Editorial

Familial chylomicronemia syndrome: importance of diagnostic vigilance

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Introduction

Hypertriglyceridemia (HTG) is a common disorder which is typically polygenic in nature and is often associated with other metabolic abnormalities (1,2). In contrast, HTG due to primary monogenic chylomicronemia or familial chylomicronemia syndrome (FCS) is a rare inherited condition with an estimated prevalence of 1/1,000,000 in the population although it is probably underrecognized and underdiagnosed (1).

The most serious consequence of FCS is acute pancreatitis, which can be life-threatening. Therefore, identifying patients with FCS to implement appropriate therapy for mitigating the risk of acute pancreatitis is critically important. In the current issue of Translational Pediatrics, Shi *et al.* published a case about a 4-year-old patient with a confusing initial presentation who was ultimately diagnosed with FCS with never been reported compound heterozygous variants entitled, "*Novel pathogenic variant combination in LPL causing familial chylomicronemia syndrome in an Asian family and experimental validation in vitro: a case report*" (3). This case teaches us about the importance of vigilance in FCS diagnosis.

Overview of FCS

Causes of HTG are vastly heterogeneous and identifying a specific etiology by a routine lipid profile alone is challenging. Many secondary causes of HTG, such as inadequately managed diabetes mellitus (DM), hypothyroidism, chronic renal insufficiency, nephrotic syndrome, dietary indiscretion, alcohol intake, and certain medication use (e.g., estrogen, beta-blockers, diuretics, isotretinoin, glucocorticoids, and serotonin reuptake inhibitors), should always be considered and excluded. HTG can also be seen in other rare heritable disorders; two examples are familial lipodystrophy and glycerol kinase deficiency. Lipodystrophy has two forms: heritable and acquired, and patients present with a striking physical appearance of virtual or partial lack of adiposity, or of impressive muscularity, often associated with other metabolic derangements such as HTG, DM, insulin resistance, and fatty liver. Glycerol kinase deficiency presents with pseudo-HTG due to high glycerol levels because a commonly used laboratory method measures "glycerol, triglyceride (TG)-backbone" as the "surrogate" for TG.

Moreover, a subset of severe HTG may be due to chylomicronemia. Historically, the Fredrickson classifications denote them as either type I hyperlipoproteinemia, which represents FCS or type V hyperlipoproteinemia, which is a polygenic disorder. Notable characteristics of these conditions are compared in *Table 1*. To differentiate between them, looking at the value of apolipoprotein B (apoB)-100 may be most informative. Low levels of apoB-100, which is typically measured (versus apoB-

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Table 1 Comparison of commonly observed characteristics: monogenic FCS *vs.* polygenic chylomicronemia (modified with permission from *Annals of Internal Medicine*) (4)

	FCS		Polygenic chylomicronemia
General features			
Electrophoresis	Type I hyperlipoproteinemia		Type V hyperlipoproteinemia
Genetics	Monogenic (bi-allelic, autosomal recessive)		Polygenic, familial clustering possible
Prevalence	1 in 100,000 to 1,000,000	<<	Approximately 1 in 600
Disease onset	Childhood/adolescence > adulthood		Mostly adulthood
Major associated morbidity	Life-threatening pancreatitis, minimal risk of CVD		Evidence of increased risk of CVD
Clinical features	Pancreatitis (70–80%)		Pancreatitis (~10%)
	Abdominal pain	>>	Abdominal pain (rare)
	Eruptive xanthomas	>>	Eruptive xanthomas (rare)
	Lipemia retinalis	>>	Lipemia retinalis (rare)
	Hepatosplenomegaly		Not common
Lipoprotein profile			
Major lipoproteins	Chylomicrons		Chylomicrons and VLDL
Features of chylomicronemia	TG >1,000 mg/dL or >11.3 mmol/L	>>	TG >1,000 mg/dL or >11.3 mmol/L
	Lactescent plasma	>	Lactescent to cloudy plasma
	TG/TC >5 (mg/dL)/(mg/dL) or >2.2 (mmol/L)/(mmol/L)	>	TG/TC >5 (mg/dL)/(mg/dL) or >2.2 (mmol/L)/(mmol/L)
	TG/ApoB ≥8.8 (in mg/dL) or ≥10 (mmol/L)/(g/L)	>	TG/ApoB ≥8.8 (in mg/dL) or ≥10 (mmol/L)/(g/L)
Apolipoprotein B	<75 mg/dL or <0.75 g/L	<	≥75 mg/dL or ≥0.75 g/L

FCS, familial chylomicronemia syndrome; CVD, cardiovascular disease; VLDL, very-low-density lipoproteins; TG, triglyceride; TC, total cholesterol.

