Familial chylomicronemia syndrome: a novel mutation in the lipoprotein lipase gene

S. Van Biervliet[1], S. Vande Velde[1], P. De Bruyne[1], B. Callewaert[2], P. Verloo[3], R. De Bruyne[1]

(1) Pediatric gastroenterology, hepatology and nutrition department, Ghent University Hospital, Ghent, Belgium; (2) Center for medical genetics, Ghent University Hospital, Ghent, Belgium; (3) Center for metabolic diseases, Ghent University Hospital, Ghent, Belgium.

Abstract

Familial chylomicronemia syndrome (FCS) (OMIM: 238600) is a rare autosomal recessive disease caused by a biallelic loss-of-function mutation in the lipoprotein lipase (LPL) complex which includes LPL and its co-factors. Patients with FCS have severe hypertiglyceridemia (> 2000 mg/dL). We describe a 15-month-old boy with repeated pancreatitis episodes caused by severe hypertriglyceridemia. Genetic analysis revealed a novel homozygous mutation in the LPL gene, i.e. c.626T>G; p.(Leu209*). The mutation, carried by both parents, has been classified as a type 4 mutation which is likely pathogenic. Treatment aims at decreasing hypertriglyceridaemia by a low-fat diet (< 20g/day) eventually supplemented with medium chain triglyceride (MCT) fat to ensure caloric intake. In 2019, volanesorsen was approved by the European Medicines Agency (EMA) as adjunct treatment for adult patients with genetically proven FCS and persisting episodes of pancreatitis despite the diet. (Acta gastroenterol. belg., **2024,** 87, **326-328**).

Keywords chylomicronemia, pancreatitis, lipoprotein lipase, hypertriglyceridemia, child

Abbreviations: ApoC2 Apolipoprotein C2; ASO antisense therapeutic oligonucleotide; EMA European Medicines Agency; FCS Familial Chylomicronemia syndrome; LPL lipoprotein lipase; MCT medium chain triglyceride; 2'-MOE: 2′-O-methoxyethyl.

Introduction

As first example of an inborn error in plasma lipid metabolism, chylomicronemia was attributed to LPL deficiency by Havel et al. (1). Familial chylomicronemia syndrome (FCS, OMIM: 238600) is a rare autosomal recessive disorder caused by a mutation in the genes coding for lipoprotein lipase (LPL) or its regulators. The LPL complex plays a key role in the handling of both exogenous and endogenous fat. The, in the intestine absorbed, fat is converted into triglyceride-rich chylomicrons. The LPL complex which is anchored to the vessel wall, hydrolyses the *sn*-1/*sn*-3 ester bonds of triglycerides resulting in the production of fatty acids and monoglycerides and reducing the triglyceride content of the chylomicrons. The chylomicron remnant will then be transported to the hepatocytes. Attached to apolipoproteins, triglycerides and other fats will then be carried from the hepatocytes to other tissues. LPL further plays an important role in the hydrolysis of triglycerides from the very-low-density lipoproteins. Although LPL expression is widely distributed throughout the body, the highest levels are present in tissues with important lipid handling, such as muscles (heart and skeletal) or tissues responsible for energy storage such as adipose tissue (2,3).

To reduce the instability of LPL, several chaperones are essential to obtain a proper LPL functioning. Lipase maturation factor 1 regulates LPL expression, ensures proper folding and stabilises LPL during parenchymal production (2,3) Heparan sulfate proteoglycans stabilise LPL during the secretory pathway and in the extracellular matrix (4). Glycosylphosphatidylinositol Anchored High Density Lipoprotein Binding Protein 1 is responsible for the transport of LPL from the abluminal endothelial surface to the site of action (5). Apolipoprotein CII (apoC2) activates the LPL enzymes whereas apoA5 stabilizes the LPL-apoC3 complex by promoting the binding of triglyceride-rich lipoproteins to heparan sulfate proteoglycan (6,7).

Although FCS can be caused by mutations in the genes of either of these proteins, most of the more than 200 known mutations are present in the *LPL* gene especially in exons 4, 5 and 6 (8). We report a 13 month old boy with a clinical picture compatible with FCS and homozygous mutation in the *LPL* gene, *c.626T>G; p.(Leu209*)*.

