Editorial

Familial chylomicronemia syndrome in children: a diagnosis challenge

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Genetic rare diseases are often challenging to diagnose and treat (1). First, because their rarity and diversity of symptoms limits knowledge of them among clinicians. Second, because their diagnosis workflow usually requires laboratory tests that are not always accessible in clinical settings. Third, many of them have no specific therapy. Such is the case of familial chylomicronemia syndrome (FCS), a very rare genetic dyslipidaemia (1-2 cases/million people) presenting with persistent chylomicronemia refractory to conventional treatment. Eruptive xanthomas, lipemia retinalis and/or hepatosplenomegaly have been described in patients with FCS and, as the most severe manifestation, recurrent episodes of abdominal pain and acute pancreatitis that are potentially fatal (2).

FCS is caused by the presence of biallelic pathogenic variants in the five genes encoding the enzyme and proteins directly involved in the lipolytic cascade of triglycerides. Most cases appear in the *LPL* gene, but also *APOC2*, *APOA5*, *GPIHBP1* and *LMF1* harbour FCS causative variants. LPL is the main enzyme that catalyses the hydrolysis of circulating triglycerides; ApoC-II and ApoA-V are its activators, Gpihbp1 its interstitial shuttle and support on the endothelium, and Lmf1 a lipase chaperone responsible for its correct folding, as Shi and Wang depict in the article which is object of this editorial (3). The direct consequence of these genetic alterations is the lack of LPL activity that causes a sharp elevation of chylomicrons known in the literature as type I hyperlipidaemia (4).

As a genetic disease, FCS often manifests in infancy (5). However, many patients are diagnosed in adulthood and the start of symptoms in childhood is assessed retrospectively (*Table 1*). As mentioned, the diversity of symptoms and the difficulty of performing genetic and biochemical tests can explain, at least partially, the delay in achieving an FCS diagnosis. In addition, symptoms overlap with those of other chylomicronemia syndromes such as multifactorial chylomicronemia (MCS), lipodystrophy, glycogen storage disease and the presence of autoantibodies against LPL or Gpihbp1 (2,11-13). Furthermore, most cases of chylomicronemia and even pancreatitis in children and adolescents are due to secondary causes (14).

The article by Shi and Wang presents a paediatric patient who was referred to her Thrombosis and Hemostasis centre due to an abnormal coagulation profile, although she was asymptomatic. The girl was finally diagnosed as having FCS due to *LPL* gene variants in compound heterozygosity. The main importance of this article is based on four key points. Firstly, the indicator which lead these authors to the final diagnosis was simply the observation of milky serum. Secondly, they performed *in vitro* functional studies to

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Table 1 Clinical features of paediatric cases reported with FCS due to pathogenic variants in *LPL*

References	Paediatric cases, n	Age	Asymptomatic patients, n	Panc/Ap	HSPL	EX	LR	Other symptoms	RR, n	Different *LPL* variants, n	LPL act./IVS
(5)	13	<1 y	4	1[b]	4	1	5	A, D, F, I, M, P, S, V	13	3	Yes/No
(6)[a]	20	3 d–16 y	5	8	7	6	5	D, F, M, V	10	20	Yes/Yes
(7)	2	3 m–12 y	1	1	0	0	0	D, V	1	2	Yes/No
(8)	2	1 m–1 y	1	1	1	0	0	NM	1	2	No/No
(9)	1	3.5 m	1	0	0	0	0	F, V	0	1	No/No
(10)	10	1 m–10 y	4	3	1	4	1	NM	0	NS	No/No
(3)	1	4 y	1	0	1[c]	0	0	NM	0	2	No/Yes

[a], pediatric cases revised from the original references cited in the article (number 28, 29, 30, 31, 34, 35, 36, 42, 43, 47, 49, 50, 55. Studies from 1991 to 2001). [b], episode occurred as adolescent taking contraceptives. [c], splenomegaly observed after examination. The age at the onset of symptoms at presentation or from RR is shown as: y: years; d: days; m: months. FCS, familial chylomicronemia syndrome; Panc/Ap, number of cases that have had at least one pancreatitis or abdominal pain episode; HSPL, hepatosplenomegaly; EX, eruptive xanthomas; LR, lipemia retinalis; other symptoms: A: anaemia; D: diarrhoea; F: fever; I: irritability; M: melena episode; P: pallor; S: seizures; V: vomiting; NM, not mentioned in the original article; RR, retrospective records; LPL act./IVS, LPL activity measurements/*in vitro* studies; NS, not specified in the original article.

prove variants pathogenicity. Thirdly, the authors extend the genetic study to the patient's family providing it with segregation data. Finally, their work contributes to make FCS known among clinicians not necessarily specialised in lipidology.

