Section: Paediatrics

Case Report

CONGENITAL DIARRHOEA DISORDER WITH DGAT1 MUTATION: A CASE REPORT FROM INDIA

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Abstract

Congenital diarrhoea disorders are a group of rare but severe enteropathies with similar clinical presentations but different outcomes. The defect occurs due to mutation in various genes encoding brush border, pancreatic enzymes necessary for digestion of glucose, fructose, etc. The following case of congenital diarrhoea disorder is of DGAT-1 mutation present on chromosome 8. It is an autosomal recessive disorder with an estimated probability of homozygosity of approximately 1 in 50 to 100 million births. DGAT-1 gene encodes for acyl CoA: diacylglycerol acyl transferases which catalyses the final step of triglyceride synthesis. Thus, mutation of this gene causes defective triglyceride synthesis. It is associated with early onset of non-bloody diarrhoea, vomiting and protein losing enteropathy. This leads to severe dehydration as well as weight loss within the first few days of life, causing hinderance to the attainment of milestones and failure to thrive.

INTRODUCTION

A collection of uncommon but severe enteropathies known as congenital diarrhoea disorders share similar clinical presentations but have distinct prognoses. It presents with early onset of severe neonatal watery diarrhoea along with electrolyte imbalances specific to each subtype. Pathogenesis constitutes monogenic gene mutations leading to various subtypes of this disease depending on the gene affected. For instance, a mutation in the SLC26A3 gene on chromosome 7q31.3 results in congenital chloride disorder. The enzyme DGAT1 (diacylglycerol acyl transferase 1), which is located on chromosome 8 splice variant, 145541756 A→G in the splice donor 32 of exon 8, is implicated in an autosomal recessive disorder in this case, leading to conversion go GT to GA. In humans, glycerol and fatty acids are broken down into triglycerides. These triglycerides are necessary for the fat-soluble vitamins to be absorbed, energy storage, steroid hormone synthesis, etc. However, in the DGAT 1 mutation, the last step of triglyceride synthesis fails to take place in the liver. Hence, there's loss of nutrients leading to protein-losing enteropathy. Newborns with this disorder usually present with chronic diarrhoea, failure to gain weight, and delay in attainment of milestones. The main aim of treatment is to replenish the nutrients and prevent infections. These kids need to receive intralipid supplements and parenteral nutrition for certain periods.[1] The long term prognosis differs depending on the type of CDD; intestinal transplantation may be considered in extreme cases. Described below is a case of congenital diarrhoea disorder- DGAT1 mutation.

CASE PRESENTATION

The parents of a five-month-old boy brought him to the hospital with the main complaint of nonexplosive loose stools that had been occurring for four days, yellowish in colour, variable in volume, watery in consistency, non foul smelling, not associated with blood or mucous. Loose stools were associated with high-grade, continuous type of fever for 4 days, relieved on taking medications. The child has had episodes of vomiting 3-4 times a day for 4 days, as soon as milk was fed. There has been increased work of breathing for 2 days. A history of decreased acceptance of feeds is present, a history of dull activity is present and the child presented with perianal rash. There is no yellowish discolouration of the eyes. No history of crying during micturition. No history of seizures.

The patient has had 3 previous hospital admissions in the past. The first admission was on 3rd day of life due to passage of upto 20-25 episodes per day of loose stools of watery consistency, decreased urine output, and increased work of breathing. 2nd admission was on the 40th day of life with similar complaints of loose stools 15-20 episodes per day,

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associated with fever. 3rd admission was on the 60th day of life with severe dehydration and sepsis. All episodes of loose stools were watery in nature, yellow in colour, non foul smelling, and not associated with blood or vomiting. All episodes were treated for severe dehydration, and sepsis, and discharged on special formula feeds.

The baby was a product of a non-consanguineous marriage, 3rd in birth order. The first child started having similar complaints of loose stools when he was 3 months of age and had multiple hospitalisations for the same and passed away at 6 months of age. The second child is healthy, and thriving well, presently at 5 years of age. The present child is a product of natural conception, antenatal and natal history were uneventful with the birth of the baby at full term. As a result of the lack of labor progress, a lower-segment caesarean section was performed. Upon delivery, the newborn, promptly emitted cry and weighed 2.75kg. Additionally, the baby excreted meconium within the first 24 hours. The baby had to be admitted into the neonatal ICU after delivery for 1 day given transient tachypnoea of newborn. Baby was breastfed for 3 days after which he was started on special formula feeds. Neck holding was not attained even in 5th month.