Case report

A 13-month-old boy of Afghan origin presented at the emergency ward due to recurrent episodes of irritability and discomfort. The aetiology of the pain and irritability was a recurrent pancreatitis as demonstrated by a severe increase in serum lipase. During the first 2 episodes, he had not used any medication, no viral cause could be identified and the sweat test was normal. Genetic work-up for familial pancreatitis (CFTR, SPINK1, PRSS1) was negative. Magnetic resonance cholangiopancreatography did not reveal any abnormalities besides a mild splenomegaly. Parents were third degree relatives but had no medical history of note. Their first child passed away

Correspondence to: Stephanie Van Biervliet, C. Heymanslaan 10, 9000 Ghent, Belgium.
Email: Stephanie.vanbiervliet@ugent.be

Submission date: 30/05/2023
Acceptance date: 26/07/2023

15-Van Biervliet.indd 326 22/06/2024 09:49

in Afganistan at the age of 8 months, due to a pneumonia but in retrospect the clinical picture seemed very similar to the presentation in this boy according to the parents. There is also a healthy 2-month-old sister.

On admission, the clinical picture was compatible with a recurrent pancreatitis episode. The boy had a diffuse tender abdomen, tachycardia and superficial tachypnoea. His lab results displayed inflammation (CRP 70 mg/L (normal value <5 mg/L)), increased lipases (380 U/L; <40U/L) and hypertriglyceridemia 2369 mg/dL (22-99 mg/dL). A creamy layer of chylomicrons was apparent on the top of his blood sample (fig 1). There was no lipemia retinalis but he had xanthomas on his elbows. He was started on intravenous fluids and antalgics. Once his pancreatitis was controlled, a diet limited in fat (<20g/day) was started. His triglycerides decreased to 1390 mg/dL at discharge and further decreased during follow-up to 911 mg/dL. He developed only one other episode during the following 2 years and has been thriving well (height +0.2 SD; weight +0.2 SD). Dietary follow-up checked for essential fatty acid intake and fat soluble vitamins remained normal.

The genetic testing revealed a homozygous new mutation in the *LPL* gene, i.e. *c.626T>G; p.(Leu209*)*. This mutation has not been reported so far in the gnomAD database and is to our knowledge not described in the literature. As approximately 30% of known pathogenic mutations are stop codons or frameshift mutations according to Genereviews NBK1308, the mutation was classified as class 4 (i.e. probably pathogenic).

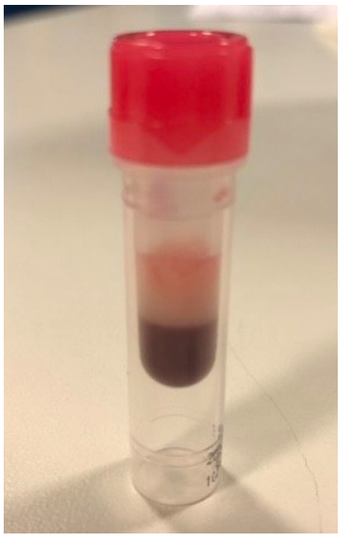

Fig 1. — Blood sample demonstrating the creamy layer of chylomicrons on top of the blood cells after resting the sample.

Discussion

The primary causes of acute pancreatitis in childhood are blunt abdominal trauma, viral infections, gallstones,

Table 1. — **Diagnostic criteria for primary chylomicronemia** (2)

