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Persistent Chylomicronemia

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Abstract

Persistent chylomicronemia is a rare but serious metabolic disorder characterized by extremely high triglyceride levels - often surpassing 1,000 mg/dL - and the abnormal presence of fasting chylomicrons. This results from severely impaired clearance of chylomicrons, leading to their continuous accumulation and posing a major risk for recurrent, potentially fatal acute pancreatitis. Its etiology includes monogenic and polygenic forms. The monogenic form, known as familial chylomicronemia syndrome, is extremely rare and caused by biallelic mutations in genes essential for lipoprotein lipase function, such as lipoprotein lipase, APOC2, APOA5, GPIHBP1, and LMF1. In contrast, the polygenic/multifactorial form is far more common and results from the combined effect of multiple genetic variants together with secondary factors such as uncontrolled diabetes, obesity, hypothyroidism, alcohol intake, nephrotic syndrome, and certain medications. Clinically, the most severe consequence is acute pancreatitis, triggered by capillary obstruction and toxic free fatty acid release within the pancreas. Other manifestations include eruptive xanthomas, lipemia retinalis, hepatosplenomegaly, and neurological symptoms linked to hyperviscosity. Diagnosis involves identifying markedly elevated triglycerides (typically >885 mg/dL) and fasting chylomicrons, sometimes evident as lactescent plasma. Genetic testing is useful when familial chylomicronemia syndrome is suspected. Management requires lifelong intervention, with strict dietary fat restriction (10-15% of daily calories), avoidance of simple sugars and alcohol, and lifestyle measures such as weight loss and smoking cessation. Traditional triglyceride-lowering drugs - fibrates, omega-3 fatty acids, and niacin—are often ineffective in familial chylomicronemia syndrome due to absent lipoprotein lipase activity. Emerging therapies focus on lipoprotein lipase - independent pathways. APOC-III inhibitors, including volanesorsen, olezarsen, and plozasiran, produce substantial triglyceride reductions across various forms of chylomicronemia. Patients with residual lipoprotein lipase activity may also

benefit from ANGPTL3 inhibitors. Improved recognition, education, and personalized treatment based on clinical phenotype - not solely genetics - are essential to reduce complications and mortality.

Keywords: Diet; Genetic; Hyperchylomicronemia; Lipase; Treatment

Abbreviations

ANGPTL3: Angiopoietin-Like Protein 3
APOC-III: Apolipoprotein C-III
FCS: Familial Chylomicronemia Syndrome
LPL: Lipoprotein Lipase
VLDL: Very Low-Density Lipoproteins

Introduction

Persistent chylomicronemia is a rare but clinically significant metabolic disorder marked by extremely elevated plasma triglyceride levels, often exceeding 1,000 mg/dL, and the presence of fasting chylomicrons - a feature that is abnormal under physiological conditions. In healthy individuals, chylomicrons, which are large lipoprotein particles responsible for transporting dietary triglycerides and cholesterol from the intestines to peripheral tissues, are cleared from the bloodstream within a few hours after a meal. However, in individuals with persistent chylomicronemia, this clearance mechanism is severely impaired, leading to sustained accumulation of chylomicrons even during fasting periods. This pathological state stems from a profound disruption in triglyceride metabolism and poses significant clinical risks, particularly the development of acute pancreatitis, which can be recurrent and life-threatening if not managed effectively (1,2).

The etiology of persistent chylomicronemia is heterogeneous and can be broadly classified into monogenic (familial) and polygenic (multifactorial) forms. The monogenic form, often referred to as familial chylomicronemia syndrome (FCS), is exceedingly rare, affecting approximately 1 to 2 individuals per million population. It follows an autosomal recessive inheritance pattern and is most commonly caused by mutations in the lipoprotein lipase (LPL) gene, which encodes LPL - an enzyme essential for hydrolyzing triglycerides in chylomicrons and very low-density lipoproteins (VLDL) into free fatty acids and glycerol (2,3). In addition to LPL mutations, other genes implicated in FCS include apolipoprotein C2 (APOC2), apolipoprotein A5 (APOA5), glycosylphosphatidylinositol anchored high density lipoprotein binding protein 1 (GPIHBP1), and lipase maturation factor 1 (LMF1), all of which are involved in either the structural formation, transport, or activation of the LPL complex.

On the other hand, the polygenic or multifactorial form, sometimes termed multifactorial chylomicronemia syndrome, is significantly more common, with an estimated prevalence of 1 in 600 individuals (3). This form arises from the combined effects of multiple genetic variants that individually exert minor effects on triglyceride metabolism, but collectively contribute to significant hypertriglyceridemia, particularly when compounded by secondary metabolic stressors. These include poorly controlled type 2 diabetes mellitus, obesity, metabolic syndrome, hypothyroidism, excessive alcohol consumption, nephrotic syndrome, and the use of cer-

tain medications (e.g., estrogens, corticosteroids, isotretinoin, and some antipsychotics). The interplay between genetic susceptibility and environmental/lifestyle factors makes diagnosis and management of multifactorial chylomicronemia syndrome particularly challenging.

