MINI REVIEW

Short assessment on multifactorial chylomicronemia syndrome

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ABSTRACT

The most common cause of severe hypertriglyceridemia is multifactorial chylomicronemia syndrome (MCS or type V hyperlipoproteinemia), which is linked to an increased risk of acute pancreatitis, cardiovascular disease, and non-alcoholic steatohepatitis. Because their therapies are so dissimilar, distinguishing between familial chylomicronemia syndrome and MCS is critical. Several cohort studies have helped to distinguish these two illnesses in recent years, and new data reveals that MCS is a heterogeneous condition. This article reviews the research on MCS, focusing on the genetic drivers of metabolic risk as well as the most recent breakthroughs in pharmacological and non-pharmacological therapy options for these individuals.

Key Words: *chylomicronemia syndrome; cardiovascular disease; mcs susceptibility; hypertriglyceridemia*

INTRODUCTION

Fasting Triglyceride (TG) content of less than 10 mmol/L is considered severe Hypertriglyceridemia (HTG). A pathogenic bui-ldup of circulating chylomicrons (chylomicronemia) is virtually invariably found in the plasma at this TG threshold [1]. The most prevalent form of chylomicronemia and severe HTG is Multifactorial Chylomicronemia Syndrome (MCS), also known as "type V hyperlipoproteinemia" or "late-onset chylomicronaemia" according to the Fredrickson classification. Despite the fact that the exact prevalence of MCS in the general population is unknown, there must be an underlying genetic predisposition to poor TG metabolism in order to develop MCS [2].

The existence of secondary variables such as a diet high in fats and simple carbs, reduced activity levels, obesity, metabolic syndrome, alcohol consumption, and uncontrolled diabetes eventually triggers the complete development of the MCS phenotype [3]. Due to impaired Lipoprotein Lipase (LPL) activity, as well as hepatic overproduction of VLDLs and poor clearance, both chylomicrons and Very Low-Density Lipoproteins (VLDLs) are elevated in circulation in these patients. After blood sampling, centrifugation, and overnight storage at 4°C, a creamy supernatant layer on the top of the tube indicates the presence of chylomicrons, but a hazy and latescent bottom layer (infranatant) indicates the presence of VLDLs. The prevalence of eruptive xanthomas, lipemia retinalis, stomach pain, and poor concentration are the most common clinical symptoms of MCS. MCS is also linked to an elevated risk of significant health problems such Acute Pancreatitis (AP), Cardiovascular Disease (CVD), and Non-Alcoholic Fatty Liver Disease (NAFLD).

Complications of MCS

MCS patients have a 7-fold increased risk of AP compared to normolipidemic individuals in the general population and a 2- to 9-fold increased risk of CVD [4, 5].

The presence of TG-rich lipoprotein remnants in circulation that can penetrate the arterial wall, as well as the presence of atherogenic comorbidities like obesity or diabetes, could explain the elevated cardiovascular risk, while the actual processes linking HTG and AP are yet unknown. Patients with HTG, on the other hand, have a more severe clinical course of AP, with higher morbidity and death. NAFLD is a chronic liver condition defined by excessive fat buildup in the liver, and it is either the hepatic component of or a result of the metabolic syndrome. The prevalence of NAFLD is believed to be around 25% in the general population [6]. NAFLD can lead to nonalcoholic steatohepatitis, which can lead to cirrhosis and associated consequences. One of the risk factors for the development of NAFLD is a high level of circulating TG. The prevalence of NAFLD in MCS patients was examined for the first time utilizing transient elastography in a recent study (Fibro Scan). Surprisingly, there was a negative connection between hepatic fat increase and the risk of AP in these patients. This could imply that as more TG accumulates in the liver, less is accessible to contribute to the pathophysiology of AP. These findings, however, must be repeated in a larger cohort of MCS patients due to the study's limited sample size.

Differences between MCS and FCS

FCS (also known as type I hyperlipoproteinemia, LPL deficiency, or monogenic chylomicronemia) is a rare autosomal recessive condition that is associated with severe HTG and the risk of life-threatening AP. The presence of chylomicrons in these patients explains the severe HTG in the fasting state. FCS is less prevalent than MCS, with an estimated frequency of 1 to 10 per million [3]. Because the phenotypes of FCS and MCS are so similar, determining the difference between the two disorders can be difficult. Making an accurate diagnosis, on the other hand, is critical for guiding suitable treatment. The clinical disparities between FCS and MCS patients have piqued researcher's interest in recent years.

