AACE Clinical Case Rep. 10 (2024) 240–243

Clinical Case Reports™
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Case Report

Unmasking a Rare Genetic Mutation: The Importance of Genetic Testing in Refractory Hypertriglyceridemia

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ARTICLE INFO

Article history:
Received 15 February 2024
Received in revised form
29 July 2024
Accepted 16 August 2024
Available online 22 August 2024

Key words:
hypertriglyceridemia
next generation sequencing
hyperlipoproteinemia type I
apolipoprotein V

ABSTRACT

Background/Objective: Genetic causes of hypertriglyceridemia like familial chylomicronemia syndrome can be overlooked in everyday practice. We report a patient with a rare genetic mutation, highlighting the importance of genetic testing for timely diagnosis and prevention of complications.
Case Report: A 45-year-old Hispanic female presented with serum triglyceride levels of 749 mg/dL, refractory to rosuvastatin 10 mg daily and omega-3 ethyl esters 2 g daily. Initial studies showed total cholesterol of 278 mg/dL and high-density lipoprotein of 38 mg/dL. Physical examination was negative for hepatosplenomegaly and xanthoma, with no reported history of acute pancreatitis. Despite treatment escalation with gemfibrozil, fenofibrate, and icosapent ethyl, her triglyceride levels remained elevated, peaking at 4300 mg/dL. Seven years after presentation, genetic testing revealed homozygosity for c.11delC of the apolipoprotein A5 gene, confirming the diagnosis of familial chylomicronemia syndrome. Postdiagnosis, the patient adhered to a strict low-fat diet with daily fat intake of less than 15-20 g, limited simple sugars, refined carbohydrates, and alcohol, leading to a nadir of serum triglycerides of 197 mg/dL.
Discussion: The identified mutation is exceedingly rare (<0.01%), as most associated mutations involve the lipoprotein lipase gene. There are no approved therapies for genetic hypertriglyceridemia. The mainstay of treatment is a very low-fat diet to prevent complications.
Conclusion: We underscore the importance of genetic testing in refractory hypertriglyceridemia despite a lack of clinical signs. A definitive diagnosis can alleviate patient burden, improve therapeutic adherence, and enhance the patient-physician relationship.

Introduction

Hypertriglyceridemia (HTG) is a common condition with a complex genetic background and challenging clinical management. A fasting triglyceride (TRG) level >150 mg/dL (1.7 mmol/L) is required for the diagnosis of HTG, while severe is defined as >500 mg/dL (11.3 mmol/L).[1] Because of their rare prevalence, genetic syndromes can be missed in everyday practice. Familial chylomicronemia syndrome (FCS), traditionally type I hyperlipoproteinemia according to the Frederickson classification,[2] is a rare genetic cause of HTG with a prevalence of 1 in 100 000 to 1 000 000.[3] FCS is characterized by complete deficiency (bi-allelic mutations) of the lipoprotein lipase (LPL) gene or genes regulating the LPL activity.[3] These genes include apolipoprotein C2, lipase maturation factor 1, glycosylphosphatidylinositol-anchored high density lipoprotein binding protein 1, apolipoprotein A5 (APOA5), cAMP-responsive element binding protein 3 like 3, and glycerol-3-phosphate dehydrogenase 1.[4] Clinical presentations include severe, refractory HTG, eruptive xanthomas, lipemia retinalis, and hepatosplenomegaly, and may be accompanied by recurrent episodes of abdominal pain.[5] The complication with the highest morbidity and mortality is acute pancreatitis (AP), which can be recurrent.[6] FCS can have a significant psychological toll on the patients. Helping patients better understand the genetic nature of their condition can lead to more focused lifestyle choices and relieve some of their uncertainty.

Abbreviations: AP, acute pancreatitis; APOA5, apolipoprotein A5; FCS, familial chylomicronemia syndrome; HTG, hypertriglyceridemia; LPL, lipoprotein lipase; TRG, triglyceride.

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https://doi.org/10.1016/j.aace.2024.08.006

Here, we report a patient who presented at an outpatient endocrine clinic with refractory HTG and was diagnosed with a rare FCS-resulting genetic mutation.

Case Report

Our patient, a 45-year-old Hispanic female, presented in April of 2015 to get a second opinion on the management of her refractory HTG. Her medications were rosuvastatin 10 mg once daily and marine omega-3 ethyl esters 2 g twice daily. Her past medical history included recurrent episodes of abdominal pain, thyroid nodule, depression, mitral valve prolapse, and inguinal hernia repair. She reported that her mother also had a history of "elevated cholesterol and triglycerides."

Physical examination of the patient was negative for lipemia retinalis, eruptive xanthoma, hepatosplenomegaly, or abdominal tenderness. A palpable thyroid nodule and a mid-systolic click were noted during thyroid palpation and cardiac auscultation. Her body mass index was 22.31 kg/m^2. Her initial fasting laboratory results showed a serum TRG level of 794 mg/dl (reference range 0-149), total cholesterol of 278 mg/dl (reference range 100-199), high-density lipoprotein cholesterol of 32 mg/dl (reference range > 39), and thyroid stimulating hormone of 1.5 mIU/L (reference range 0.5-5.0). The patient was then referred to a nutritionist, and from 2015 until 2022, she was treated with different combinations of rosuvastatin, gemfibrozil, omega-3 ethyl esters, and icosapent ethyl. During that time, the mean TRG level was 1628 mg/dl. The highest TRG level recorded was 4300 mg/dl after the initiation of oral contraceptive pills by her gynecologist, dropping to 566 mg/dl after discontinuing the oral contraceptive pills.