Clinically, the most dangerous complication of persistent chylomicronemia is acute pancreatitis, which may present with sudden-onset severe epigastric pain, nausea, vomiting, and elevated pancreatic enzymes. Chylomicron-induced pancreatitis results from pancreatic capillary obstruction and local lipolysis, which releases free fatty acids that can damage acinar cells and provoke a systemic inflammatory response. Recurrent episodes of pancreatitis not only impair quality of life but may also lead to long-term pancreatic insufficiency and diabetes. Additionally, patients with severe hypertriglyceridemia may also present with eruptive xanthomas (yellow papules on the skin, particularly the buttocks and extremities), lipemia retinalis (milky appearance of retinal vessels), hepatosplenomegaly, and neurological symptoms such as memory impairment or irritability, likely due to hyperviscosity.

The diagnosis of persistent chylomicronemia is established based on clinical findings, biochemical profiles (triglyceride levels often > 885 mg/dL or 10 mmol/L), and the identification of chylomicrons in fasting plasma samples. A "milky" or lactescent appearance of plasma, especially after refrigeration (where a creamy top layer forms), can provide a visual clue. Genetic testing may be warranted in suspected cases of monogenic FCS, particularly in young patients with a history of recurrent pancreatitis and without secondary contributors to hypertriglyceridemia.

Management of persistent chylomicronemia requires a multifaceted and lifelong approach. Dietary fat restriction is the cornerstone of therapy. Patients are advised to consume less than 10-15% of their total daily caloric intake from fat, and to avoid simple sugars and alcohol, both of which exacerbate triglyceride levels. Adherence to a low-fat, high-complex carbohydrate diet is often difficult but crucial in preventing complications. Regular physical activity, smoking cessation, and weight reduction (in overweight or obese individuals) are also essential lifestyle interventions.

Pharmacological treatment varies based on the underlying cause. In polygenic or secondary forms, fibrates (e.g., fenofibrate), omega-3 fatty acids (particularly eicosapentaenoic acid - EPA and docosahexaenoic acid - DHA), and niacin may help reduce triglyceride levels by enhancing lipolysis and VLDL clearance. However, in monogenic FCS, these traditional agents are often ineffective, since they rely on the presence of functional LPL activity. As a result, emerging LPL-independent therapies have been developed to target alternative pathways of triglyceride metabolism.

Inhibition of angiopoietin-like protein 3 (ANGPTL3), an emerging target for the treatment of a broad spectrum of lipid disorders from severe refractory hypercholesterolemia (4) to severe hypertriglyceridemia, operates through LPL-dependent mechanisms, such that patients with persistent chylomicronemia of any cause (without LPL activity) do not respond, or respond very little, to ANGPTL3 inhibitors (5). However, patients who have some residual LPL activity, such as those with intermittent or episodic chylomicronemia, severe hypertriglyceridemia, or mixed dyslipidemia, often respond to fibrates and ANGPTL3 inhibitors (6).

Lipoprotein lipase independent therapies: apolipoprotein C-III (APOC-III) inhibitors

APOC-III is a glycoprotein that inhibits the activities of LPL and hepatic lipase by an independent mechanism of LPL, participates in the assembly and secretion of VLDL, decreases the clearance of chylomicrons, VLDL and its remnants. APOC-III inhibitors (APOC3i) were developed following the discovery of loss-of-function (LoF) variants of APOC-III associated with low plasma triglyceride levels (7,8).

Clinical studies with volanesorsen, an antisense oligonucleotide not N-acetylgalactosamine (GalNAc) inhibitor of APOC-III, reduced plasma triglyceride levels by 50%-88% in patients with FCS, severe hypertriglyceridemia, or partial lipodystrophy (9-11).

The volanesorsen studies included patients with persistent chylomicronemia of different causes. Next-generation anti-APOC-III agents, currently in clinical development or already available, can effectively target a broad spectrum of disorders presenting with severe hypertriglyceridemia, including intermittent chylomicronemia and persistent chylomicronemia. These new agents include olezarsen, a GaLNac APOC-III antisense oligonucleotide, currently in phase 3, which has demonstrated substantial reduction in triglycerides after 6 months of treatment in patients with genetically proven FCS (12), and Plozasiran, a short-interfering RNA (siRNA) GalNaC also targeting APOC-III, also in phase 3, which significantly decreased triglyceride levels in patients with persistent chylomicronemia (both genetically proven FCS and FCS clinical) after 10 months of treatment (13).

Conclusion

Improved recognition through pragmatic definitions, enhanced education, and focus on high-risk patients with alarm features could significantly reduce morbidity and mortality from acute pancreatitis (14). The emphasis on equitable access to personalized treatment based on clinical phenotype rather than genetic confirmation marks a crucial advancement in managing this life-threatening condition.

Acknowledgments

None.

Conflict of interest

None.

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