48, the product of *APOB* mRNA editing), are seen in FCS, whereas elevated levels of apoB-100 are observed in polygenic chylomicronemia because more very-low-density lipoproteins (VLDL), particles are present in circulation (5).

Since FCS is rare and inherited in the autosomal recessive manner, previous family history of FCS may be absent. Moreover, HTG may not be the first recognized feature. Typically, the initial presentation is "abdominal pain" of varying intensity due to smoldering acute pancreatitis, ranging from nagging abdominal discomfort to incapacitating pain, in childhood or adolescence. Unfortunately, these symptoms are often either disregarded as a common viral or childhood illness or worse, misdiagnosed as an acute abdomen, prompting unnecessary exploratory procedures. To make matters more complicated, artifactual laboratory abnormalities due to HTG or chylomicronemia such as pseudohyponatremia (6) and abnormal coagulation studies due to the plasma turbidity via optical analyzer (7) as described in the case report, may prompt extraneous workups, and cause a delay in arriving at the correct diagnosis.

Other notable and reversible FCS-associated clinical manifestations include eruptive xanthomas, lipemia retinalis, and hepatosplenomegaly. Eruptive xanthomas are localized or wide-spread small or yellowish dermatological papules with erythematous base of 3–5 mm, due to TG accumulation in subcutaneous macrophages on the torso, elbows, or buttocks. They are commonly non-pruritic and painless unless they appear on sensitive areas. Lipemia retinalis is a description of milky lipid-filled retinal vessels observable via funduscope. Engulfment of TG-rich lipoproteins (TRL) by macrophages in the reticulo-endothelial cells may result in hepatosplenomegaly (4,8).

Regardless, because acute pancreatitis is potentially life-threatening, FCS should be considered high in differential diagnoses, and a lipid profile should be assessed promptly when a young patient complains about abdominal

Table 2 Known FCS-causal genes and LPL-associated roles

Genes	Locus	Role in LPL-dependent lipolysis
LPL	8p21.3	Main enzyme for lipolysis of triglyceride
APOC2	19q13.32	Necessary activating co-factor for LPL lipolysis
LMF1	16p13.3	Chaperone protein for LPL, required for folding, assembly, and transportation
GPIHBP1	8q24.3	Role in LPL dimerization, tethering, and stabilization to the endothelium
APOA5	11q23.3	LPL-apoC-II stabilizing co-factor and modulator of hepatic TG metabolism

FCS, familial chylomicronemia syndrome; *LPL*, lipoprotein lipase; *APOC2*, apolipoprotein C-II or (apoC-II); *LMF1*, lipase maturation factor 1; *GPIHBP1*, glycosylphosphatidylinositol-anchored high-density lipoprotein-binding protein 1; *APOA5*, apolipoprotein A-V (apoA-V); TG, triglyceride.

discomfort repeatedly. The plasma lipid profile should include total cholesterol (TC), TG, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and ideally, apoB. An opaque and turbid appearance of fasting plasma indicates chylomicronemia (likely, TG >1,000 mg/dL or >11.3 mmol/L), and the TG/apoB ratio ≥8.8 (mg/dL)/(mg/dL) or ≥10 (mmol/L)/(g/L) may be informative (9,10). A clinical diagnosis of chylomicronemia should be considered with the calculated value of TG/TC ratio >5 (mg/dL)/(mg/dL) or >2.2 (mmol/L)/(mmol/L) in untreated patients. As mentioned earlier, a low apoB (<75 mg/dL or 0.75 g/L) or low normal value can be a great indicator of FCS, distinguishing it from type V hyperlipoproteinemia (5).

Lipoprotein lipase (LPL; OMIM 238600) and apolipoprotein CII (apoC-II; OMIM 608083) deficiencies due to bi-allelic loss-of-function (LOF) mutations in the *LPL* and the *APOC2* gene, respectively, are well-characterized causes of FCS with autosomal recessive inheritance. These conditions present with apparent LPL functional deficiency, which may be somewhat of a misnomer because defective apoC-II, a crucial cofactor, can impair LPL functional activity despite having "normally" functioning LPL protein. Mutations in the *LPL* gene are the most common causes of FCS, and currently, over 200 disease-causing mutations have been reported in the Human Gene Mutation Database (HGMD; www.hgmd.cf.ac.uk). Mutations in the genes encoding for lipase maturation factor 1 (*LMF1*: OMIM 246650), glycosylphosphatidylinositol-anchored high-density lipoprotein-binding protein (*GPIHBP1*; OMIM 615947), and apoA-V (*APOA5*; OMIM 144650) are also rare causes of FCS (*Table 2*) (8,9).

