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A low-fat amino acid diet reverses intestinal failure and shows good growth trends in five infants with diacylglycerol transferase 1 (*DGAT1*) deficiency: a prospective cohort study

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Abstract

Background Congenital diarrheas and enteropathies (CODEs) caused by diacylglycerol transferase 1 (*DGAT1*) mutations often cause disease within 2 weeks after birth. If not treated properly, the disease can be life-threatening; therefore, early diagnosis and rational treatment strategies are essential. This study was conducted to improve the understanding of congenital diarrhea caused by *DGAT1* deficiency.

Methods Clinical data from five congenital diarrhea infant cases caused by *DGAT1* deficiency were analyzed. Infants were prospectively provided with a nutritional intervention with a low-fat amino acid formula for special medical purposes (FSMP). Their gastrointestinal symptoms and nutritional complications before and after interventions were compared.

Results Due to poor weight gain and gastrointestinal symptoms after birth, infants were treated by our clinical nutritionist. Genetic testing confirmed a compound heterozygous mutation in *DGAT1*. Neither hydrolyzed nor high-medium chain triglyceride (MCT) formula significantly alleviated diarrheal symptoms; however, a low-fat amino acid diet rapidly relieved symptoms and significantly improved nutritional status, with infants showing better tolerance to dietary fat content with age.

Conclusions Infants with *DGAT1* deficiency can be diagnosed by genetic testing. A low-fat amino acid FSMP formula and diet can quickly relieve diarrhea, vomiting, and other symptoms, and also improve infant growth and development.

Trial registration Ethical approval was obtained from the Medical Ethics Committee of the Children's Hospital of Fudan University (reference code: No.(2022)405).

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Keywords Congenital diarrhea, Diacylglycerol transferase 1 (*DGAT1*) mutation, Growth retardation, Low-fat amino acid diet, Prospective cohort study

Introduction

In infants, congenital diarrheas and enteropathies (CODEs) are a group of rare inherited intestinal diseases mostly caused by single gene mutations, and are characterized by persistent severe diarrhea and malabsorption in the first few weeks after birth, which can be life-threatening [1]. Identifying genetic variants associated with congenital diarrheal disease is important for a proper diagnosis and appropriate treatment selection. Lipid metabolism is an important physiological function in the body, and includes the digestion and absorption of lipid products from foods. Congenital lipid metabolism errors can lead to many symptoms, from nerve damage to hypertriglyceridemia. Triglycerides (TGs) are the main energy substrates stored in human adipose tissue [2, 3]. In intestinal cells, TGs are stored in lipid droplets (LDs) or packaged in chylomicrons, and then transported to the lymphatic system. DGAT1 is a key enzyme involved in TG synthesis. Diacylglycerol (DAG) and fatty acyl-coenzyme A are used as substrates to catalyze TGs, which have important roles in lipid formation, absorption, and transport, and participate in lipid metabolism, signal transduction, and intestinal fat absorption [4, 5]. CODEs caused by *DGAT1* mutations, also known as diarrhea type 7, often cause disease within 2 weeks after birth, and are mainly manifested by chronic diarrhea, vomiting, growth retardation, hypoalbuminemia to varying degrees, and some associated with hypogammaglobulinemia and hyperlipidemia. Endoscopy usually shows no specific changes [6–8]. If not treated properly, the disease can be life-threatening; therefore, early diagnosis and rational treatment strategies are essential. In this paper, five infants with *DGAT1* deficiency are described. After treatment with a reasonable low-fat amino acid FSMP formula and diet, their symptoms improved rapidly and their growth and development soon caught up.

The *DGAT1* mutation in this study extends the molecular and phenotypic spectrum of CODEs and adds evidence for the treatment of CODEs caused by the *DGAT1* mutation. Low-fat amino acid FSMP formula and diets should be regarded as the first choice for the treatment of diarrhea in infants with *DGAT1* deficiency.

Methods

The cohort included five infants with *DGAT1* deficiency who received nutritional treatment in the Clinical Nutrition Department, Children's Hospital of Fudan University from December 2021 to July 2023. After being diagnosed with congenital diarrhea caused by *DGAT1* deficiency, infants were treated with low-fat amino acid FSMP formula. Through the self-control of infants' symptoms before and after intervention, the effectiveness of the nutrition support strategy was tested. Approval for the low-fat amino acid FSMP formula and informed consent from infants' families was reviewed and approved by the Ethics Committee of the Children's Hospital of Fudan University. The study was based on Helsinki Declaration principles (Fortaleza revision, 2013). Demographic information, nutritional status, laboratory examinations, whole exon sequencing (WES), nutritional therapy, and clinical outcomes were collected. All members of the research team checked data completeness, clarity, consistency, and accuracy. Figure 1 shows a flowchart of the prospective cohort study.