As mentioned, most FCS cases are due to pathogenic variants in *LPL*. A revision of paediatric patients from different publications (with patients' ages ranging from a few days after birth to 16 years old) suggests that FCS symptoms in children are more elusive than those in adults (*Table 1*). Seventeen cases out of 50 were asymptomatic at presentation and clinicians just observed febrile episodes, vomiting and/or diarrhoea, and lactescent serum after examination. Physical manifestations of chylomicronemia (hepatosplenomegaly, eruptive xanthomas and/or lipemia retinalis) were observed in 26 cases either at presentation or after examination. Among cases summarised in *Table 1*, only one child failed to thrive and acute pancreatitis or abdominal pain was reported in 14 of these children (28%). In the adult FCS series, pancreatitis prevalence is higher (>85%) (15,16). Apart from a possible selection bias in these studies and patients' individual susceptibility to pancreatitis, the shorter time of exposition to chylomicronemia can explain the lower prevalence in children. In fact, some of the patients shown in *Table 1* had pancreatitis episodes later, in adulthood.

Shi and Wang found an extremely prolonged activated partial thromboplastin, prothrombin and thrombin times in their patient. It has been extensively described that a lipemic serum can interfere with biochemical measurements (17). However, fewer studies report the alteration of haemostasis parameters (18). The girl studied has splenomegaly but, fortunately, she has not had pancreatitis episodes and she thrives well. These "mild" and diverse symptoms exhibited by some FCS paediatric patients highlight the importance of authors' observations of an altered coagulation profile as another non-specific observation to take into account in FCS paediatric patients.

The development of next-generation sequencing (NGS) techniques over the last decade has facilitated genetic testing greatly. The correct assessment of pathogenicity to variations identified is crucial in order to achieve a correct diagnosis. However, with the massive amount of information generated, variant interpretation becomes a challenge. Computational analyses help in taking into consideration the potential pathogenicity of variants with unknown clinical significance. Nevertheless, taking them as the only source of evidence to assign pathogenicity can lead to wrong interpretations. For instance, *LPL* premature stop codons are predicted *in silico* to be pathogenic. However, based on biochemical and/or functional studies, pathogenicity should not be accredited automatically (19).

The *LPL* variants described by Shi and Wang can be classified as pathogenic based on four pieces of evidence, in accordance with the recommendations of the American College of Medical Genetics and Genomics (ACMG): allele frequency, computational predictions, family segregation data and, very importantly, the functional *in vitro* validation performed by the authors (20). Similarly, most of the *LPL* variants described in the references summarised in *Table 1* have confirmed pathogenicity because LPL activity deficiency was proved and *in vitro* functional studies were performed. These initial studies carried out in the nineties provide us with valuable knowledge to interpret variants identified in the current "NGS times".

Shi and Wang found that the patient's family had hypertriglyceridaemia (HTG) and performed whole exome sequencing (WES) with samples from the entire family. Compared to a targeted strategy that would focus on the five canonical genes for FCS, WES allows detection of genetic defaults responsible for other chylomicronemia syndromes mentioned before. Interestingly, no other TG-rising variants than the *LPL* pathogenic changes described were found in the patient's parents and grandparents. In previous studies, it has been shown that heterozygous carriers of *LPL* pathogenic variants can be normolipemic (16). As the authors point out in their paper, the impact of harbouring heterozygous loss-of-function variants depends on secondary factors. We might also speculate that many variants with unknown clinical significance—among those revealed with WES—could be having an influence in the patient's family. In fact, most cases with severe HTG are genetically undefined (21). This situation links up with the need to improve predictions of functionality (pathogenicity) as this effect remains hidden for the great majority of the variants identified. Additionally, epigenetic factors can also have an influence on the manifestation of HTG but they cannot be revealed with sequencing approaches (22). Finally, HTG is a condition that increases the risk of cardiovascular disease (CVD). The incidental discovery of HTG in the patient's family will contribute to a convenient follow-up of these people that might reduce their CVD risk.

Among the studies summarised in this editorial, only five appear in paediatric journals. The diffusion among paediatricians of the nature, diversity of symptoms and diagnosis strategies of FCS in children is essential to achieve an early diagnosis. The most important goal is to reduce the risk of episodes of acute pancreatitis and its consequences. Volanesorsen, a novel antisense oligonucleotide targeting Apo C-III mRNA, has proven to be effective in treating adult FCS patients (23). On the other hand, treatment based on fat-restricted diet and medium-chain triglycerides (MCT) supplements must be used to reduce the risk of pancreatitis in paediatric patients (24,25).

To conclude, the article mentioned in this editorial contributes to our knowledge of FCS and shows that an interdisciplinary approach—clinical, genetic and biochemical—seems the best way to face the FCS diagnosis challenge to ensure children's wellbeing, which is the most important task that, in fact, we all bear in mind.

