be a good dietary complement for some patients. Both our patients showed excellent improvement after the initiation of the diet.

CONCLUSION
This study describes the cases of 2 sisters with heterozygous mutations in the DGAT1 gene that manifested as growth retardation and diarrhea. To our knowledge, these are the first 2 patients with this diagnosis in Latin America. These cases allow us to expand our knowledge about congenital diarrhea in general and about DGAT1 deficiency in particular. Given the potentially severe course of this disease, pediatricians should consider this condition in young infants with chronic diarrhea and growth retardation after other more common causes have been ruled out.

REFERENCES