Results

Five infants with *DGAT1* mutations were treated, two of whom were first diagnosed in our hospital and the others in local hospitals. They were all full-term infants with normal birth length and weight. The age of disease onset was between 3 and 14 days after birth. Clinical manifestations included chronic diarrhea (4/5), vomiting (4/5), abdominal distension (1/5), electrolyte disturbance (5/5), and vitamin D deficiency (3/5). Gene mutations were all double heterozygous mutations and their parents were unrelated Han couples. All cases showed prominent hypoalbuminemia. Breast milk, infant formula, extensively hydrolyzed formula, amino acid formula, and high MCT formula were tried at other hospitals, but persistent diarrhea or abdominal distension was not improved, and severe malnutrition (underweight, stunting, and wasting) occurred. Four infants (80%) received tube feeding and parenteral nutrition support. After the diagnosis was confirmed, infants received nutritional support from our nutrition team through in-hospital consultation or online nutrition clinic because of the COVID-19 pandemic. The children were recommended to be fed with low-fat amino acid formula (3% of the total energy is provided by fat). Gastrointestinal symptoms were significantly improved and all were weaned off parenteral nutrition support or albumin transfusion with normal albumin levels. They had regular follow-up visits at our outpatients department, and guardians accepted nutritional recipes. The infants gradually tolerated increasing dietary fat energy supply ratios and achieved catch-up growth. At the last follow-up, dietary fat energy supply ratios in infants reached 21%, 20%, 21%, 13%, and 11%, respectively, with normal growth and development (weight for age Z score all > -1, height/length for age Z score all > -2), and normal levels of fat-soluble vitamins and trace elements.

