Article

Variants in DGAT1 causing enteropathy: a case report and review of the literature

Liselotte Eke Bijker [a], Sophie Uyttebroeck [b], Bruno Hauser [a], Yvan Vandenplas [a], Koen Huysentruyt [a]

[a] KidZ Health Castle, UZ Brussel, Vrije Universiteit Brussel
[b] Centre for Medical Genetics, UZ Brussel, Vrije Universiteit Brussel

liselottebijker@gmail.com

Keywords

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Abstract

Background: Diacylglycerolacyltransferase 1 (DGAT1) is an enzyme that catalyzes the final step of triglyceride synthesis and genetic variants have been described in association with congenital diarrhea.

Methods: We present a patient with a novel variant in the DGAT1 gene and a review of previously published cases. A search was conducted in PubMed, Cochrane Library and Embase until December 2020 and 22 cases of children diagnosed with variants in DGAT1 and gastrointestinal disease were identified from 8 articles. Data on patient characteristics, clinical presentation, diagnostic findings and treatment were extracted and analyzed.

Case description: Our patient presented with failure to thrive, vomiting and diarrhea and was diagnosed with protein-losing enteropathy. The novel homozygous variant c.469-2A>G in DGAT1 was found and after starting with parenteral nutrition and a fat-free diet, she showed a favourable evolution with dramatic improvement of growth.

Results: A vast majority of patients presented with symptoms of failure to thrive, vomiting and diarrhea within the first three months of life but not necessarily at birth. Parenteral nutrition was required in 78.2% of cases and 61.1% of them weaned off. At follow-up, 73.7% were receiving a fat-restricted diet. Mortality was 17.4%.

Discussion: DGAT1 deficiency is a rare but severe disorder, that will likely be encountered more often in the future as DGAT1 is added to screening panels for congenital diarrhea. Key to the treatment is restriction of enteral fat with appropriate parenteral supplementation, but more detailed information on nutritional management strategies and their effects on clinical outcome is needed.

Background

Chronic diarrhea in infants can be either aqcuired, for example after infection or surgery, or congenital. Inherited causes, termed congenital diarrheas and enteropathies (CODEs), are less common but can be extremely severe. Most CODEs are monogenic, autosomal recessive disorders with onset typically early in life. In the majority of CODEs, the genetic variant directly affects the intestinal epithelium, whereas in others epithelial function is impaired secondarily by dysregulation of the immune system (1, 2).

Congenital protein-losing enteropathy (PLE) is a subtype of CODE that is characterized by increased protein loss from the gastrointestinal system. Monogenic causes of congenital PLE include variants in CCBE1, CD55 and PLVAP (3-5). Also, several loss-of-function variants in the gene encoding for diacylglycerolacyltransferase type 1 (DGAT1) have been described in patients with congenital PLE. DGAT1 is an enzyme that plays a central role in the final step of triglyceride synthesis, catalyzing the reaction of diacylglycerol and fatty acyl-CoA to triacylglycerol. Diacylglycerolacyltransferase type 2 (DGAT2) catalyzes the same reaction but is expressed in the liver, whereas DGAT1 is mainly expressed in the small intestine (6). The mechanism causing PLE in DGAT1 deficient patients is not yet fully understood, but experimental studies show impaired lipid droplet formation in DGAT1 deficient cells compared to healthy controls (7). Lipid droplets are cytosolic organelles that play an important role in dietary fat absorption and protect enterocytes from lipotoxic effects caused by excessive postprandial concentrations of fatty acids and sterols (8). This was confirmed in vitro, with cell death occurring at significantly lower doses of oleic acid in DGAT1 deficient cells compared to healthy cells, suggesting that lipotoxicity-induced enterocyte apoptosis might be the underlying mechanism of PLE in DGAT1 deficiency (Figure 1A) (7). Previously, a reversible loss of apical transporters leading to altered polarity with impaired integrity of tight junctions between enterocytes was observed in duodenal tissue of a patient with DGAT1 deficiency, which might be another possible explanation for the resulting PLE (Figure 1B) (9).

Here, we describe a patient with a DGAT1 variant and failure to thrive. We performed a literature review of all previously reported cases of this rare but severe disorder and analyze patient characteristics, clinical presentation, laboratory and histologic features, treatment and outcome. We then discuss optimal nutritional management of patients with DGAT1 variants. This overview will support clinicians in diagnosis and management of these children.

