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Editorial

Chylomicrons: When you can't direct the wind, adjust the sail

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Relegated to a lipid specialist's realm and the need for specialized laboratory testing, the diagnosis of chylomicronemia is one that is unfamiliar to most physicians. The complex diagnostic possibilities, from rare monogenic disorders to the cumulative effects of genetic predisposition, poor lifestyle, disglycemia and obesity, coupled with the lack of diagnostic capabilities in most clinical laboratories (ultracentrifugation, high-performance liquid chromatography) have made the diagnosis of severe hypertriglyceridemia fraught with therapeutic uncertainties.

Here, Paquette et al. [1] describe two groups of well characterized groups of French-Canadian subjects with severe hypertriglyceridemia and fasting chylomicronemia. There is tremendous heterogeneity in clinical presentation, age of onset, co-morbidities and outcomes. Furthermore, they show that current therapies other than intensive lifestyle changes are, at best, of uncertain utility. This data adds to our current level of understanding of orphan lipoprotein diseases and of more common severe hypertriglyceridemia, in keeping with previous reports [2].

Primary chylomicronaemia affects approximately 1:600 adult individuals; of these > > 95% are affected by polygenic inherited susceptibility and monogenic autosomal recessive chylomicronemia is rare. Familial chylomicronemia syndrome (FCS) refers to the presence of at least one clinical feature accompanying primary chylomicronemia, such as eruptive xanthomas, lipemia retinalis, pancreatitis or hepatosplenomegaly and are required for diagnosis [3].

There are striking differences between patients with the familial chylomicronemia syndrome caused by a deficiency in the lipoprotein lipase (*LPL*) gene and those with multifactorial hyperchylomicronemia (MCM), summarized in Fig. 1. Other genes than LPL cause the FCS (*GPIHBP1, APOC2, APOA5* and *LMF1* genes), but these are extremely rare [4,5]. *LPL* deficiency has a prevalence of $\sim 1/10^6$, with a higher prevalence in regions with founder effects, such as in the province of Québec, Canada. It is an autosomal recessive disorder and heterozygous mutations at the *LPL* gene have little consequence on carriers. In the present study, the Authors carefully followed 25 subjects with documented LPL deficiency [1]. The clinical presentation is made early in life (11 ± 10 years) and acute pancreatitis is the major life-threatening complication. These patients have few cardiovascular risk factors and have a lower body mass index (21.7 ± 3.0). The development of diabetes later in life in patients with LPL deficiency is usually caused by destruction of the pancreas by repeated bouts of acute pancreatitis.

In marked contrast, in 36 patients with MCM, the age of presentation was more than two decades older (36 ± 10 years). The genetic basis of moderately severe hypertriglyceridemia was in great part elucidated by combining data from multiple genetic databases, identifying variants that have an effect on plasma triglyceride levels and realizing that the cumulative effect of variants in these genes is associated with increase in plasma triglyceride levels [6]. For instance, the *APOE4* variant is more frequent in the MCM group than in the FCS patients (Table 1 in Paquette et al. [1]). However, the phenotypic expression of MCM appears to be determined by poor lifestyle (obesity –BMI 28.5 ± 3.2); alcohol intake, cigarette smoking and higher cardiovascular risk factors including hypertension and diabetes (Fig. 1). Importantly, patients with MCM also have higher gamma glutamyl transferase levels, an early sign of hepatic steatosis and higher levels of non-HDL-C levels (8.29 IQR 5.84–12.23 vs. 5.84 IQR 3.25–6.72 mmol/L in the FCS patients), suggesting that in addition to chylomicrons, VLDL and remnant particles are also increases in MCM patients. Pancreatitis, in this group is infrequent and may be multifactorial with alcohol intake and biliary stones potential contributors. The major long-term consequence of MCM is an increased risk of atherosclerotic cardiovascular disease.

Another form of chylomicronemia, not described here, is estrogen-associated severe hypertriglyceridemia. This rare syndrome is seen in women during pregnancy, or on exogenous estrogens. It presents a great management challenge for mother and fetus [7].

The data of Paquette et al. [1] should help clinicians in determining a therapeutic approach. First, a genetic diagnosis based on sequencing the *LPL* gene, then the *GPIHBP1, APOC2, APOA5* and *LMF1* genes (although only available in research settings in Canada) may be required for a proper diagnosis allowing eventual access to orphan drugs. Second, a better understanding of triglyceride-rich lipoprotein