On examination, the child is conscious, poorly built, sick looking [Figure 1,2] and pallor was present. The spine is centrally located, genitalia are normal, and multiple skin folds are seen over limbs. Rashes were present in the perianal region. Abdomen was distended, flanks free. No visible veins, pulsations, no guarding rigidity, no organomegaly. Bowel sounds were heard. The child presented with rachitic rosary and subcostal retractions. Apex beat present over left 4th intercostal space. The baby was able to move all four limbs, tone was normal, and superficial and deep tendon reflexes were normal. Anterior fontanelle open and sunken. Anthropometry revealed length<1st percentile, head circumference<3rd percentile, weight for height <3 standard deviation.

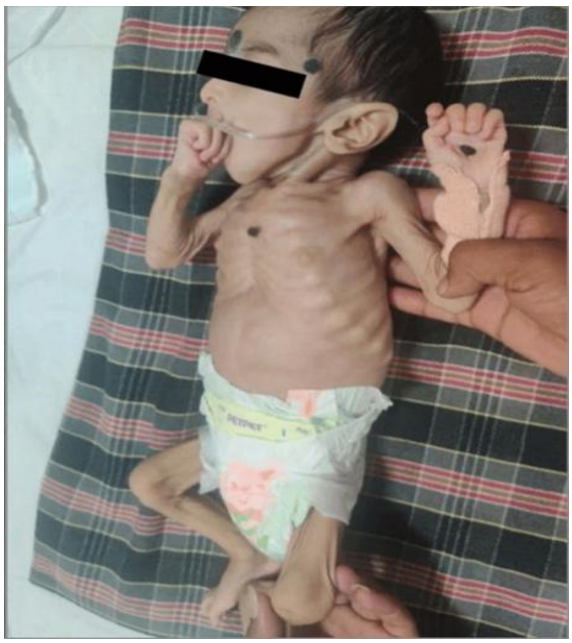

Figure 1: Picture of baby showing Rachitic rosary

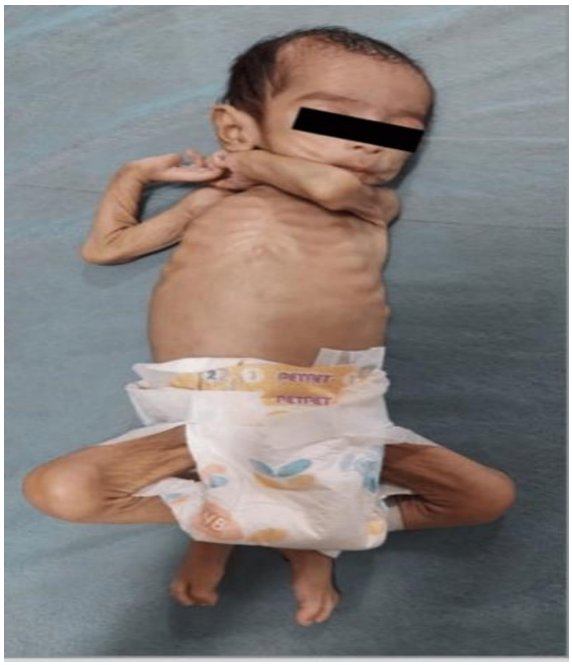

Figure 2: Picture of baby showing multiple skin folds

Stool examination revealed that it was positive for reducing substances, vitamin D3 was found in stools at a concentration of 6.53ng/dl. Ova and cysts were not present. Stool culture and stool elastase were negative. Complete blood picture revealed normocytic hypochromic anisocytosis with haemoglobin -7.6gm%, WBC count-20,300 cells/mm3, PCV-26%, MCHC-29%, RDW-23%, MCV-95 cubic microns, RBC and platelet count were normal [Table 1]. Neutrophils, lymphocytes, monocytes, eosinophils, and basophils were normal in count (table2). Serum electrolytes revealed hypochloremia (34 Meq/L), hypocalcemia (6.5 mg/dL), and sodium and