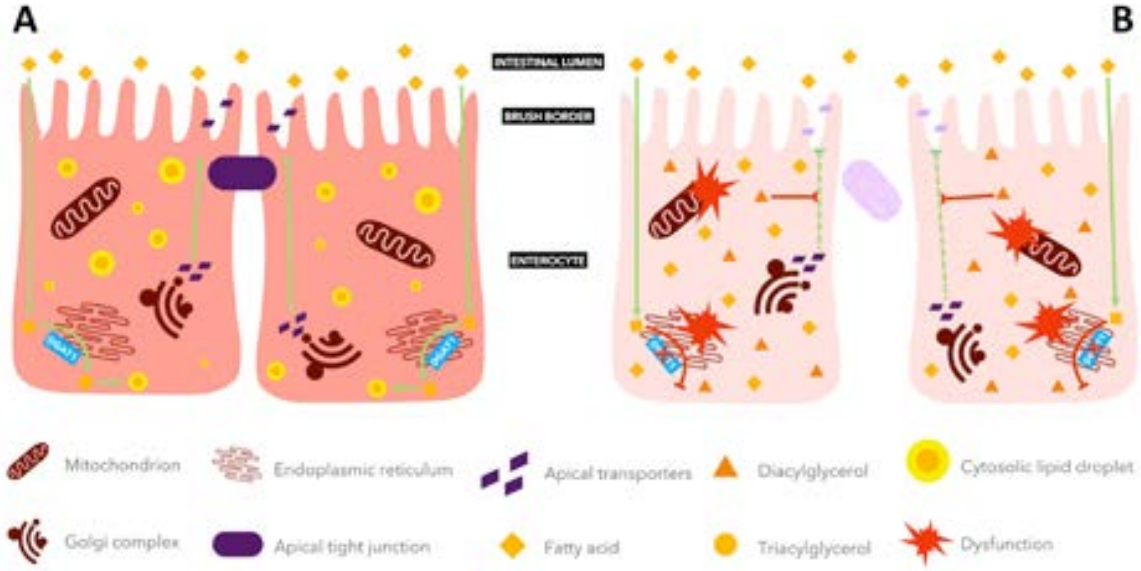
Methods

A search conducted in PubMed, Cochrane Library and Embase using 'DGAT1 deficiency', 'DGAT1 mutation', 'DGAT1 diarrhea', 'DGAT1 enteropathy', 'DGAT patients' and the Emtree term 'diacylglycerol acyltransferase 1' singly combined with Emtree terms 'enzyme deficiency', 'gene mutation', 'diarrhea' and 'protein losing enteropathy' until December 2020 provided 306 results. All relevant articles were in English and full text versions were available. Additional search on 'DGAT1 hypogammaglobulinemia' and 'DGAT1 hypoalbuminemia' and review of the references of these articles did not yield any extra publications. We identified 22 cases of children diagnosed with variants in DGAT1 and gastrointestinal disease from 8 articles. Data on patient characteristics, clinical presentation, diagnostic findings and treatment were extracted and analyzed. Continuous data are presented as median and categorical variables are reported as counts and percentages. If a variable was not determined, it is not included in the denominator.

Case description

A 2.5-month-old previously healthy girl presented with diarrhea and feeding difficulties. She was born in Belgium, to consanguineous parents of Turkish origin, after an uncomplicated full-term pregnancy. At first presentation, she had an acute episode of vomiting and diarrhea, complicated by Klebsiella sepsis and hip arthritis, severe metabolic derangement and hypoalbuminemia. She stabilized after treatment with antibiotics and intravenous fluids. She was