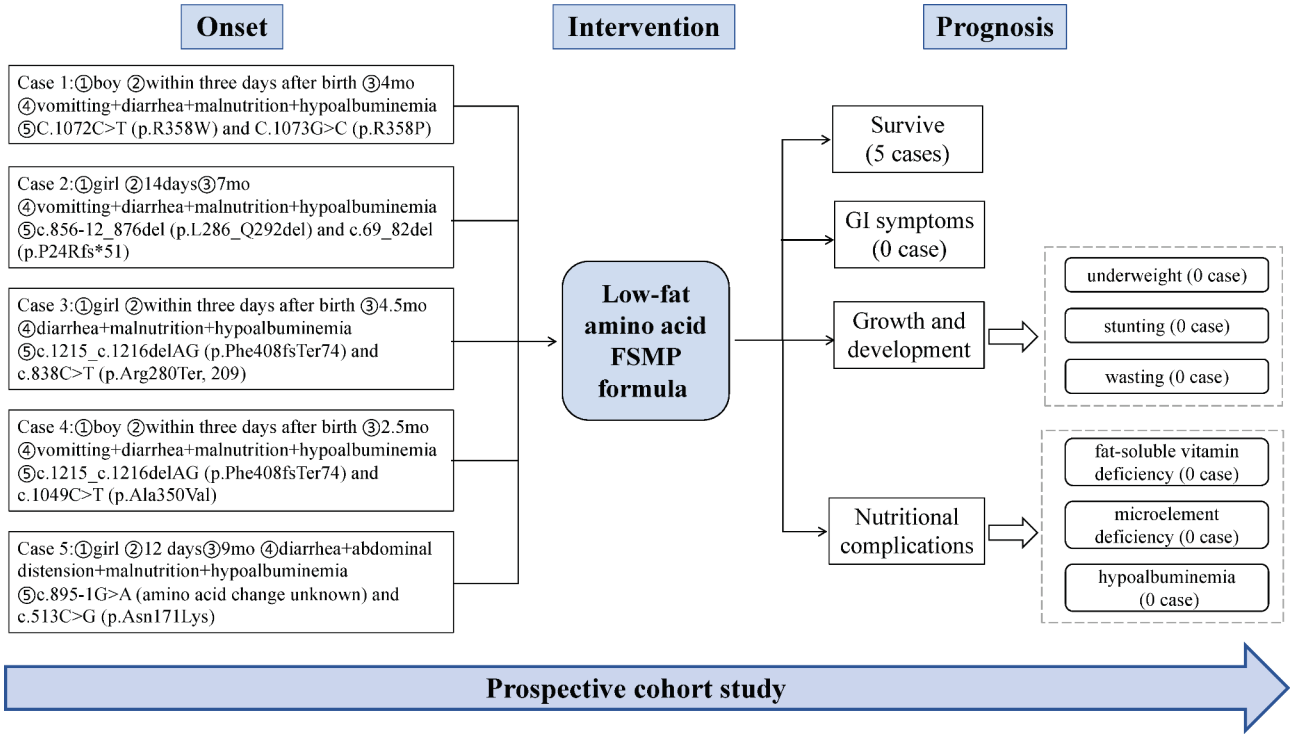

Fig. 1 A flowchart showing the prospective cohort study. ① Sex ② Age of onset ③ Age of diagnosis ④ Clinical manifestations ⑤ *DGAT1* gene mutation sites

The nutritional intervention with a low-fat amino acid diet rapidly improved diarrhea symptoms in infants with *DGAT1* deficiency, reversed intestinal failure, and facilitated catch-up growth, with no adverse reactions during treatments. Detailed information related to onset, referral, diagnosis, treatment, and prognosis in the five cases can be found in Supplementary word. Figure 2 shows the changing trend in formula, total energy intake, and the dietary fat energy supply ratios with increases in case 1's age. The dietary survey results of cases 2–5 are also shown (Fig. 3). Infants' clinical information, laboratory tests before and after treatment, dietary surveys, and recommendations are also listed (Tables 1 and 2 and Table S1, respectively). In Table 2, laboratory test results before and after the nutrition treatment are shown.

Discussion

Congenital diarrhea is a rare cause of severe chronic diarrhea in infants, usually occurring in the neonatal period or early infancy, and is a single-gene inherited disorder. With advances in genome sequencing, many genes causing congenital diarrhea have been identified, including *DGAT1*. Multiple *DGAT1* mutation sites have been reported in China and overseas, including splice site, missense, frameshift, full-length, insertion/deletion, and nonsense mutations [6–13]. Figure S1 shows the mutations of five infants with *DGAT1* deficiency in this study.

Importantly, different clinical manifestations can occur depending on the gene mutation; infants with missense mutations have mild clinical manifestations as these mutations only cause partial, functional DGAT1 protein loss [10, 14]. Diarrhea is the most common clinical symptom in *DGAT1*-deficient infants. In some reported cases, *DGAT1* deficiency can cause severe or even lethal protein-losing enteropathy (PLE), which is characterized by an uncompensated loss of plasma proteins from the intestine that causes hypoproteinemia and malnutrition [15]. Diarrhea and PLE manifestations caused by *DGAT1* deficiency remain unclear, but may be related to toxic effects caused by excessive DAG or fatty acids (FAs) in intestinal cells [16]. It is accepted that dietary lipids are taken up as FAs by the intestinal epithelium [17]. Then, DGAT1 (enzyme) converts FAs to TGs, which are stored in cytoplasmic LDs or packaged in chylomicrons [18]. DGAT1 is required for LD-mediated resistance to lipid-induced endoplasmic reticulum stress in the intestinal epithelium [19, 20]. In the absence of *DGAT1*, LD formation is reduced, which increases sensitivity to lipotoxicity and apoptosis in intestinal epithelial cells. Mucosal injury in the intestine may cause diarrhea and PLE in *DGAT1*-defective infants [21] and may explain why diarrhea in such infants is rapidly relieved after a low-fat amino acid formula is provided. Similarly, in other lipid metabolic disorders, such as Niemann-Pick disease type C with inflammatory bowel disease, lipid toxic-induced