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potassium were within normal ranges [Table 3]. SGOT elevated to 98.8U/L, SGPT-192.6U/L, and ALP-1694.4 U/L respectively on liver function tests. Serum proteins reduced to 6.2gm%. Serum albumin, globulin, and bilirubin were within normal ranges [Table 4]. The lipid profile showed reduced HDL (54mg/dL). Total cholesterol, triglycerides, LDL, VLDL were normal (table 5). Urine culture and blood culture were negative. ABG analysis revealed Ph-7.198, pCO2-30.7mmHg, HCO3- -12.7mEq/L, and pO2 was within normal range. The anion gap was 12 corresponding to a normal anion gap metabolic acidosis (table 6) urine metabolic profile, tandem mass spectroscopy, and gas chromatography-mass spectroscopy showed no abnormalities.

On genome sequencing, a homozygote non-sense variant c1374 G→A in exon 17 of the DGAT1 gene resulting in amino acid substitution p.Trp.458 was identified. This was categorised as likely pathogenic based on the ACMG guidelines for variant interpretation. Based on the chief complaints, history, clinical examination, investigations, and confirmation by genome sequencing, definitive diagnosis of congenital diarrhoea disorder - DGAT1 was established. The child was treated with one fluid bolus and later started on oral ReSoMal. Nasopharyngeal O2 therapy (2L/ min) is given for management of metabolic acidosis. Along with the management of severe dehydration, antibiotic treatment was started. One packed RBCs was transfused for the decreased haemoglobin levels. During the hospital stay, despite taking special formula feeds and total parenteral nutrition, the child had intermittent episodes of loose stools and vomiting with signs of dehydration and did not gain weight.

RESULTS

Table 1: Hemogram.

	Result	Normal range
Haemoglobin	7.6 gm/dL	9.5 - 14.1 g/dL
RBC	2.7 millions/mm3	3.10 - 5.10 millions/mm3
Packed Cell Volume	26%	29 - 41%
Mean Corpuscular Volume	95 fl	74- 108 fl
Mean Corpuscular Hemoglobin Concentration	29%	28 - 36 g/dL
Red cell Distribution Width	23%	12 - 15%
White Blood Cells	20,300/mm3	6000 - 17500/mm3
Platelets	3,80,000/mm3	1,50,000 - 4,50,000/mm3

Table 2: Differential leucocyte count

	Result	Normal range
Neutrophils	76%	40 - 80 %
Lymphocytes	16%	20 - 40 %
Monocytes	8%	2 - 10 %
Eosinophils	1%	1 - 6 %
Basophils	-	< 1-2 %

Table 3: Serum Electrolytes

	Result	Normal Range
Chloride	112 mEq/L	96-106 mEq/L
Sodium	136 mEq/L	135-145 mEq/L
Potassium	4.8 mEq/L	3.5- 5.0 mEq/L
Calcium	6.5 gm%	8.7-10.5 mg/dl

Table 4: Liver Function Tests

	Result	Normal Range
SGOT	192 U/L	5-40 U/L
SGPT	98.8 U/L	5-35 U/L
ALP	1694.4 U/L	82 - 383 U/L
Total Serum Proteins	6.2 gm%	6.0-8.2 g/dl
Serum Albumin	4.1 gm%	3.8-5.4 g/dl
Serum Globulin	2.1 gm%	2.0-3.5 g/dl
Bilirubin	0.45 mg/dl	0.3-1.20 mg/dl
BUN	10.6 mg/dl	8-20 mg/dl
Serum creatinine	0.14 mg/dl	0.6-1.2 mg/dl

Table 5: Lipid Profile

	Result	Normal Range
HDL	54 mg/dl	> 60 mg/dl
LDL	43 mg/dL	< 120 mg/dl
VLDL	26 mg/dL	< 30 mg/dl
Triglycerides	122 mg/dL	< 150 mg/dl

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Total cholesterol	165 mg/dL	< 200 mg/dl