Figure 1 : *Schematic overview of proposed hypotheses regarding the underlying mechanisms causing protein-losing enteropathy in DGAT1 deficiency. A: In healthy enterocytes, fatty acids are absorbed from the intestinal lumen, and then directed from the apical membrane to the endoplasmic reticulum for triacylglycerol synthesis. This process is catalyzed by DGAT1 and results in the formation of neutral lipid storage organelles called cytosolic lipid droplets, thereby protecting the epithelium from lipotoxicity. Trafficking and insertion of apical transporters and junctional proteins result in polarization of the epithelial cells, which is necessary for effective absorption of nutrients and junctional integrity. B: If enterocytes lack DGAT1, triacylglycerol synthesis is impaired, leading to fewer cytosolic lipid droplets and excess of fatty acid and diacylglycerol (upstream products in the pathway of triacylglycerol synthesis). These high amounts of intracellular lipids lead to endoplasmic reticulum stress and mitochondrial dysfunction, resulting in cell death. In addition to this lipotoxicity, deficits in apical transporter trafficking caused by intracellular diacylglycerol and alterations in intercellular junctions of enterocytes that have been observed in DGAT1 deficient cells might contribute to malabsorption and protein loss.*



initially assumed to have cow's milk protein allergy because of elevated IgE levels specific for casein and because she improved slightly when started on elemental formula. However, this was insufficient to explain the clinical course: she persistently failed to thrive and she had recurrent episodes of diarrhea and vomiting whenever enteral feeding was restarted or increased despite the use of different formula feeds, including extensive hydrolyzed whey protein and amino acid based-formula. Gastroduodenal and colonic endoscopy showed no macroscopic or microscopic abnormalities. She developed hypoalbuminemia and hypogammaglobulinemia and technetium 99m-labeled human serum albumin scintigraphy confirmed the diagnosis of PLE. She received several albumin infusions and parenteral nutrition every time she relapsed. The clinical course was complicated by recurrent catheter-related thrombosis for which she received low molecular weight heparin. She also suffered from iron deficiency anemia, for which she received packed cell transfusion and iron supplementation, and from an episode of acute gastro-enteritis due to rotavirus for which she was rehydrated with oral rehydration salts.

A congenital diarrhea gene panel analysis containing 64 genes (DIA00v17.1) was performed, using next generation sequencing (NGS) by the Illumina NGS sequencing system (10). A novel homozygous variant c.469-2A>G in DGAT1 was found, explaining the clinical presentation through aberrant gut epithelial lipid metabolism (7). Both parents and the older brother were identified as heterozygous carriers. No other pathogenic or likely pathogenic variants were found.

After establishment of this diagnosis at the age of 9 months, she was started on a fat-restricted diet and parenteral lipid administration, after which we observed a favorable evolution with normalization of stool pattern and a very good weight gain from far below -2 standard deviation (SD) to more than 0 SD in three months time (Figure 2B). Her height and head circumference increased from approximately -2 SD and -1.5 SD to +1 SD and +1.5 SD respectively at the age of eighteen months (Figures 2A and 2C). Also, weight for height increased from below -2 SD to more than +1 SD before stabilizing around 0 SD (Figure 2D). Until the age of eighteen months, a fat-free diet was continued in the form of extensively hydrolyzed whey protein maltodextrin mixture via nasogastric tube, fruit and vegetables. She was then weaned off parenteral feeding, but as she developed deficiencies of linoleic and arachidonic acid, monthly infusions of SMOFlipid were administered. At the age of 26 months she started vomiting and developed edema, severe lactic acidosis and a combined cardiogenic and distributive shock caused by a thiamine deficiency. She is now 31 months old, completely weaned off parenteral nutrition since one month and thriving with a fat-free formula via nasogastric tube and oral intake of solid food with a maximum of six grams fat per day.