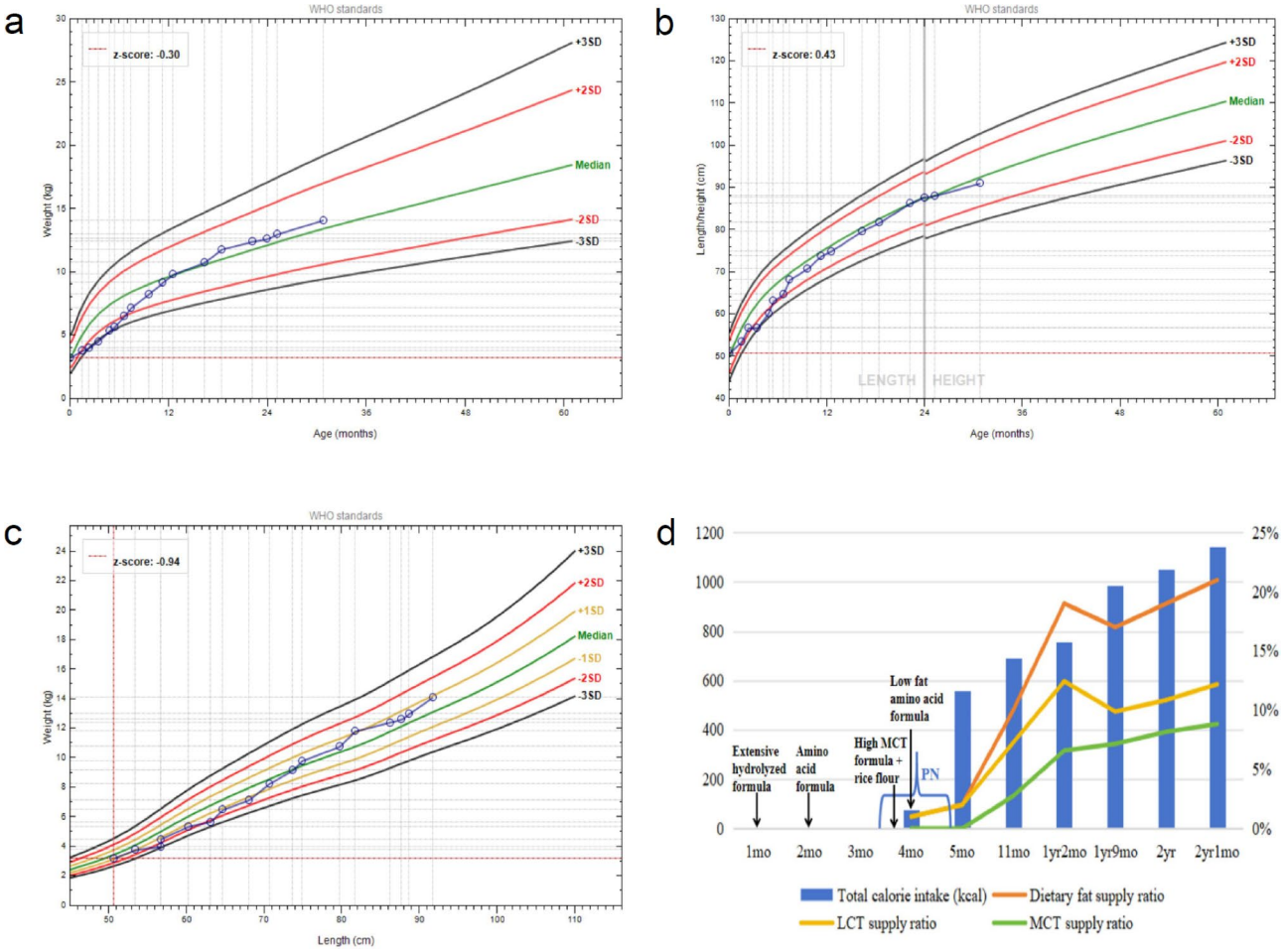

Fig. 2 **(a)** The weight for age Z score with increasing age in case 1. **(b)** The length/height for age Z score. **(c)** The weight for length/height Z score. **(d)** The changing trend in formula and dietary survey results for case 1. The abscissa is the age of the infant. The left ordinate is the daily calorie intake. The right ordinate is dietary fat, LCT, and MCT supply ratios

intestinal cell dysfunction is also caused by endoplasmic reticulum stress or induced autophagy [22].

Diarrhea may be related to apical transporter and connexin loss in intestinal epithelial cells, and also decreases in some enzymes, including Na^+-dependent glucose transporter 1 (SGLT1), dipeptidyl peptidase-IV (DPPIV), and Na^+/H^+ exchanger 3 (NHE3) [23]. As previously reported, in gastroenteritis caused by rotavirus (RV) infection, DGAT1 is degraded in RV-infected cells by a proteasome-dependent mechanism. *DGAT1* loss reduces apical brush border enzymes which are required for normal enterocyte homeostasis. Eukaryotic translation initiation factor 2 alpha (eIF2α) is a regulator of global cellular translation, with increased phosphorylated eIF2α levels in RV-infected cells and human $DGAT1^{-/-}$ intestinal enteroids putatively responsible for downregulated protein expression which leads to malabsorptive diarrhea [24]. Whether the same mechanism is at play in infants with *DGAT1* deficiency requires further exploration. Additionally, *DGAT1* deficiency may affect bile acid metabolism, with bile acid malabsorption implicated in some diarrhea cases [25]. However, in this study, fecal bile acid levels were not measured. Vomiting is another common symptom and may arise due to *DGAT1* deficiency inhibiting chylomicron secretion and delaying gastric emptying [26].