Table 6: Arterial Blood Gas Analysis

	Result	Normal Range
Ph	7.198	7.35 - 7.45
pCO2	30.7 mmHg	35 mmHg- 45 mmHg
pO2	94.8 mmHg	75 mmHg - 100 mmHg
HCO3	12.7 mEq/L	22 mEq/L - 26 mEq/L
Anion gap	12	4 - 12 mmol/L

DISCUSSION

Congenital diarrhoea disorders refer to a collection of uncommon yet serious conditions affecting the intestines. These conditions are characterised by the occurrence of severe diarrhoea in newborns, which can be categorised as osmotic, secretory, or inflammatory, depending on the specific subtype of the disease. Diarrhoea is mainly caused by the structural abnormalities the small intestine. The osmotic form of diarrhoea improves on fasting whereas secretory and inflammatory types of diarrhoea cannot be managed by the same. The case given above presented as Congenital Diarrhoea Disorder- DGAT1 mutation. This subtype is classified as caused due to disorders of epithelial enzymes and metabolism under modified canani terrin classification.[2] [Figure 3].

In the case given above, the main criteria that led to suspicion and diagnosis of congenital diarrhoea disorder were

1. Complaints of severe loose stools beginning from day 3 of life.
2. The child has not attained the age designated milestones
3. Positive family history, where the first child had similar complaints and passed away due to severe dehydration.
4. Presence of the signs and symptoms of dehydration
5. Criteria for Severe Acute Malnutrition (SAM) must be checked, to assess for malnutrition in the child due to the condition. The criteria includes-

- Weight-for-height below a -3 Z score, as per WHO guidelines
- MUAC (Mid upper arm circumference) <11.5cm for kids of age 6-59 months
- Presence of bilateral pedal edema

Individuals carrying the CDD-DGAT1 mutation experience a significant onset of diarrhoea during the early stages of life, accompanied by protein loss in the intestines, decreased albumin levels, and increased triglycerides levels in the blood.[1] It is a monogenic diarrhoea as it is a single gene defect on chromosome 8 splice variant causing DGAT1 mutation.

The DGAT1 gene is responsible for producing diacylglycerol o-acyltrasferase 1 (DGAT1), an enzyme with high expression in the microsomes of various tissues including testis, adrenal cortex, small intestines and adrenal medulla.[4] In human beings, DGAT 1 and its isoenzyme DGAT2, perform the last step of TG using fatty acyl CoA and diacyl glycerol[5]. Consequently, assisting the small intestine's triglyceride absorption.[4] Nevertheless, only DGAT1 exhibits a significant level of expression in the intestine of humans.[4] Less expression of DGAT1 is linked to decreased fat content, enhanced insulin sensitivity, and decreased body weight. Thus, the enzymatic activity of DGAT1 is crucial for the absorption and transportation of TAG and other nutrients in the body through chylomicrons.[3] Deficiency of diacylglycerol O acyl transferase 1(DGAT1) encompasses various consequences disrupting the metabolism as well as molecular nutrition of individuals. These include deficiency of vitamin D, low levels of calcium (hypocalcemia), low levels of phosphorus (hypophosphotemia), and insufficient iron levels (iron deficiency).[3]

Disease	OMIM number	Transmission and incidence	Mechanism
Genes encoding brush-border enzymes			
Congenital lactase deficiency (LD)	223000	AR, 1:60.000 in Finland; lower in other ethnic groups	Osmotic
Congenital sucrase-isomaltase deficiency (SID)	222900	AR, 1:5.000; higher incidence in Greenland, Alaska and Canada	Osmotic
Congenital maltase-glucomaylase deficiency (MGD)	--	Few cases described	Osmotic
Enterokinase deficiency (EKD)	226200	AR	Osmotic
Genes encoding membrane carriers			
Glucose-galactose malabsorption (GGM)	606824	AR, few hundred cases described	Osmotic
Fructose malabsorption (FM)	138230	-	Osmotic
Fanconi-Bickel syndrome (FBS)	227810	AR	Osmotic
Acrodermatitis enteropathica (ADE)	201100	AR, 1:500.000	Osmotic
Congenital chloride diarrhea (CCD, DIAR 1)	214700	AR, sporadic; frequent in some ethnies	Osmotic
Congenital sodium diarrhea (CSD, DIAR 3)	270420	AR	Osmotic
Lysinuric protein intolerance (LPI)	222700	AR, about 1:60.000 in Finland and in Japan; rare in other ethnic groups	Osmotic
Primary bile acid malabsorption (PBAM)	613291	AR	Secretory
Cystic fibrosis (CF)	219700	AR, 1:2.500	Osmotic
Genes encoding pancreatic enzymes and pancreatic ions transporters			
Hereditary pancreatitis (HP)	167800	AD	Osmotic
Congenital absence of pancreatic lipase (APL)	246600	--	Osmotic
Genes encoding proteins of lipoprotein metabolism			
Abetalipoproteinemia (ALP)	200100	AR, about 100 cases described; higher frequency among Ashkenazi	Osmotic
Hypobetalipoproteinemia (HLP)	107730	Autosomal co-dominant	Osmotic
Chilomicron retention disease (CRD)	246700	AR, about 40 cases described	Osmotic
Genes encoding ribosomial proteins			
Shwachman-Diamond syndrome (SDS)	260400	AR 1:10–200.000	Osmotic

