# Chronic Congenital Diarrhoea Linked to DGAT 1 Mutation

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## ABSTRACT

Chronic diarrhoea causes morbidity and mortality in low-income countries in the paediatric population. There are many causes of chronic diarrhoea, including diacylglycerol o-acyltransferase 1 (DGAT1) deficiency, an enzyme deficiency, caused by the DGAT1 gene mutation, that leads to accumulation of DGAT1 lipid substrates, fatty acids and diacylglycerol, causing vomiting and chronic diarrhoea, and potentially more severe effects. In this case, a 2-year-old toddler presented in distress and prolonged diarrhoea progressing to multi-organ dysfunction requiring paediatric intensive care unit (PICU) admission. All work-ups for common causes of chronic diarrhoea were negative. However, the DGAT1 gene mutation was positive, prompting management through dietary fat control.

**Key Words:** *DGAT1 deficiency, DGAT1 gene mutation, Chronic diarrhoea.*

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## INTRODUCTION

Diarrhoea is one of the top four causes of hospital admissions in low-income countries, a subset of which lands into the paediatric intensive care unit (PICU) due to complications.[1]

Chronic diarrhoea can have multifactorial causes, including infectious, post-infectious, and allergic causes. Anatomical causes, like gastroschisis, necrotizing enterocolitis (NEC), and volvulus causing short-bowel syndrome also result in chronic diarrhoea.[2] A sub-set of chronic diarrhoeas, labelled as congenital diarrhoea and enteropathies (CODE), has severe clinical manifestations that usually present with diarrhoea after birth or during early infancy.[2,3]

Congenital diarrhoeas and heterogeneous enteropathies often have a lengthy evaluation process with only a sub-set of cases reaching a definitive diagnosis.[4,5] Often, these cases require significant and extensive interventions with customised diet plans and parenteral nutritional support to achieve appropriate growth and nutritional targets.[6]

Many children suffering from congenital diarrheal disorders also suffer from other pathologies related to enzyme deficiencies, exocrine pancreatic failure or lipid transport.[6] One of those enzyme disorders causing chronic diarrhoea is diacylglycerol o-acyltransferase 1 (DGAT1) deficiency, expressed in small gut and adrenal glands.[4] This isoenzyme catalyses the final stage of triglyceride synthesis by using diacylglycerol (DAG) and fatty acyl CoA.[6,7]

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Recent studies link DGAT1 gene mutation to chronic infantile diarrhoea.[5-8] We hereby report a case of a toddler who presented to the emergency room with chronic diarrhoea and developed multi-organ dysfunction, who was later diagnosed with a homozygous DGAT1 gene mutation.

## CASE REPORT

A 2-year-old toddler was admitted to the emergency room (ER) with a two-day history of fever and diarrhoea. His previous history was significant for multiple visits for diarrhoea, weight loss, and gross developmental delay, for which he had been empirically treated by dietary modifications and physiotherapy for motor delay without any resolution.

On examination, his weight was 10.8 kg ($5^{th}$ centile, z score -1.6), and height 90 cm ($50^{th}$ centile, z score 0). He was pale and only responding to verbal commands on alert, verbally responsive, pain responsive, Unresponsive (AVPU) scale. He had severe respiratory distress with subcostal and intercostal recessions, as well as cardiac dysfunction. He was started on ionotropic infusion, non-invasive respiratory support, broad-spectrum antibiotics, intravenous fluids, and transfused packed red cells to optimise tissue oxygen delivery. He was intubated later on and admitted to the PICU with the diagnosis of septic shock with multi-organ failure.

The previous workup was negative for cystic fibrosis and celiac disease. His baseline workup during the current illness revealed macrocytic anaemia (haemoglobin: 4.9 g/dL), low vitamin B12 levels (92 pg/mL), low faecal elastase (77 ug/mL), high anion-gap metabolic acidosis with high lactate (4.7 mmol/L), and transaminitis (ALT 111 IU/L; AST 73 IU/L). Cerebrospinal fluid (CSF) analysis and non-contrast CT scan head were unremarkable. Magnetic Resonance Imaging (MRI) of the brain suggested global hypoxic ischaemia.