Due to a lack of DGAT2 (DGAT1 isoenzyme) expression, the human gut may be more sensitive to *DGAT1* mutations [25]. DGAT2 has the same functional characteristics as DGAT1, and catalyzes DAG and fatty acyl-CoA to generate TGs in the liver [27]. However, these enzymes share no protein sequence or domain homologies, and their expression levels are different across different tissues. DGAT1 expression is highest in the small intestine, followed by the testis, adipose tissue, and thymus, while DGAT2 is mainly distributed in the liver, adipose tissue, and mammary glands [28]. Previous studies reported that intestinal organoids with *DGAT1* deficiency were more sensitive to FA-induced lipid toxicity, while DGAT2 expression in organoids partially compensated

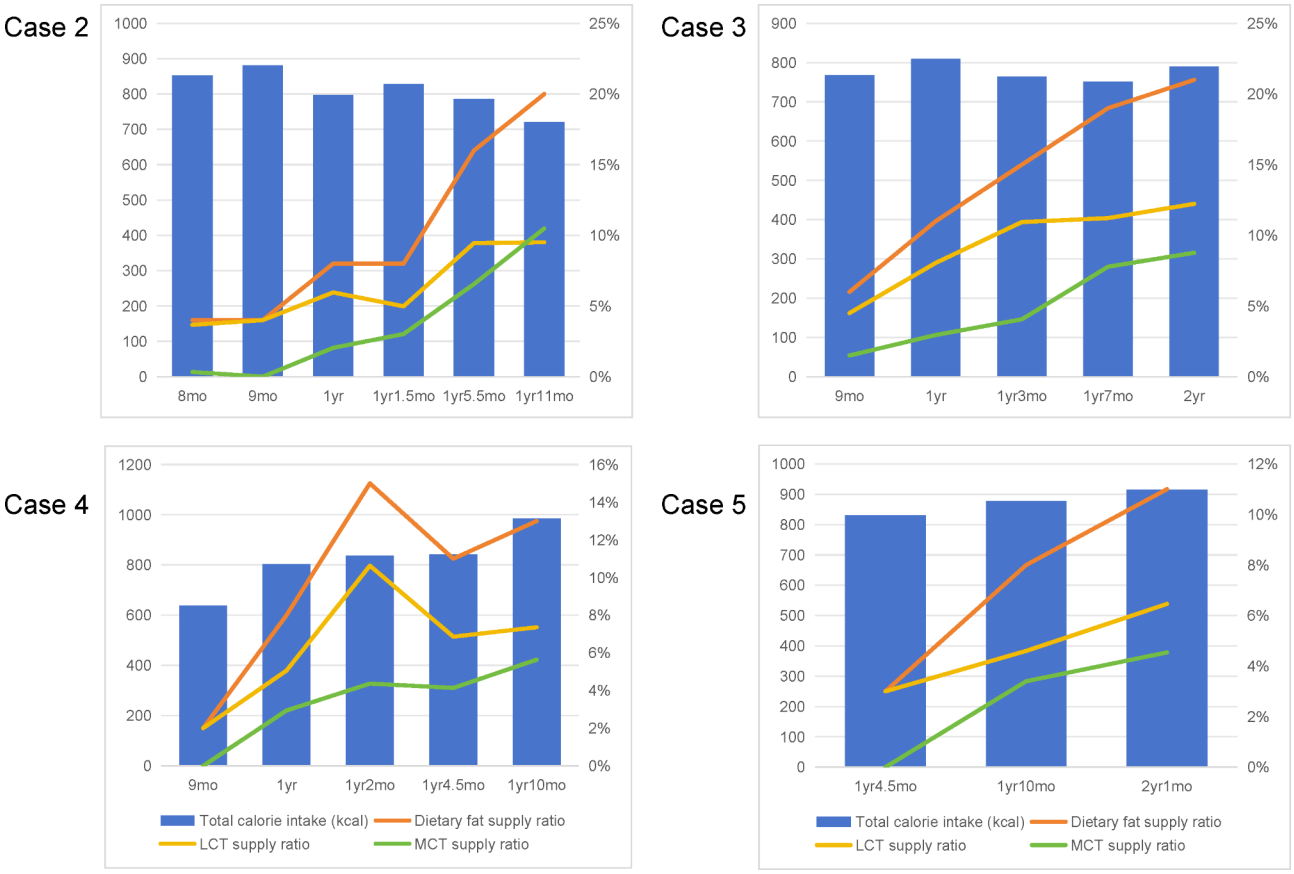

Fig. 3 Dietary survey results of cases 2–5. The abscissa is the age of the infants. The left ordinate is the daily calorie intake. The right ordinate is dietary fat, LCT, and MCT supply ratios