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Genetics of Severe Hypertriglyceridemia

Genetic testing using a targeted next-generation DNA sequencing panel remains the gold standard for the differential diagnosis of FCS and MCS in patients with severe HTG. Other methods for identifying FCS patients have been reported elsewhere [7]. While the presence of homozygous or compound heterozygous uncommon variations in canonical TG metabolism genes (LPL gene or, less frequently, its modulators: APOC2, GPIHBP1, APOA5, and LMF1 genes) is symptomatic of FCS, the genetic foundation of MCS is more complex. Indeed, MCS susceptibility is determined by the existence of a single detrimental uncommon variant in one of the five key TG genes (heterozygous) or the aggregation of many Single-Nucleotide Polymorphisms (SNPs) related with TG concentration (polygenic).

A polygenic risk score based on common SNPs collected from genome-wide association studies is used to quantify polygenic vulnerability to MCS. Recent research has shown the disease's intricate genetic architecture, as well as the proportion of each of the major categories of genetic determinants identified in the severe HTG population. It's worth noting that half of the cohort was genetically undetermined. Non-canonical secondary TG genes have been proposed as one of the possible mechanisms explaining the severe HTG in these patients with no known genetic foundation [2].

There are also multiple polygenic risk scores available, each with a different number of SNPs and the ability to be weighted. However, it should be noted that the TG-associated SNPs included in polygenic scores are mostly from genome-wide association studies conducted in Europe. There is a founder effect for specific detrimental uncommon mutations in some isolated groups, which raises the percentage of heterozygous carriers.

Risk Stratification and Heterogeneity of MCS

Although the clinical and biochemical differences between FCS and MCS patients are now more understood, the phenotypic variability among MCS patients is still poorly researched. The clinical differences between MCS patients with (positive-MCS) and without (negative-MCS) a rare detrimental variation in the five canonical genes involved in TG metabolism were investigated for the first time in a recent study.

Patients with a history of AP had a higher prevalence of uncommon variations in the canonical genes implicated in TG metabolism than those without a history of AP in a study of 103 Chinese adults with TG ≥ 5.65 mmol/l and no secondary causes of HTG. However, the variant in question was a mutation of questionable significance for several of these cases [8]. The maximum TG value was also substantially different between those with an AP history (16.6 mmol/L) and those without an AP history (11.3 mmol/L) [8].

Treatment

The major goal of MCS treatment is to get the TG concentration below the threshold so that AP doesn't happen. The secondary goal of treatment is to lower the risk of cardiovascular disease. Secondary variables related with HTG such as physical inactivity, obesity, metabolic syndrome, alcohol consumption, and uncontrolled diabetes, as well as pharmacological treatment with fibrates, are the first-line treatments for these patients. Fibrates lower TG levels by boosting LPL-mediated lipolysis, which is one of the methods through which they do so. As a result, while this medicine is often effective in MCS patients who have some LPL activity, it is ineffective in FCS patients who have a significant reduction or complete loss of LPL function. Using fibrate, however, none of the FCS patients ever achieved a TG reduction of greater than 30%. [9]. Despite the fact that MCS patients have a usually positive response to fibrate medication, the efficacy of fibrate is very variable among these patients.

As a result, the therapy goal of lowering the risk of AP is rarely met. Furthermore, even if fibrates are prescribed for the treatment of severe HTG, no study has specifically proved that their usage is connected with a reduction in AP risk, and clinical trials have shown that adding a fibrate to statin therapy has little or no cardiovascular benefit. Fortunately, new treatments for hypertriglyceridemia are being developed, and some of them are showing promise in individuals with severe HTG. Molecules targeting apoC-III (volanesorsen, AKCEA-APOCIII-LRx, and AROAPOC3) [10] and ANPTL3 (evinacumab and AROANG3) [11], as well as 3 krill oil, are among the new treatments.

CONCLUSION

Recent research has helped to better understand MCS and the metabolic issues that come with it. Differences between both chylomicronemia syndromes (FCS and MCS) have been well defined in recent years. The variation in genetic susceptibility profiles, which leads to different phenotypic severity, is a novel aspect of our understanding of MCS. Recent research has revealed that MCS vulnerability is primarily polygenic, rather than being caused by a single unusual causal variant in the five classical TG metabolism genes. This second aetiology, on the other hand, is linked to a more severe type of MCS and a higher likelihood of life-threatening AP. Furthermore, measuring apoB in patients with severe HTG could be an important initial step in identifying people who are at higher risk. Despite these new findings, the mechanisms that underlie the variation in AP risk in MCS patients are still unknown, and additional research is needed in this area. Both low-fat and low-carbohydrate diets have been shown to reduce TG by 50% in these individuals, providing for greater flexibility in the application of lifestyle therapies that may encourage better compliance.

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