Results

Patient characteristics

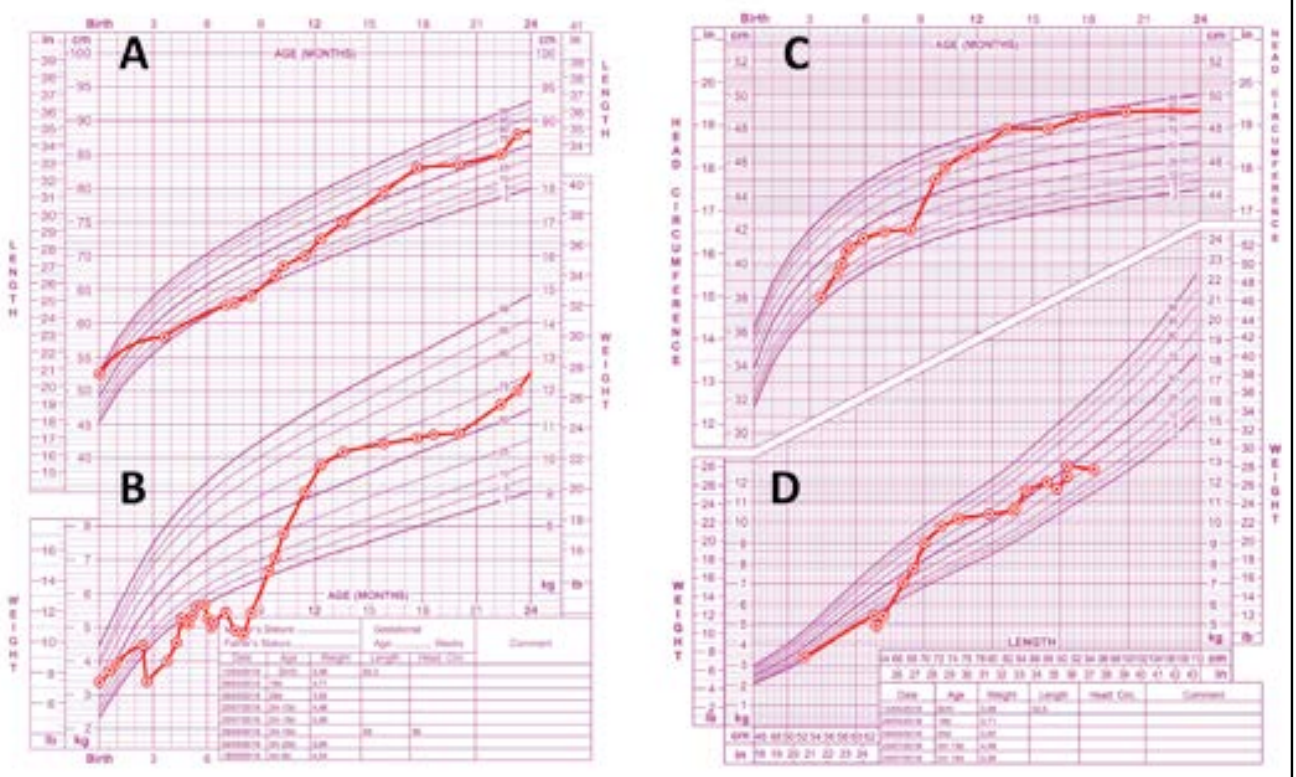
Children with DGAT1 variants present at a very young age: the age of onset was less than one month in 65.2%, and less than three months for 95.7% of all patients. Of all cases, 39.1% were female. Ten affected children (43.5%) were born to consanguineous parents. Thirteen genetic variants of DGAT1 were reported in sixteen families. Two patients had a compound heterozygous variant, the others were homozygous (Table 1).

Clinical presentation

Clinical presentation and laboratory findings are summarized in Table 1. Most patients presented with failure to thrive (18/20 = 90%). Two patients did not fail to thrive: one because he underwent surgery for an incarcerated inguinal hernia and received parenteral nutrition from birth, the other because he was started on a fat-restricted diet very shortly after birth to treat vomiting because he had an older sibling who was thriving on a similar diet. For three patients, no information on thriving was available. Vomiting was present in sixteen patients and diarrhea in twenty patients.

Laboratory findings showed hypoalbuminemia in eighteen patients (18/21 = 85.7%), but in only seven of them edema was present. Although hypertriglyceridemia appears to be a feature of human DGAT1 deficiency (6, 11), it was assessed in only fourteen cases and elevated in eight of them (57.1%, range 112-739 mg/dL). Derangement of electrolytes was described in four patients, mainly low serum bicarbonate, magnesium, phosphorus, sodium and potassium levels. In four cases low vitamin D, low calcium, secondary hyperparathyroidism and/or osteopenia were described. Our case also had decreased levels of vitamin A and zinc. Metabolic acidosis was mentioned in four patients. Newborn screening and/or additional metabolic

Figure 2 : *Growth of reported index case in World Health Organization growth standards. A: Length for age; B: Weight for age; C: Head circumference for age; D: Weight for length.*



screening was performed in six patients, showing no evidence of inborn errors of metabolism. Alpha-1-antitrypsin was elevated in stool of nine patients (9/11 = 81.8%). Stool elastase levels were low in two cases (2/7 = 28.6%).