for lipid-induced endoplasmic reticulum stress [21]. Using hepatocyte-specific *DGAT1* ablation in mice, *DGAT1* was implicated in the complete lipidization and maturation of very low density lipoprotein cholesterol, which determined its particle size but not secretion. In the absence of *DGAT1*, DGAT2 had compensatory roles in terms of secreting lipoproteins [29]. Also, in fibroblasts and organoids derived from patients with *DGAT1* mutations, DGAT1 protein expression decreased resulting in reduced LD formation after oleic acid addition, while full-length DGAT2 expression restored LD formation. The dietary fat energy supply ratios of the infants in this study increased with age, and they showed good tolerance and weight growth trends. Hypothetically, DGAT2 expression in the small intestine may have increased with age to adapt to *DGAT1* deficiency; therefore, inducing DGAT2 expression may be a feasible therapeutic strategy for infants with *DGAT1* mutations.

At present, since no effective treatments are available to increase or restore intestinal DGAT1 activity, the main therapeutic options are parenteral nutrition support, low-fat diet feeding, regular albumin infusions, and other supportive treatments. Reasonable treatments can redistribute apical transporters in intestinal epithelial cells and improve clinical prognosis outcomes. After treatments with parenteral nutrition, high-MCT and hydrolyzed formulas, symptoms such as diarrhea and vomiting were not significantly alleviated in previously reported cases, and also infants in this study [30]; some infants were growth retarded and even died [12, 31]. In this study, after a low-fat amino acid diet was provided, symptoms were quickly relieved and infants showed good growth trends. This suggested that low-fat diets could be used first-line treatments for patients with deficient *DGAT1* expression, thereby alleviating symptoms at early disease stages. However, considering that low-fat or fat-free formula milk cannot supply sufficient lipids and energy, infants must gradually transition to low fat formula (fat=26%) and starchy complementary foods to provide energy and ensure good prognosis outcomes [10]. The dietary fat energy supply ratios tolerated by infants may be related to *DGAT1* mutation sites and DGAT1 activity levels. For example, patients with an *DGAT1* exon 8 deletion and DGAT1 inactivity tolerated a 4–7% fat energy supply ratio, while patients with a p.L105P mutation tolerated up to 10%. Small amounts and multiple intakes may also improve tolerance levels to dietary fat. Importantly, dietary fats can be titrated to tolerance levels based on

Table 1 Clinical information for all infants

Case		Case 1	Case 2	Case 3	Case 4	Case 5
Demographics	Sex	M	F	F	M	F
	Birth Weight	3.2 kg (Z=-0.3)	3.48 kg (Z = 0.53)	2.75 kg (Z=-1.11)	3.7 kg (Z = 0.7)	3 kg (Z=-0.52)
	Age of onset	within three days after birth	14days	within three days after birth	within three days after birth	12days
	Age of first visit	2mo	4.5mo	3mo	2mo	8mo
	Age of diagnosis	4mo	7mo	4.5mo	2.5mo	9mo
	Admission weight	4.56 kg (Z=-3.2)	5.2 kg (Z=-3.03)	2.2 kg (Z=-6.31)	4.4 kg (Z=-4.89)	3.5 kg (Z=-6.08)
	Admission length	56 cm (Z=-2.86)	65 cm (Z=-0.36)	53 cm (Z=-2.92)	59 cm (Z=-3.76)	68 cm (Z=-0.32)
Mutation situation	*DGAT1* gene mutation site	c.1073G > C, C.1072 C > T	c.856 – 12_876del,c.69_82del	c.1215_c.1216delAG, c.838 C > T	c.1215_c.1216 delAG ,c.1049 C > T	c.895-1G > A,c.513 C > G
	Mutant type	Compound heterozygous mutation	Compound heterozygous mutation	Compound heterozygous mutation	Compound heterozygous mutation	Compound heterozygous mutation
	Amino acid changes	p.R358P,p.R358W	p.L286_Q292del,p.P24Rfs*51	p. Phe408fsTer74, p. Arg280Ter, 209	p.Phe408fsTer74, p. Ala350Val	p.?,p.Asn171Lys
Clinical manifestations	Vomitting	√	√	×	√	√
	Diarrhea	√	√	√	√	×
	Defecation frequency	5–9 times/day	5–6 times/day	4 times/day	7–8 times/day	1–2 times/day
	Malnutrition	√	√	√	√	√
Gastroenteroscopy		duodenitis, short villi of the small intestine	Gastric sinusitis, rough duodenal mucosa, rectocolitis	Not done	Not done	Lower esophagitis, hiatal hernia? erosive gastritis
Treatment	PN	√	√	√	√	×
	Hydrolyzed formula	√	√	√	√	√
	Amino acid formula	√	√	×	√	×
	Low-fat amino acid formula	√	√	√	√	√
	Low-fat diet + MCT	√	×	√	√	√
Prognosis		weight 14.1 kg(Z = 0.4), height 91 cm (Z = -0.44) at 30 months	weight 12 kg(Z = 0.54), height 85 cm (Z = 0.12) at 22 months	weight 11.5 kg(Z = 0.12), height 79 cm (Z = -1.91) at 24 months	weight 11 kg(Z = -0.52), height 82 cm (Z = -1.02) at 21 months	weight 11.8 kg(Z = 0.65), height 80 cm (Z = -1.01) at 21 months

