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Exposing Key Features on Familial Chylomicronemia Syndrome

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Abstract

Severe hypertriglyceridemia and familial chylomicronemia syndrome are lipid disorders associated with significant cardiovascular and metabolic risks. The American Congress of Cardiology 2024 highlighted transformative developments in understanding and managing these conditions. Novel therapeutic strategies, particularly targeting genetic and molecular pathways, have emerged, offering hope for improved patient outcomes. This article emphasizes the advancements in pharmacological treatments, diagnostic technologies, and multidisciplinary care approaches. Additionally, the article explores the interplay of genetic, environmental, and secondary factors in hypertriglyceridemia, integrating insights into the clinical differentiation and management of familial chylomicronemia syndrome and multifactorial severe hypertriglyceridemia.

Key words: Genetics; Lipids; Pancreatitis; Rare disease; Tryglicerides.

Abbreviations

ACC: American Congress of Cardiology

ANGPTL3: Angiopoietin-Like Protein 3

Apo: Apolipoprotein

FCS: Familial Chylomicronemia Syndrome

LDL: Low-Density Lipoprotein

LPL: Lipoprotein Lipase

sHTG: Severe Hypertriglyceridemia

Introduction

Hypertriglyceridemia is characterized by elevated plasma triglycerides, which, in severe cases, increase the risk of acute pancreatitis and cardiovascular disease. Familial chylomicronemia syndrome (FCS), a

rare autosomal recessive disorder caused by mutations in the lipoprotein lipase (LPL) gene or its cofactors, leads to chylomicronemia and extreme hypertriglyceridemia. Multifactorial severe hypertriglyceridemia (sHTG) results from the interaction of common genetic variants with secondary factors or medications affecting triglyceride levels, such as diabetes, corticosteroids, and antiretroviral therapies.

Standard care for these conditions focuses on dietary management and triglyceride-lowering agents, but it often fails to address underlying causes or long-term complications. This review synthesizes breakthroughs presented at American Congress of Cardiology (ACC) 2024, emphasizing emerging therapies, advanced diagnostics, and multidisciplinary approaches (1-5).

Emerging Therapeutics

The ACC 2024 spotlighted several promising therapies for sHTG and FCS, including:

1. Gene therapy: advances in precision medicine have enabled the development of gene-editing tools targeting mutations in the LPL gene. Preliminary clinical trials demonstrated significant reductions in fasting triglyceride levels and improvements in lipid profiles among FCS patients.
2. Angiopoietin-Like Protein 3 (ANGPTL3) inhibitors: antisense oligonucleotides and monoclonal antibodies targeting ANGPTL3 reduced triglyceride levels by up to 80% in sHTG patients. These therapies enhance LPL activity, offering a novel mechanism of action.
3. Apolipoprotein C-III (ApoC-III) modulators: ApoC-III inhibitors prevent chylomicron accumulation and reduce triglycerides levels independently of dietary modifications. Phase III trials revealed their efficacy and safety profiles, marking a significant advancement for patients resistant to conventional therapies.

Advances in Diagnostics

Improved diagnostic tools for sHTG and FCS were another focus of the congress:

1. Genetic screening panels: expanded genetic screening enables earlier and more accurate identification of FCS, essential for distinguishing monogenic FCS from multifactorial sHTG.
2. Biomarkers: novel biomarkers, including triglycerides-rich lipoprotein remnants and circulating ANGPTL3 levels, enhance risk stratification and treatment monitoring. Laboratory findings such as low apolipoprotein B (ApoB) levels (≤0.9 g/L) also help differentiate FCS from multifactorial sHTG.

Clinical and genetic considerations

FCS typically presents in childhood or adolescence with sHTG, recurrent abdominal pain, and acute pancreatitis. In contrast, multifactorial sHTG often presents later in life and is influenced by secondary factors such as obesity, metabolic syndrome, or medications. FCS patients commonly exhibit normal or low body mass index, while overweight and obesity are more typical in multifactorial sHTG. The response to triglyceride-lowering therapies also helps differentiate these conditions, as FCS patients rarely show significant reductions with fibrates or omega-3 fatty acids.

Complications of sHTG and FCS

- Acute pancreatitis: sHTG (≥2000 mg/dL) increases the risk of acute pancreatitis, with higher incidence and mortality in FCS due to the profound triglyceride elevations.

Multifactorial sHTG patients, however, may experience more prolonged hospital stays due to comorbidities.

- Cardiovascular disease: multifactorial sHTG is associated with elevated cardiovascular risk due to the accumulation of remnant lipoproteins and small, dense low-density lipoprotein (LDL) particles. In FCS, reduced LDL levels and ApoB concentrations mitigate atherogenicity, but cohort studies confirm a higher cardiovascular risk in multifactorial sHTG patients.

Genetic testing

FCS is a Mendelian recessive condition caused by biallelic pathogenic variants in genes such as LPL, ApoCII, ApoA5, Glycosylphosphatidylinositol anchored high density lipoprotein binding protein 1 (GPI-HBP1), and lipase maturation factor 1 (LMF1). In contrast, multifactorial sHTG has a polygenic basis, with a cumulative effect of common genetic variants contributing to elevated triglyceride levels. Genetic testing is crucial for children with sHTG, aiding diagnosis, prognosis, and access to emerging therapies. However, for adults, triglyceride levels remain the primary guide for management due to the complex genetic architecture of sHTG.

Multidisciplinary care approaches

A collaborative approach involving lipidologists, genetic counselors, dietitians, and endocrinologists is critical for managing these complex disorders. Case studies presented at ACC 2024 demonstrated improved adherence and outcomes when care was personalized and multidisciplinary.

Implications for clinical practice

The innovations presented at ACC 2024 mark a paradigm shift in the management of sHTG and FCS. While challenges such as high treatment costs and accessibility remain, the potential for transforming patient outcomes is significant. Clinicians are encouraged to adopt these emerging therapies and integrate advanced diagnostics into their practice. Personalized, multidisciplinary care strategies tailored to the unique genetic and clinical profiles of patients will be essential.

Conclusion

The ACC 2024 underscored progress in understanding and treating sHTG and FCS. From novel therapeutics targeting genetic underpinnings to advanced diagnostic and care strategies, these advancements promise to enhance quality of life for affected individuals. Further research and collaboration will be essential to fully realize the potential of these breakthroughs.

Acknowledgments

None.

Conflict of interest

None.

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