Criterion	
A:	Presence of plasma triglycerides ≥ 1000 mg/dl after at least 12 hours fasting + presence of chylomicrons in serum (cream layer after 24 hours stand at 4°C/ ultracentrifugation / electrophoresis)
B: Clinical manifestations	1. Recurrent episodes of pancreatitis / abdominale pain
	2. Eruptive xanthomas
	3. Lipemia retinalis
	4. Hepato- and/or splenomegaly
	5. Dyspnea
	6. Neurologic symptoms: cognitive impairment, memory impairment, depression
C: Laboratory	1. LPL activity and/or protein in post heparin plasma, adipose tissue or macrophages is absent or markedly decreased (<10% of normal)
	2. Apolipoprotein C-II absent or markedly decreased (<10% of normal)
	3. Apolipoprotein A-IV absent or markedly decreased (<10% of normal)
	4. Autoantibodies against LPL, heparin, Apolipoprotein C-II or Glycosylphosphatidylinositol Anchored High Density Lipoprotein Binding Protein 1
D: Genetic test	identification of causative mutation(s): *LPL, APOC2, GPIHBP1, LMF1, APOA5*
E: Differential diagnosis	Type 3 hyperlipidemia, familial combined hyperlipidemia (FCHL), and secondary hyperlipidemia due to following: excess alcohol intake, nephrotic syndrome, anorexia nervosa, pregnancy, diabetes mellitus, lipodystrophies, Weber-Christian disease, hypothyroidism, acromegaly, Cushing's syndrome, Nelson's syndrome, multiple myeloma, systemic lupus erythematosis, malignant lymphoma, sarcoidosis, etc.; medications such as estrogens, steroids, diuretics, β-blockers, antipsychotics including selective serotonin reuptake inhibitors (SSRIs), retinoids such as isotretinoin, antiretroviral protease inhibitors, immunosuppressants, etc.
Diagnosis: – Definite: Entry criterion (A) associated with at least one item from C or D. − Probable: Entry criterion (A) associated with at least one item from B1-4. − Possible: Entry criterion (A) associated with or without item(s) from B5-6.	

15-Van Biervliet.indd 327 22/06/2024 09:49

drug-induced and alcohol. In case of recurrent pancreatitis anatomic anomalies, cystic fibrosis, hereditary pancreatitis and hypertriglyceridemia need to be ruled out. A Serum triglyceride level above 1000 mg/dL significantly increases the risk for pancreatitis and is suggestive for a hereditary trait (2). Using the table with diagnostic criteria as stated by Okazaki et al can help to evaluate the likelihood of primary chylomicronemia (table 1) (2). The described patient fulfils the criteria A, B1, B2 and D.

FSC is a rare ($1/10^6$ persons), potentially life threatening autosomal recessive disease. The diagnosis is based on the clinical picture supported by genetic analysis. The disease usually becomes clinically apparent during childhood with 25% of patients presenting before the age of 1 year (2). The treatment focusses on lowering the hypertriglyceridemia by dietary fat restriction (< 20g/day) eventually associated with medium chain triglycerides (2,9). This diet is however challenging to maintain. In absence of an effective treatment with the constant risk of pancreatitis episodes, the disease has an important impact on the quality of life (10). Conventional lipid-lowering drugs are typically ineffective in patients with familial LPL deficiency (11).

Genetic confirmation is important as since 2019, volanesorsen is EMA approved as adjunct therapy to diet in adults with genetically proven FCS and insufficient control of symptoms. Volanesorsen is a second-generation 2′-O-methoxyethyl (2′-MOE) chimeric antisense therapeutic oligonucleotide (ASO) that selectively reduces apolipoprotein C3 messenger ribonucleic acid (mRNA), leading to dose-dependent decreases in plasma apolipoprotein C3 and triglyceride levels through LPL-independent pathways (12). This medication is not yet approved for children.

Although FCS is a rare disorder, an early diagnosis is of particular importance as dietary fat restriction (≤20 g/day or 15% of total energy intake), along with medium chain triglycerides, are usually sufficient to reduce plasma triglyceride levels hence keeping the individual symptom free and preventing complications such as pancreatitis.

In conclusion, we here describe a novel mutation within the *LPL* gene, i.e. *c.626T>G; p.(Leu209*)* in a child leading to a typical clinical picture of FCS. Clinicians should be aware of this rare disease as early treatment will reduce the number of pancreatitis episodes and prevent severe complications. Additionally, adequate genetic counselling can be offered to the parents and the family.

Conflict of interest, funding

None of the authors have received funding nor was there a conflict of interest concerning this article

Declarations

Parents gave their consent to publish the story of their son in a scientific medical journal. The consent is registered in the medical file.