In nineteen patients endoscopy was performed, but macroscopic abnormalities were not seen in any of them. Histologic findings were abnormal in nine patients (9/19 = 47.4%). The abnormalities found in these patients consisted of duodenal enterocytic lipid accumulation, shortening and rarefaction of microvilli, focal vacuolization and partially blunted villi, CD10 positive globules, laterally located microvilli, blunting of duodenal mucosa and patchy gastric metaplasia, focal acute colitis with cryptitis, mild chronic inflammation, focal foveolar metaplasia and dystrophic microvilli.

Extra-intestinal manifestations and comorbidities were present in seventeen children. Recurrent infections or sepsis were described in ten of them (10/17 = 58.8%), probably at least partially related to hypogammaglobulinemia, which was present in fifteen patients (15/18 = 83.3%). Malabsorption led to iron deficiency anemia in three patients. Venous thrombotic disease was seen in three patients. Two affected siblings were diagnosed with Gilles de la Tourette syndrome and treated with dexamphetamine. Other comorbidities were corneal cystine crystal accumulation, nephrolithiasis, hepatomegaly with jaundice due to fibrosis and cholestasis and crossed fused renal ectopia with hydronephrosis. Developmental delay was seen in two patients and hypotonia in one.

Treatment and outcome

Eighteen patients required parenteral nutrition (18/23 = 78.2%). Eleven patients were weaned off parenteral nutrition but insufficient details were available to determine a median age of weaning. At follow-up, fourteen children received a diet with some degree of fat restriction (14/19 = 73.7%), varying from a regular diet without dairy products to a completely fat free diet with parenteral lipid administration. Nutritional management was not described in detail for every case, but most children were started on an elemental formula feed.

The two patients with low fecal elastase received supplementation of pancreatic enzymes, after which stool frequency improved. Although the youngest of these children is still below the third percentile for height and weight, symptoms resolved after two years in the older one.

Two children were treated with cholestyramine; one started at the age of 27 months because of combined hyperlipidemia and was thriving on an unrestricted diet at the age of 46 months, the other child did not need any adaptation of enteral diet. Only one other child received a normal diet, but she was still not thriving and depended on parenteral nutrition due to a complicated course after small bowel transplantation because of a misdiagnosis of microvillus inclusion disease.

Supportive treatment with albumin and/or red blood cell transfusion was given in eleven cases and six children received intravenous immunoglobulines during the course of the disease.

Four patients passed away (4/23 = 17.4%). Two of them died of sepsis at the age of 6 and 17 months. Age and cause of death of the other two patients were not specified.

Discussion

In this review, we provide an overview of the clinical presentation of 23 patients with DGAT1 variants. DGAT1 deficiency is a rare disorder that can result in severely impaired growth and dependence on parenteral nutrition. Moreover, delayed diagnosis and complications of treatment impede clinical progress in these children. Mortality was demonstrated to be 17.4% in published cases. Supportive and nutritional management with a focus on fat restriction leads to resolution of symptoms and improved growth in the majority of patients, and sometimes even appears to be needed only temporarily. As DGAT1 is included in gene panels for congenital diarrhea it is likely that the diagnosis of DGAT1 deficiency will be encountered more often by clinicians. Therefore, practical guidelines for nutritional management of these patients will become increasingly important.

Table 1 : *Patient characteristics, presentation and laboratory findngs * = index patient; † = died; M = male; F = female; U = unknown; ND = not determined or not described; N = normal; H = high; L = low. References: patients 2-11 (7), patients 12 and 13 (12), patient 14 (9), patient 15 (17), patients 16-18 (11), patients 19 and 20 (6), patient 21 and 22 (18), patient 23 (19)*