LPL, along with hepatic lipase (HL), pancreatic lipase (PL), and endothelial lipase (EL), is a member of the TG-lipase family, and the lipase family plays a central role in lipoprotein metabolism. LPL is a glycoprotein bound to the luminal surface of endothelial cells via heparan sulfate proteoglycan (HSPG), and also with GPIHBP1. LPL forms homodimers and functions dually as a TG hydrolase and a ligand for receptor-mediated lipoprotein uptake, expressed mainly in adipose tissues, and heart and skeletal muscles (10). Endothelial cell-bound LPL, after being activated by apoC-II, hydrolyzes dietary and endogenous TGs carried in chylomicrons and VLDL, respectively, releasing fatty acids to be utilized for cellular energy or storage (11).

FCS diagnosis

Current schemes for FCS diagnosis have been outlined in several publications (12,13). When lipid values are suspicious for FCS, it is important to assess for other features associated with FCS. Family history can also be instrumental although there may be no affected family members in prior generations. However, parents who are both FCS-causal variant carriers, have a 1/4 (25%) chance of having a child with FCS each time, and it is not unusual to have multiple children with FCS in a family. In such case, family history with a pedigree can be highly informative in deciphering the autosomal recessive inheritance pattern and confirming FCS diagnosis.

Traditionally, diagnosing FCS has relied on LPL enzyme activity analysis, which is only offered at specialized centers. LPL activity is typically measured by collecting two sets of plasma, before and after an intravenous heparin bolus injection (60 U/kg body weight), which releases LPL tethered to the endothelium into the circulation. Absent or markedly reduced LPL activity after excluding HL activity in the post-heparin plasma is diagnostic for LPL functional deficiency (2). Then, apoC-II deficiency can be delineated by restoration of LPL activity upon addition of apoC-II or

"normal" plasma (8). Since no standardized LPL activity assay is available (14,15) and expanding availability of genetic testing, molecular diagnosis using single- or multi-gene panels targeting FCS-associated genes is becoming the more favored diagnostic approach. A list of clinical laboratories is searchable at Genetic Testing Registry (GTR: https://www.ncbi.nlm.nih.gov/gtr/).

With the exciting advent of next-generation sequencing (NGS), it is now feasible to sequence and to analyze multiple genes simultaneously although Sanger sequencing is still considered as the gold standard and is usually used to confirm NGS findings. Whole exome sequencing (WES) and whole genome sequencing (WGS) are now available "clinically" although additional specialized methods may be required for identifying or confirming certain variants (e.g., structural changes). Any research results would require clinical confirmation.

For the patient in the case report, TG of 22.5 mmol/L, along with the turbid appearance and TG/TC ratio of 4.14 (mmol/L)/(mmol/L) were indicative of chylomicronemia, and TG/apoB ratio of 27.1 (mmol/L)(g/L) provided a hint for the clinical diagnosis of FCS, despite apoB of 0.83 g/L.

Although no other family members presented with the similar level of TG as the patient, the patient's extremely high level of TG and her very young age were clues for a monogenic cause of HTG. It is well-known that certain *LPL* heterozygous carriers can present with moderately elevated TG, which seemed to have been the case in this family. Moreover, a good response to the fat-restricted diet and ineffectiveness of a fibrate were consistent with the features of FCS.

The *LPL* gene

The *LPL* gene which consists of 10 exons, encodes for a protein with 475 amino acid (aa) residues, including a 27-signal-peptide (16). Most mutations are missense and are found in exons 5 and 6, which include the catalytic triad (Serine-132, Asp-156, and His241) (17,18). The reported variants, paternal c.461A>G, p.His154Arg, and maternal c.788T>A, p.Leu263Gln are both located in the proximity to the triad, making them more likely to affect the functionality and/or structural integrity of LPL. Although the paternal variant has been reported, the maternal variant has never been reported. They were also absent from HGMD or ClinVar, NCBI. Therefore, this particular variant combination can be considered novel.

Whenever any variant is identified, the next step is to determine its pathogenicity or its role in the disease in question. In the United States (US), the American College of Medical Genetics (ACMG) (19) along with the Association for Molecular Pathology (AMP) have published Standards and Guidelines for the interpretation of sequence variants (20). Until certain criteria are met, a novel variant is considered as a variant of uncertain significance (VUS). Categories used to determine variant classification are population data, computational and predictive data, functional data, segregation data, *de novo* data, allelic data, other database, and other data. Many US clinical laboratories follow these guidelines.