clinical improvements, essential FA levels, and age-appropriate growth criteria [10].

Osmolality is another concern during neonatal feeding. The American Academy of Pediatrics recommends that osmolality in infant formula should not exceed 450 mOsm/kgH_2O [32]. Excessively high osmolality in formula may inhibit gastrointestinal motility, increase the probability of gastroesophageal reflux, disturb intestinal flora, and damage kidney health [4, 6, 33, 34]. As gastrointestinal functions in *DGAT1*-deficient infants are not optimal, infants are more vulnerable to harm generated by high osmolality formula. By comparing osmolality levels between extensively hydrolyzed and amino acid formulas, an appropriate blending ratio was selected to make the osmolality more tolerable. The osmolality was 311 mOsm/kgH_2O, and infants showed good growth and development trends without feeding intolerance and digestive tract discomfort.

Additionally, only 3% of calories in this low-fat amino acid formula came from fat. To prevent essential FA deficiency while ensuring energy requirements and curative effects, the formula, parenteral nutrition dosages, and complementary food intake were all adjusted in a timely manner based on infant tolerance and clinical manifestations. During long-term follow-up, no essential FA deficiency symptoms appeared, such as dry/scaly skin,

Table 2 Laboratory tests before and after treatment for all infants

Laboratory tests	Case 1		Case 2		Case 3		Case 4		Case 5	
	before treatment	after treatment	before treatment	after treatment	before treatment	after treatment	before treatment	after treatment	before treatment	after treatment
WBC	16.5	8.4	18.24	9.59	10.82	3.4	12.84	8.29	12.67	10.88
HGB	83	104	110	112	106	123	63	103	77	119
EO#	1.36	0.5	0.46	0.18	0.14	0	0.47	0.03	0.2	0.18
TP	39.2	52	45.6	58.3	44	64.4	33.5	61.3	51.8	62.3
Alb	27.43	39	29.47	39.22	32.6	44.6	17.5	42.2	29.3	45.8
AST	172.8	57	53.71	45.52	125	50	85	72	184	52.2
ALT	232.75	63.6	74.71	76.26	136	40	46	95	435.5	36.2
TC	2.32	2.62	2.72	4.03	4.15	3.73	4.59	3.89	3.11	3.01
TG	2.33	0.57	1.14	1.16	1.7	0.77	2.01	0.65	3.79	2.21
HDL-C	0.51	0.89	1.09	1.14	0.92	0.81	0.21	0.9	0.58	0.58
LDL-C	1.53	1.41	1.57	2.43	2.52	2.52	3.11	2.6	1.77	1.43
LDL-C lowest	0.92		1.57		2.52		0.84		1.43	

WBC (leukocyte): $\times 10^9$/L; HGB (hemoglobin): g/L; EO# (eosinophil absolute count): $\times 10^9$/L; TP (total protein): g/L; Alb (albumin): g/L; AST (aspartate aminotransferase): U/L; ALT (alanine aminotransferase): U/L; TC (total cholesterol): mmol/L; TG (triglycerides): mmol/L; HDL-C (high-density lipoprotein cholesterol): mmol/L; LDL-C (low-density lipoprotein cholesterol): mmol/L

desquamation, sparse hair, red macular papule, fatty liver, renal degeneration, and reproductive system damage [35–37].

Since DGAT1 has key roles in intestinal lipid uptake and absorption, several DGAT1 inhibitor studies have been conducted. Such inhibitors have significantly improved glucose and lipid metabolism, reducing liver and intestinal cell lipid accumulation, lipoprotein secretion, and postprandial blood lipids in multiple in vivo and in vitro disease models, suggesting that *DGAT1* can be used as an anti-metabolic disease target [29, 38, 39].