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aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Merker VL, Slobogean B, Jordan JT, et al. Understanding barriers to diagnosis in a rare, genetic disease: Delays and errors in diagnosing schwannomatosis. Am J Med Genet A 2022;188:2672-83.
2. Goldberg RB, Chait A. A Comprehensive Update on the Chylomicronemia Syndrome. Front Endocrinol (Lausanne) 2020;11:593931.
3. Shi H, Wang Z. Novel pathogenic variant combination in LPL causing familial chylomicronemia syndrome in an Asian family and experimental validation in vitro: a case report. Transl Pediatr 2022;11:1717-25.
4. Rioja J, Ariza MJ, García-Casares N, et al. Evaluation of the chylomicron-TG to VLDL-TG ratio for type I hyperlipoproteinemia diagnostic. Eur J Clin Invest 2020;50:e13345.
5. Feoli-Fonseca JC, Lévy E, Godard M, et al. Familial lipoprotein lipase deficiency in infancy: clinical, biochemical, and molecular study. J Pediatr 1998;133:417-23.
6. Rodrigues R, Artieda M, Tejedor D, et al. Pathogenic classification of LPL gene variants reported to be associated with LPL deficiency. J Clin Lipidol 2016;10:394-409.
7. Rahalkar AR, Giffen F, Har B, et al. Novel LPL mutations associated with lipoprotein lipase deficiency: two case reports and a literature review. Can J Physiol Pharmacol 2009;87:151-60.
8. Chokshi N, Blumenschein SD, Ahmad Z, et al. Genotype-phenotype relationships in patients with type I hyperlipoproteinemia. J Clin Lipidol 2014;8:287-95.
9. Li Y, Hu M, Han L, et al. Case Report: Next-Generation Sequencing Identified a Novel Pair of Compound-Heterozygous Mutations of LPL Gene Causing Lipoprotein Lipase Deficiency. Front Genet 2022;13:831133.
10. Araujo MB, Eiberman G, Etcheverry N, et al. Familial chylomicronemia syndrome: pediatric experience in Argentina. Arch Argent Pediatr 2022;120:e123-7.
11. Béliard S, Di Filippo M, Kaplanski G, et al. Highly efficacious, long-term, triglyceride lowering with rituximab therapy in a patient with autoimmune hypertriglyceridemia. J Clin Lipidol 2018;12:883-7.
12. Eguchi J, Miyashita K, Fukamachi I, et al. GPIHBP1 autoantibody syndrome during interferon β1a treatment. J Clin Lipidol 2019;13:62-9.
13. Fang LJ, Abuduxikuer K, Yan XM, et al. An infant presenting with extreme hypertriglyceridemia diagnosed as glycogen storage disease type Ia. J Pediatr Endocrinol Metab 2020;33:803-8.
14. Wilson DP, Williams L, Kavey RW. Hypertriglyceridemia in Youth. J Pediatr 2022;243:200-7.
15. Hegele RA, Berberich AJ, Ban MR, et al. Clinical and biochemical features of different molecular etiologies of familial chylomicronemia. J Clin Lipidol 2018;12:920-927.e4.
16. Ariza MJ, Rioja J, Ibarretxe D, et al. Molecular basis of the familial chylomicronemia syndrome in patients from the National Dyslipidemia Registry of the Spanish Atherosclerosis Society. J Clin Lipidol 2018;12:1482-1492.e3.
17. Castro-Castro MJ, Candás-Estébanez B, Esteban-Salán M, et al. Removing Lipemia in Serum/Plasma Samples: A Multicenter Study. Ann Lab Med 2018;38:518-23.
18. Lippi G, Plebani M, Favaloro EJ. Interference in coagulation testing: focus on spurious hemolysis, icterus, and lipemia. Semin Thromb Hemost 2013;39:258-66.
19. Ariza MJ, Pérez-López C, Almagro F, et al. Genetic variants in the LPL and GPIHBP1 genes, in patients with severe hypertriglyceridaemia, detected with high resolution melting analysis. Clin Chim Acta 2020;500:163-71.
20. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med 2015;17:405-24.
21. Hegele RA, Dron JS. 2019 George Lyman Duff Memorial Lecture: Three Decades of Examining DNA in Patients With Dyslipidemia. Arterioscler Thromb Vasc Biol 2020;40:1970-81.
22. Guardiola M, Ibarretxe D, Plana N, et al. DNA methylation pattern of hypertriglyceridemic

subjects. Patrón de metilación en ADN de sujetos hipertrigliceridémicos. Clin Investig Arterioscler 2022;34:27-32.
23. Witztum JL, Gaudet D, Freedman SD, et al. Volanesorsen and Triglyceride Levels in Familial Chylomicronemia Syndrome. N Engl J Med 2019;381:531-42.
24. Thajer A, Skacel G, de Gier C, et al. The Effect of a Fat-Restricted Diet in Four Patients with Familial Chylomicronemia Syndrome: A Long-Term Follow-Up Study. Children (Basel) 2021;8:1078.
25. Navarro Hermoso A, Valdivielso P. Treatment of chylomicronemia. Clin Investig Arterioscler 2021;33 Suppl 2:75-9.

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