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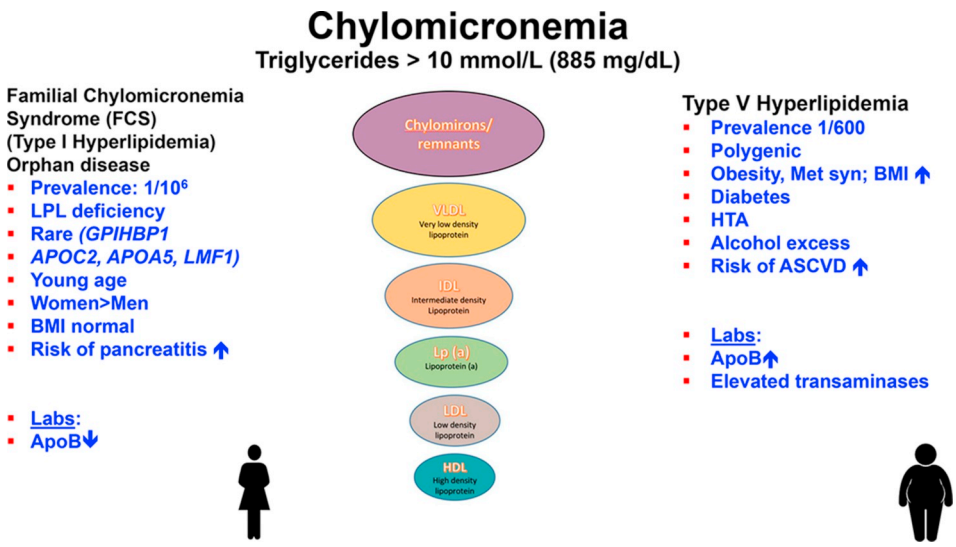

Fig. 1. Chylomicronemia.

metabolism will help clinicians in designing a therapeutic plan for acute episodes of severe hypertriglyceridemia and long-term treatment. Plasma triglycerides have long been used as a measure of therapeutic success and a > 20% reduction is considered as a sign of efficacy. There are problems with this approach. A 20% variation in plasma triglyceride levels is well within biological variability; second, little information is available on the relationship between percent reduction in triglyceride levels and clinical outcomes. Current therapies, including fibric acid derivatives (fibrates), fish oils (omega-3 triglycerides), medium chain triglycerides and niacin have limited efficacy and little clinical trial data supporting their use [2]. While popular, fish oils for the treatment of hypertriglyceridemia were shown not to be useful [8].

Clinicians should understand the plasma half-life of chylomicrons in the familial chylomicronemia syndrome. In severe hypertriglyceridemia, clearance of intestinal-derived chylomicrons is markedly delayed. Thus, limiting oral intake of fats and decreasing post-prandial triglyceride peaks can be accomplished without the need for apheresis –a technique that has not been validated as a useful therapeutic modality. A period of fasting and intravenous hydration, followed by the use of isocaloric, lipid-free frequent feeds (e.g. every 2 hours) may be the best therapeutic approach. In the MCM, the delayed triglyceride-rich lipoprotein clearance, coupled with increased hepatic VLDL production complicates management. However, the same principles apply, with meticulous control of glycemia. In the acute setting, pharmacological modulation of triglycerides with fibrates, fish oils or niacin is of doubtful usefulness.

Novel therapies, reviewed in Brahm and Hegele [2], include LPL gene therapy, Microsomal triglycerides transfer protein inhibitor, diacylglycerol 0-acytltransferase 1 inhibitor (DGAT1), APOB interference, APOC3 interference and ANGPTL3 interference. Alipogene tiparvovec (Glybera®) consisted of a locally (muscle) delivered gene therapy designed to reverse LPL deficiency. Cost was a major limitation to its use and, the treatment has been withdrawn. The microsomal triglyceride transfer protein inhibitor lomatipide has been used in the FCS with some degree of success, but side effects and concerns over long-term hepatic steatosis limit its use [9]. DGAT1 inhibitors as a therapeutic target will need to overcome observed clinical adverse events [10]. *APOB* gene interference with Mipomersen is of limited efficacy in FCS. The most promising long-term treatment for FCS and severe hypertriglyceridemia may be *APOC3* gene RNA interference. In clinical trials the first of these compounds, volanesorsen (Waylivra ®) showed a reduction in plasma APOC3 levels by 71–90% and triglyceride levels by 56–86%. All patients had a triglyceride level of less than 5.7 mmol/L (500 mg/dL) with treatment [11]. Interestingly, apo CIII is an inhibitor of LDL but decreased triglyceride levels in patients with LPL deficiency, suggesting an LPL-independent role for apo CIII in triglyceride metabolism. However, the FDA did not grant approval for Waylivra in FCS patients [12]. Finally, AKCEA-ANGPTL3-L_{Rx} is a ligand conjugated antisense drug designed to reduce angiopoietin-like 3 protein and is being tested in patients with hypertriglyceridemia [2].

So, when the strong winds of hypertriglyceridemia create havoc, adjusting the sail of personalized treatment, based on a sound understanding of triglyceride-rich lipoprotein production and clearance should enable clinicians to guide effective treatment. In the case of FCS, lifelong avoidance of fats is the current best treatment, with hope from trials of anti-apoCIII, while in MCM, lifestyle changes, weight reduction, careful and meticulous treatment of diabetes coupled with statin therapy may be the best approach [13].

Conflict of interest

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