Figure 3: Modified Canani Terrain Classification

Protein losing enteropathy patients experience an increase in the production of albumin while albumin is lost in the intestines, likewise, the body is unable to fully compensate.[6,7]

Consequently, proteins that have a longer duration of activity, like albumin and immunoglobulins, are impacted, while proteins with shorter duration, like pre-albumin, are less impacted. This helps us understand the aspects of hypoalbuminemia and protein losing enteropathy.[10] Protein losing enteropathy is identified by a range of biochemical irregularities, including dehydration and decreased levels of copper, potassium, phosphorus, calcium, zinc, iron, and serum sodium. It leads to low levels of serum albumin, immunoglobulins, and fibrinogen; metabolic acidosis, as well as elevated levels of triglycerides, and VLDL, elevated transaminases and reduced levels of HDL. Frequently, stool contains clusters of fat and increased levels of stool α-1-antitrypsin (typically

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<3mg per gm of stool), the increased α-1-antitrypsin indicates an increased intestinal permeability, thus causing protein loss. The biopsy may reveal focal mild chronic inflammatory changes in the oesophagus, colon, and stomach, gastric metaplasia, gastric eosinophilia, and abnormal duodenal microvilli.[3,11] The concentrations of visceral proteins like albumin, pre albumin, transferrin, serum iron, as well as retinol binding protein help assess the grade of malnutrition in patients with such chronic illnesses, as the half-life of these serum proteins helps distinguish between long-term and short term malnutrition.

The proper lifelong management of these patients doesn't lie in frequent visits to the hospital, but in proper control over their daily food intake. patients with a deficiency of DGAT1 typically expirience positive outcomes when following a diet that is low in fat. An early implementation of such a diet could potentially avert the progression of a fully manifested protein-losing enteropathy (PLE) in patients.[8] Moreover, the administering of short chained fatty acids as a dietary supplements proven effectiveness in improving the health of specific patients.

It is advisable to avoid consuming dairy products. The dietary fat intake is restricted, usually accounting for 2-10% of the total calorie consumption. It is recommended to consume small amounts of fat throughout the day, rather than consuming large amounts at once. Patients with high triglyceride levels have been treated with omega-3 fatty acids.[9] The maintenance doses of fat soluble vitamin A, E, D, and K need to be administered. Other micronutrients such as zinc, folate, and magnesium deficiency must also be evaluated and corrected if necessary. If symptoms warrant their application, temporary benefits can be obtained from administration of Intravenous albumin, amino acid mix, lipids, immunoglobulins, antibiotics, and mainly accompanied by total parenteral nutrition.[9]

As the child grows in age, their diet must consist of food with a proper portion of fibre intake, along with proteins and carbohydrates in appropriate amounts, with low fat containing foods.

CONCLUSION

The accurate identification of the underlying ailment has frequently been prolonged or difficult to determine, contributing to the prolonged suffering of the child and the parents alike along with the substantial financial strain of treatment.

The clinical application of emerging genetic techniques such as exome sequencing along with other histochemical and molecular techniques is likely to increase the chances of early detection of such rare causes of chronic diarrhoea, and accurate management of such disorders, ultimately leading to a substantial decrease in the economic burden.

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