The Genome Aggregation Database (gnomAD) is an example of population database where 125,748 exome sequences and 15,708 WGS (v2.1.1) or 76,156 genomes of diverse ancestries from unrelated individuals are available. Neither *LPL* p.H154R nor *LPL* p.L596Q is found in their population studied, making these variants exceptionally rare. With the additional data, *in-vitro*, and activity results of each variant, provided in the case report (3), this compound heterozygous combination can be considered "likely pathogenic" and is probably the cause of FCS in the patient. Finding additional patients with the same variant combination who present with the similar features would solidify this claim.

Management of FCS

Nutrition therapy

Currently, the main therapy for FCS is medical nutrition therapy. Normally, >90% of circulating TG from the intestine are secreted as chylomicrons following a meal, and these large lipoproteins are typically cleared within a few hours. However, in FCS, chylomicron clearance is severely impaired, leading to plasma TG accumulation (2). To keep FCS patients symptom-free, it is often necessary to restrict dietary fat to ≤15% of total energy intake, ideally to maintain TG <500 mg/dL. The recommended fat-intake is to limit fats to 20–30 g/day, by reducing saturated, unsaturated, and trans-fatty acids. Nonetheless, long-term adherence to an extremely low-fat diet is challenging (2,8), and requires continual reinforcement.

Outpatient TG-lowering medications

Approved TG-lowering medications are indispensable in

common or polygenic HTG (8,21,22). Fibrates and fish oils including newer omega-3 formulation can favorably alter lipids, especially, TG. Despite uncertainties about cardiovascular benefits, niacin remains a potential option to lower TG. However, niacin is seldom used due to its side effects. Although these medications are typically used as adjuncts, they are all marginally effective for TG-lowering in FCS. Therefore, non-responsiveness to approved medications strongly suggests the diagnosis of FCS (12), underscoring the need for new therapies.

Inpatient TG-lowering management

Food being the major source of chylomicrons, fasting is one sure way to lower extremely high TG in FCS if feasible. However, in case of acute pancreatitis, therapeutic plasma exchange (TPE) with fresh frozen plasma (FFP) may be effective in quickly alleviating the symptoms and lowering TG levels. This is especially valuable in patients with apoC-II deficiency because FFP can supply missing apoC-II but may also be helpful in other types of FCS.

Novel biological agents in development

Gene therapy had been touted as the best solution for many rare genetic disorders, including a type of FCS, LPL deficiency. Alipogene tiparvovec, an adeno-associated virus with a lipoprotein lipase gene, had been approved for commercial use in Europe. However, it was abruptly withdrawn from the market in 2017, mostly due to the lack of demand, lack of proven long-term safety and efficacy, and an associated high cost.

Fortunately, several promising novel biological molecules are under development and investigation for TG-lowering. ANGPTL3 and apoC-III are attractive targets for suppression since they potently modulate LPL activity. By suppressing ANGPTL3 or apoC-III, their inhibitory effects are alleviated, enhancing the residual LPL activity. A single dose of the ANGPTL3 monoclonal antibody inhibitor profoundly reduced TG in patients with dyslipidemia (–76%) (23). A multiple-dose study of *APOC3* antisense messenger RNA (mRNA) compound confirmed a remarkable TG reduction, as much as 70.9% in patients with HTG (24). Notably, the antisense mRNA inhibition of *APOC3* lowered TG levels by 56–86% to TG <500 mg/dL, even in three patients with FCS with a minimally detectable LPL activity (25). Therefore, more therapeutic options may become available for patients with FCS in the future.

Prognosis

Preventing acute pancreatitis is central to the management in FCS because of its associated morbidity and mortality. Reducing TG levels below the threshold of pancreatitis, can transform patients' clinical course. Hence, the prognosis depends on physicians' awareness and understanding of FCS, and their ability to guide patients to master their own dietary regimen. Once patients understand and embrace the living with FCS, they are more likely to follow the recommendations (4).

Even though recent studies have reported some correlation between LPL levels or certain *LPL* genotypes with CHD risks (26), the specific relationship between FCS or FCS-associated *LPL* mutations and CHD risks is still an active area of investigation.

Conclusions

Since therapies required for FCS differ greatly from other HTG conditions, it is important for physicians to be aware of this rare disorder. Prescribing the dietary recommendations for common HTG can have grave consequences, provoking acute pancreatitis in patients with FCS. As often occurs in rare diseases, unfamiliarity with FCS can delay the diagnosis and adversely affect the clinical course. It is also important to keep in mind about atypical presentations of FCS. Since genetic testing is widely available clinically at commercial laboratories, definitive diagnosis of FCS is feasible, and additional family members can be screened. Once diagnosis of FCS is confirmed, beyond simply prescribing approved medications, referral to a lipid specialist and a registered dietitian who specializes in rare lipid disorders should be considered and may be lifesaving or life-altering for patients with FCS.

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