Patient	Sex	Origin	Consan-guinity	Variant	Age of onset	Failure to thrive	Vomiting	Diarrhea	Edema	Serum triglycerides	Hypoalbu-minemia	Hypogamma-globulinemia	Alpha-1-antitrypsin in stool	Elastase in stool
1*	F	Belgium, Turkish	+	c.469-2A>G	2.5 months	+	+	+	+	H	+	+	ND	ND
2	M	Turkey, Turkish	+	c.1202G>A, p.W401X	Birth	+	+	+	+	H	+	+	ND	ND
3†	F	Turkey, Turkish	+	c.1202G>A, p.W401X	Birth	+	+	+	+	N	+	+	ND	ND
4	F	Turkey, Turkish	+	c.573_574delAGinsCCCATC-CCACCCTGCCCATCT	3 weeks	+	+	+	+	H	+	+	N	N
5	M	Turkey, Turkish	+	c.937-1G>A	2 months	+	+	+	-	N	+	+	ND	ND
6	M	Turkey, Turkish	+	c.953insG, p.I319Hfs*31	40 days	+	+	+	-	ND	+	+	ND	L
7	M	Turkey, Turkish	+	c.953insG, p.I319Hfs*31	2.5 months	+	+	+	-	N	+	+	ND	L
8	M	The Netherlands, Caucasian	+	c.629_631delCCT, p.S210_Y211delinsY	First month	-	+	-	-	ND	-	ND	ND	ND
9	M	The Netherlands, Caucasian	+	c.629_631delCCT, p.S210_Y211delinsY	First month	+	+	-	-	ND	-	ND	ND	ND
10	M	The Netherlands, Caucasian	ND	c.629_631delCCT, p.S210_Y211delinsY	Birth	+	+	+	-	ND	+	+	H	ND
11	F	The Netherlands, Caucasian	ND	c.629_631delCCT, p.S210_Y211delinsY	Birth	+	+	+	-	ND	+	+	ND	ND
12	M	South-Asian descent	ND	c.314C>T, p.L105P	Shortly after birth	+	ND	+	ND	H	-	+	H	N
13	M	South-Asian descent	ND	c.314C>T, p.L105P	Shortly after birth	+	ND	+	ND	ND	ND	ND	H	ND
14	M	Hispanic	ND	g.13827T>C, p.Ala226_Arg250del	7 weeks	+	+	+	ND	ND	+	+	N	N
15	F	Caucasian	ND	maternally c.1013_1015delTCT, p.Phe338del and paternally c.1260C>G, p.Ser420Arg	1 month	+	+	+	ND	N	+	+	H	ND
16	M	Arab-Muslim	+	c.884T>C, p.Leu295Pro	2 months	+	ND	+	+	H	+	+	H	N
17	M	Ashkenazi Jewish	-	g.13827T>C, p.Ala226_Arg250del	8 days	+	ND	+	+	N	+	-	H	N
18	M	Ashkenazi Jewish	-	g.13827T>C, p.Ala226_Arg250del	17 days	-	ND	+	ND	H	+	-	H	ND
19†	F	Ashkenazi Jewish	-	g.13827T>C, p.Ala226_Arg250del	3 days	+	+	+	ND	H	+	+	H	ND
20	M	Ashkenazi Jewish	-	g.13827T>C, p.Ala226_Arg250del	3 days	ND	ND	+	ND	H	ND	-	H	ND
21†	F	Chinese, Han or Uyghur	-	c.895-1G>A	0 months	ND	+	+	ND	ND	+	ND	ND	ND
22†	F	Chinese, Han or Uyghur	-	c.249-6T>G	30 months	ND	ND	ND	+	ND	+	ND	ND	ND
23	F	Chinese	-	maternally c.895-1G>A and paternally c.751+1G>C	Shortly after birth	+	+	+	ND	H	+	+	ND	ND

Our review shows that a majority of patients presented with failure to thrive, vomiting and diarrhea, and only a minority was described to have edema. Lack of improvement on elemental formula feeds should therefore prompt to think of PLE, even in the absence of edema. Early laboratory testing for signs of malabsorption in these children, including alpha-1-antitrypsin in stool and serum albumin level, is indicated as advised in the diagnostic algorithm proposed by Thiagarajah et al (1). Serum triglycerides are elevated in 57.1% of patients with DGAT1 deficiency, and should be measured as well. Because histologic findings are often nonspecific, endoscopy is not very useful for detecting abnormalities related to DGAT1 deficiency, although it maintains its place in the diagnostic process to rule out other conditions. Early diagnosis and adequate nutritional management might decrease the need for symptomatic treatment like albumin or red blood cell transfusions, administration of intravenous immunoglobulines or parenteral nutrition.

Infants presenting with persistent diarrhea or vomiting and failure to thrive are often started on an elemental formula because of suspected cow's milk protein allergy. However, as elemental formula feeds developed for treating cow's milk protein allergy generally contain around 30% of total calories from fat – comparable in composition to breast milk and standard infant formula – they are not expected to lead to improvement in patients with DGAT1 deficiency.