Echocardiography revealed severely reduced left ventricular function with an ejection fraction of 25%, for which inotropic medicines were started. Chest radiograph showed bilateral multiple areas of patchy infiltrates as well as zones of atelectasis. The blood culture was positive for multi-drug resistant *Salmonella typhi*. Repeat culture and tracheal culture grew *Escherichia Coli (E. coli)*, for which appropriate antibiotics were added.

During PICU admission, he developed critical illness myopathy with a high serum creatinine phosphokinase (CPK) level (271 IU/litre) prompting genetic workup. His DNA sequence analysis and deletion/duplication testing revealed homozygosity for DGAT1 gene mutation. He was started on fat-free diet that resulted in resolution of the diarrheal symptoms.

Repeat echocardiography showed improvement in left ventricular function and ejection fraction. He was treated with intravenous vitamin B12 for anaemia. Ventilator support was weaned gradually. He was extubated in PICU with the intent of comfort care as per the family decision.

A few days after his discharge from the hospital, he was brought to the emergency in a gasping state, where end-of-life care was provided for his terminal illness.

## DISCUSSION

Diarrhoeas presenting in late infancy are commonly caused by infections, cow's milk protein allergies, or food protein–induced enterocolitis.[2] DGAT1 deficiency should be considered during evaluation. The mechanism of human DGAT1 deficiency-induced diarrhoea is unclear, but it potentially causes DGAT1 lipid substrates to build-up in the intestinal mucosa or lumen. Excess diacylglycerols or fatty acids become toxic to the enterocytes, leading to malnutrition.[3,9]Clinical manifestations include repeated vomiting and body oedema caused by hypoalbuminemia.[6]

The patient in this case presented with severe diarrhoea starting in early infancy, a common presentation in the majority of cases.[2,3,9] He had failed to thrive with repeated hospital visits that progressed to multi-organ dysfunction due to malnutrition and depletion of immunoglobulins and lymphocytes, leading to infections.

Patients usually have high alpha-1 anti-trypsin levels, hypertriglyceridemia, low serum albumin, normal faecal elastase, and normal histopathology of the small intestine.[4]

Unlike other reported cases, this patient had gross developmental delay without relevant history, supported by MRI findings of global hypoxic ischaemia. Our patient had a low faecal elastase level, pointing towards severe pancreatic enzyme insufficiency that is not explained by the DGAT1 deficiency. One possible explanation could be diluted and reduced levels in high-volume chronic diarrhoea.[2]

Currently, DGAT activity cannot be restored by therapy, so the main objective for management is reduced fat intake. Results have shown significant improvement on a low-fat or fat-free diet, resulting in the normalisation of serum immunoglobulin G and total protein levels. These patients can tolerate small amounts of fat spread throughout the day.

Patients with DGAT1 deficiency should be monitored by measuring levels of fat-soluble vitamins, serum triglycerides, complete blood counts, immunoglobulin G, total protein levels, and stool antitrypsin-1 levels.[3]

The prognosis is dependent on the percentage of enzyme activity in each patient.[3] Although there is no definitive treatment for the disease, reports suggest that some patients tolerated fat-containing diet that comprised <10% of their total caloric intake.[9] However, many patients still need to be provided with essential fatty acids through lipid emulsion infusion.[6]

In conclusion, undiagnosed chronic diarrhoea is frequently encountered, especially in low-income countries. If the clinical features and investigations are consistent with enteral protein loss, rare causes like DGAT1 mutation causing deficiency of the enzyme should be considered in the differential diagnosis.

**PATIENT'S CONSENT:**
Informed consent has been obtained from the patient's parents to publish the case.

**COMPETING INTEREST:**
The authors declared no competing interest.

**AUTHORS' CONTRIBUTION:**
QA, DA, AA: Conceived the idea.
UFZ, AA: Contributed to the literature search and wrote the report with guidance.
QA, DA: Refined the report script.
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