Four of the five infants had hypo LDL levels at presentation and improved after treatment with a low-fat diet. In previous studies, liver *DGAT1*- and *DGAT2*-overexpressing mice were generated using adenovirus-mediated gene transfection. From study data, very LDL (VLDL) secretion was increased in mice overexpressing *DGAT1*. DGAT1 but not DGAT2 plays a role in VLDL synthesis [40]. LDL can be converted from VLDL via lipoprotein lipase (LPL) actions, which may partly explain hypo LDL levels in these infants.

Currently, the infants in this study have caught up in terms of body length; they have shown no significant body weight underdevelopment, no abnormal serum biochemistry, fat-soluble vitamins, blood glucose and lipid metabolism, and motor development, consistent with children their own age. However, gut barrier dysfunction caused by *DGAT1* deficiency may increase autoimmune intestinal disease risks; in a female with defective *DGAT1*, gluten-induced enteropathy developed at 10 years old and then irritable bowel disease-like inflammation developed 5 years later, suggesting the importance of an early diagnosis and optimal treatments [11].

Strengths and limitations

This prospective cohort study had several strengths. Firstly, it demonstrated rapid symptom relief in infants with *DGAT1* deficiency with the application of a reasonable low-fat amino acid FSMP formula and diet. Secondly, it clearly shows long-term detailed dietary survey and recommendations, which can provide a reference for future nutritional management. But the study also had some limitations. Firstly, essential FAs should be regularly monitored and more actively supplemented. Secondly, basic studies should be improved to further explore disease pathogenesis associated with *DGAT1* deficiency.

Conclusions

Taken together, this study described a large cohort of infants with *DGAT1* deficiency, which expands the understanding of the pathological mechanisms underlying this deficiency. Due to early onset, rapid disease progress, and difficult disease treatments, early identification and interventions are crucial. However, clinical laboratory stool tests cannot provide insights into genetic lipid metabolism disorders. A *DGAT1* deficiency should be suspected in infants with unexplained diarrhea, vomiting or abdominal distension accompanied by growth retardation. Genetic testing and intestinal pathological examinations should also be used to confirm a diagnosis. Once confirmed, low-fat amino acid FSMP formula and diets supplemented with essential FAs and fat-soluble vitamins can be used as first-line treatments to improve prognosis outcomes. Also, low fat infant formula must be developed for these special-need infants.

Abbreviations

DGAT1 Diacylglycerol transferase 1
CODEs Congenital diarrheas and enteropathies
FSMP Food for special medical purpose

MCT	Medium chain triglyceride
TGs	Riglycerides
LDs	Lipid droplets
DAG	Diacylglycerol
WES	Whole exon sequencing
LCT	Long chain triglyceride
TP	Total protein
AST	Aspartate aminotransferase
ALT	Alanine aminotransferase
TC	Total cholesterol
HDL-C	High-density lipoprotein cholesterol
LDL-C	Low-density lipoprotein cholesterol
PLE	Protein-losing enteropathy
FAs	Fatty acids
SGLT1	Na^+-dependent glucose transporter 1
DPPIV	Dipeptidyl peptidase-IV
NHE3	Na^+/H^+ exchanger 3
RV	Rotavirus
eIF2α	Eukaryotic translation initiation factor 2 alpha
VLDL	Very low density lipoprotein
LPL	Lipoprotein lipase

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12944-024-02348-x.

Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

Supplementary Material 4

Supplementary Material 5

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Author contributions
Yuanyuan Zheng has made substantial contributions to the conception, design of the work, the acquisition, analysis, interpretation of data, and has drafted the work and substantively revised it.Tian Qian is the corresponding author of the work. She has made substantial contributions to the conception, design of the work, and has substantively revised it.Yongzhen Li has made substantial contributions to the acquisition and analysis of data.Cuifang Zheng and Lin Yang have made substantial contributions to the design of the work. Chongfan Zhang has made substantial contributions to the interpretation of data.Ying Huang and Yuhuan Wang have substantively revised the work. All authors have approved the submitted version, and agreed both to be personally accountable for the author's own contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even ones in which the author was not personally involved, are appropriately investigated, resolved, and the resolution documented in the literature.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
The study was conducted in accordance with the Declaration of Helsinki. The Children's Hospital of Fudan University Ethics Committee reviewed and approved all study procedures (reference code: No.(2022)405).

Consent for publication
Patients' relatives signed informed consent sheets for the publication of their data.

Competing interests
The authors declare no competing interests.

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