Nutritional management in DGAT1 deficiency poses a great challenge, but recent findings about possible underlying mechanisms causing PLE in these patients have provided leads (7-9). Key to the treatment seems to be a restriction of enteral administration of fat with appropriate parenteral supplementation of fat and fat-soluble vitamins to bypass the impaired process of triglyceride synthesis and protection against lipotoxicity. More detailed descriptions of treatment strategies could provide clarity on which

enteral formula feeds are best given and what the maximum or tolerated range of calories from enteral fat is in patients with DGAT1 deficiency. Enteral fat tolerance might differ between genetic variants and might be determined more precisely if it would be possible to establish the degree of enzyme activity (12). From clinical practice perspective, enteral fat tolerance can be established for patients individually by starting with complete enteral fat restriction, meeting essential fatty acid needs from parenteral nutrition, followed by a progressive increase of the quantity of fat in the diet with close monitoring of symptoms. Some patients appeared to show some improvement when enteral fat was provided in the form of MCT, but the effect on symptoms, growth and need for parenteral nutrition is still largely unknown. Studies addressing the effect of MCT on lipid droplet formation by DGAT1 deficient cells might shed light on the role of MCT in the prevention of lipotoxicity and its place in the treatment of DGAT1 deficiency.

Parenteral nutrition has a prominent role in the management of DGAT1 deficiency and this leaves clinicians with a lot of choices to make about type of intravenous lipid emulsion and fat-soluble vitamin preparations, frequency, dose and way of administration and follow-up of clinical and biochemical parameters (13). Parenteral nutrition is indicated whenever enteral nutrition leads to ongoing symptoms or nutrient deficiencies including essential fatty acids deficiency. Clinicians should be aware of risks like catheter-related thrombosis and sepsis or parenteral nutrition associated liver disease. Mixed lipid emulsions appear to be associated with less liver injury in hospitalized children than soybean-based lipid emulsions (14, 15). Hypertriglyceridemia and electrolyte derangements due to the disorder could be complicating factors in the follow-up. DGAT1 deficiency was associated with higher serum levels of triglycerides in 57,1% of the patients, possibly due to overcompensation of hepatic DGAT2 (6).

Pharmacological treatments like pancreatic enzyme supplementation or cholestyramine were sporadically used in DGAT1 deficiency and had a beneficial effect on stool frequency, but the low number of patients treated and the information provided was insufficient to draw meaningful conclusions. Since pancreatic enzymes mainly affect fat digestion and cholestyramine the absorption of cholesterol, it is theoretically not very likely that DGAT1 deficient patients would benefit from these interventions.

One hypothesis about the underlying pathophysiology is that DGAT1 deficiency causes a defect in the formation of intracellular lipid droplets. Previous studies showed that DGAT1 mutant fibroblasts contained fewer cellular lipid droplets when exposed to oleate, the conjugate base of oleic acid, compared to wild-type cells. This effect on lipid droplet formation was confirmed in patient-derived cells and organoids (7, 11). While in murine intestine both DGAT1 and DGAT2 are expressed, in human intestine only DGAT1 is highly expressed (6). However, recent findings showed functional DGAT2 expression in human epithelial stem cells and the capacity of DGAT2 to compensate for lipid droplet formation when DGAT1 function was inhibited in these stem cells (16). So far, no therapies have been described to increase intestinal DGAT activity in patients with DGAT1 deficiency, but upregulation of DGAT2 expression in human mature enterocytes could be a promising target for future therapeutic interventions (16). In vivo overexpression of DGAT2 in enterocytes of patients with DGAT1 deficiency has not been described, but could theoretically explain the favorable prognosis with restored enteral fat tolerance in some patients.

A limitation of this review is that no conclusions can be drawn about the effect of different management strategies on clinical outcome, because only observational case series are available. As they differ in the level of detail provided considering treatment choices, comparisons are difficult to make. Furthermore, the rarity of the disorder impedes the implementation of prospective comparative studies.

Since an increase of cases diagnosed with DGAT1 deficiency can be expected, as the gene is added to screening panels for congenital diarrhea, sharing of detailed nutritional management strategies and their effects on clinical outcome is needed to improve and accelerate treatment of these patients and decrease morbidity, mortality and complications in the future.

Disclosure

No potential conflicts of interest were reported by any of the authors.

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