In May of 2022, 7 years after the initial presentation, next-generation sequencing testing was performed to detect mutations thought to be causative to HTG. Those genes included APOA5, apolipoprotein C2, cAMP responsive element binding protein 3 like 3, glycerol-3-phosphate dehydrogenase 1, glycosylphosphatidylinositol-anchored high density lipoprotein binding protein 1, and lipase maturation factor 1. The results indicated homozygosity for c.111delC (deletion of cytosine in position 111) of the APOA5 gene.

After the diagnosis, she was referred again to nutrition with the aim of developing a personalized very low-fat diet. Her mean TRG levels have been approximately 366 mg/dl ever since. Figure summarizes the TRG trend at presentation and after the establishment of the diagnosis, as well as the particular changes in medication and lifestyle at each time point. To date, the patient continues taking fenofibrate 145 mg once daily and icosapent ethyl 1 g twice daily. Notably, computed tomography of the patient's heart with calcium scoring indicated a calcium score of 0.0 by the Agaston method.[7]

Highlights

- Genetic causes are frequently overlooked in refractory hypertriglyceridemia.
- Next-generation sequencing confirms mutations causing hyperlipoproteinemia I and V.
- Strict low-fat diet may outperform medical therapy for genetic hypertriglyceridemia.

Clinical Relevance

In an outpatient endocrine setting, genetic mutations should not be underestimated in cases of refractory hypertriglyceridemia. Although specific treatments are not available yet, genetic testing can offer a definitive diagnosis, thereby alleviating patient distress, personalizing treatment, and helping identify candidates for relevant clinical trials.

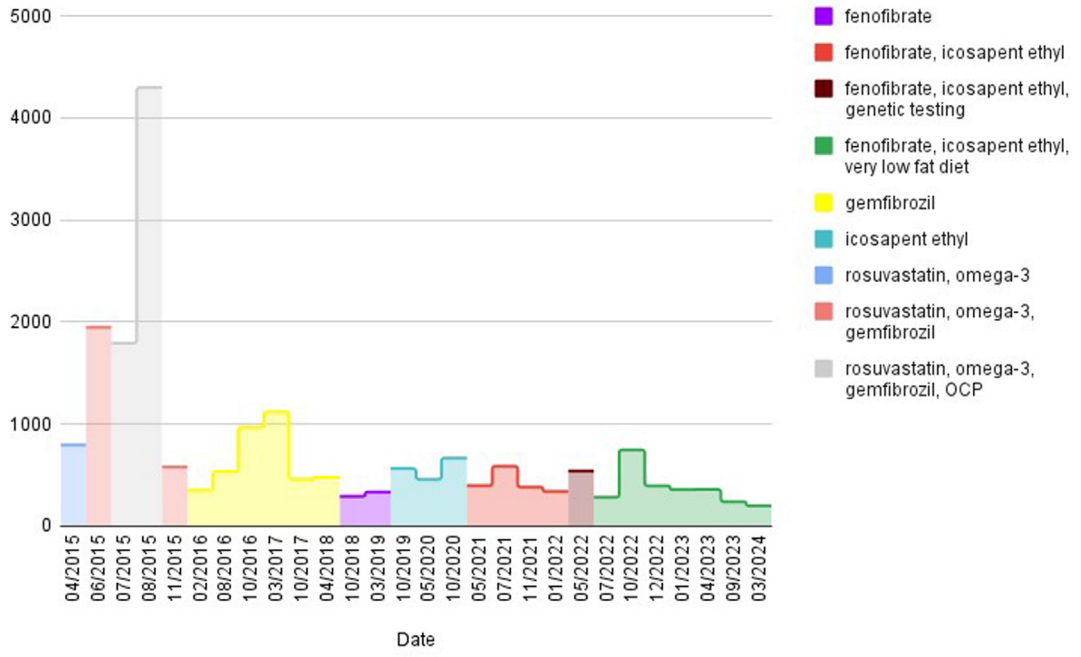

Fig. Schematic representation of the patient's serum TRG trend (y axis, mg/dL) over time (month, year) and with regard to changes in medication and lifestyle (appendix). The administration schemes were gemfibrozil 600 mg twice daily; rosuvastatin 10 mg once daily; omega-3 2 g twice daily; fenofibrate 145 mg once daily; and icosapent ethyl 1 g twice daily. *OCP* = oral contraceptive pills; *omega-3* = omega-3 ethyl esters; *TRG* = triglyceride.