Author contributions

VBS and DBR wrote the article
VDVSn DBP, CB, VP revised the article
VBS submitted the article

References

1. Havel RJ, and Gordon RS Jr. (1960). Idiopathic hyperlipemia: metabolic studies in an affected family. J. Clin. Invest. 39, 1777-1790. doi: 10.1172/JCI1 04202
2. Okazaki H, Gotoda T, Ogura M, Ishibashi S, Inagaki K, Daida H, Hayashi T, Hori M, Masuda D, Matsuki K, Yokoyama S, Harada-Shiba M. (2021) Current Diagnosis and Management of Primary Chylomicronemia. J Atheroscler Thromb. 1;28: 883-904. doi: 10.5551/jat.RV17054.
3. Péterfy M. (2012). Lipase maturation factor 1: a lipase chaperone involved in lipid metabolism/ Biochim Biophys Acta. 1821, 790-794. Doi: 10.1016/j.bbalip.2011.10.006
4. Sundberg EL, Deng Y, and Burd CG. (2019). Syndecan-1 mediates sorting of soluble lipoprotein lipase with sphingomyelin-rich membrane in the Golgi apparatus. Dev. Cell 51, 387-398. doi: 10.1016/j.devcel.2019.08.014
5. Young SG, Fong LG, Beigneux AP, Allan CM, He C, Jiang H, et al. (2019). GPIHBP1 and lipoprotein lipase, partners in plasma triglyceride metabolism. Cell Metab. 30, 51–65. doi: 10.1016/j.cmet.2019.05.023
6. Okubo M, Toromanovic A, Ebara T, Murase T. (2015) Apolipoprotein C-II Tuzla: a novel large deletion in APOC2 caused by Alu-Alu homologous recombination in an infant with apolipoprotein C-II deficiency. Clin Chim Acta. 438, 148-153. doi: 10.1016/j.cca.2014.08.022
7. Nilsson SK, Heeren J, Olivecrona G, Merkel M. (2011) Apolipoprotein A-V; a potent triglyceride reducer. Atherosclerosis. 219, 15-21. doi: 101016/j.atrherosclerosis.2011.07.019
8. Henderson HE, Ma Y, Hassan MF, Monsalve MV, Marais AD, Winkler F, Gubernator K, Peterson J, Brunzell JD, Hayden MR. (1991) Amino acid substitution (Ile194—Thr) in exon 5 of the lipoprotein lipase gene causes lipoprotein lipase deficiency in three unrelated probands. Support for a multicentric origin. J Clin Invest. 87, 2005–2011. doi: 10.1172/JCI115229
9. Santos RD, Lorenzatti A, Corral P, Nogueira JP, Cafferata AM, Aimone D, Lourenço CM, Izar MC, Lima JG, Lottenberg AM, Alonso R, Garay K, Morales AR, Vargas-Uricoechea H, Peña CAC, Roman-González A. (2021) Challenges in familial chylomicronemia syndrome diagnosis and management across Latin American countries: An expert panel discussion. J Clin Lipidol. 15(5): 620-624. doi: 10.1016/j.jacl.2021.10.004.
10. Davidson M., Stevenson M., Hsieh A., Ahmad Z., van Lennep J.R., Crowson C., Witztum J.L. (2018) The burden of familial chylomicronemia syndrome: Results from the global IN-FOCUS study. J. Clin. Lipidol. 12:898–907.e2. doi: 10.1016/j.jacl.2018.04.009.
11. Shamsudeen I, Robert A Hegele RA. (2022) Safety and efficacy of therapies for chylomicronemia. Expert Rev Clin Pharmacol. 15(4):395-405. doi: 10.1080/17512433.2022.2094768. Epub 2022 Jul 3.
12. Esan O., Wierzbicki A.S. (2020) Volanesorsen in the Treatment of Familial Chylomicronemia Syndrome or Hypertriglyceridaemia: Design, Development and Place in Therapy. Drug Des. Dev. Ther. 14:2623–2636. doi: 10.2147/DDDT.S224771.

15-Van Biervliet.indd 328 22/06/2024 09:49