Table 1
Genes Associated to MCS and FCS

Gene	Locus	Gene product function
LPL	8p21.3	Hydrolysis of triglycerides and peripheral uptake of free fatty acids
APOC2	19q13.32	Required activating co-factor for LPL-mediated lipolysis
LMF1	16p13.3	Chaperone protein, required for folding, assembly, and transportation of the LPL molecule
GPIHBP1	8q24.3	Stabilization of the LPL molecule to the endothelium
APOA5	11q23.3	Facilitating factor for the LPL-APOC2 interaction
CREB3L3	19p13.3	Regulation of APOC2 and APOA5 expression
GPD1	12q13.12,	Catalyzation of reduction reactions with a critical role in lipid and carbohydrate metabolism

Abbreviations: APOC2 = apolipoprotein C2; APOA5 = apolipoprotein A5; CREB3L3 = cAMP responsive element binding protein 3 like 3; FCS = familial chylomicronemia syndrome; GPD1 = glycerol-3-phosphate dehydrogenase 1; GPIHBP1 = glycosylphosphatidylinositol-anchored high density lipoprotein binding protein 1; LMF1 = lipase maturation factor 1; LPL = lipoprotein lipase; MCS = multifactorial chylomicronemia syndrome.

Discussion

Herein we present a 45-year-old female who presented with refractory HTG and was found homozygous for the c.111delC mutation of the APOA5 gene 7 years postpresentation, a finding consistent with the diagnosis of FCS.[8] This variant produces a translational frameshift with a premature stop codon that leads to a loss of approximately 89% of the protein mass.[9] This is an extremely rare genotype in the general population (<0.01%), according to data from GnomAD.[10] FCS is a monogenic disease and results from deficiency of the LPL gene or genes regulating the LPL function.[11] Table 1 summarizes the functions of the gene products responsible for FCS.

While LPL is the most commonly affected gene, accounting for 95% of the known monogenic mutations causing FCS, our patient's genotype revealed an APOA5 mutation. Interestingly, APOA5 mutations are responsible for only 0.6% of the FCS-causing monogenic mutations.[2] It has been reported that about 85% of patients with FCS have experienced at least one episode of AP.[12] Despite reaching TRG levels as high as 4300 mg/dl, our patient fortunately has had no episodes of diagnosed AP.

Regarding treatment, the main goal is to prevent severe complications such as AP.[11] Currently, no Food and Drug Administration-approved therapies exist for FCS. A very low-fat diet is the mainstay of treatment, as hypolipidemic agents are inefficient.[4] Targeted therapies have been assessed in completed or ongoing clinical trials, such as protein inhibitors, gene replacement therapies, and antisense nucleotides (volanesorsen).[13] A small interfering RNA targeting APOC3 (ARO-APOC3) has demonstrated a promising safety and efficacy profile with a mean serum TRG reduction of 41% to 55%.[14]

Correctly diagnosing genetic HTG can have multiple benefits. Our patient would often disclose her frustration despite her efforts with lifestyle modification and medication compliance. Correct diagnosis reportedly relieved her from the psychological burden of uncertainty and medical mistrust and helped her understand that her HTG was a result of a genetic process and not personal habits. Before diagnosis, she complied with medications but struggled to follow the provided nutrition recommendations, possibly contributing to fluctuating TRG levels. After receiving a more specific diagnosis and a better understanding of the nature of her condition, she started being more compliant with her new personalized diet plan, restricting her daily fat intake to less than 15 to 20 g/d and also limiting refined carbohydrates and simple sugars. Additionally, she was more successful in limiting her alcohol intake.[15] This led to her lowest TRG levels recorded since our first encounter of 197 mg/dl, 2 years postdiagnosis.

In clinical settings, complicated comorbidity profiles may obscure genetic factors of HTG. Physicians should maintain suspicion in cases of uncontrolled HTG despite treatment with multiple lipid-lowering agents, a history of multiple episodes of HTG-related AP, and a strong family history. Our discussed patient did not have typical clinical signs of hypertriglyceridemia such as lipemia retinalis, eruptive xanthoma, and hepatosplenomegaly, nor had she experienced any episode of diagnosed AP. In our practice, we have tested 6 more patients for genetic HTG, who all presented with refractory HTG and recurrent abdominal pain or pancreatitis. We identified FCS-related mutations in one patient and multifactorial chylomicronemia syndrome in three patients. Table 2 summarizes the patient characteristics. Although multifactorial chylomicronemia syndrome is much more common than FCS, the two have significant phenotypic overlap, varying from mild to very severe forms.[11] However, the indications for genetic testing referrals are debated.

After genetic identification, we provided a personalized and multidisciplinary approach involving lipidologists, endocrinologists, dietitians, and geneticists to create a tailored therapeutic plan. Some of our patients also required psychological counseling to cope with the effects of their condition and the strict diet restrictions on their life quality.

Table 2
Patient Characteristics

	Negative	FCS	MCS
Number of patients	2	2	3
Mean age (y)	44	23.9	50.65
Mean BMI (kg/m^2)	37.3	23.9	31.65
Episodes of pancreatitis	None	None	4 (acute), 1 (chronic)

Abbreviations: BMI = body mass index; FCS = familial chylomicronemia syndrome; MCS = multifactorial chylomicronemia syndrome.

Disclosure

The authors have no conflicts of interest to disclose.

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