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Mini Review

Chylomicronemia as a Rare Cause of Severe Hypertriglyceridemia in Children

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Abstract

There are two forms of chylomicronemia, monogenic familial chylomicronemia syndrome and polygenic multifactorial chylomicronemia syndrome. Familial chylomicronemia syndrome is a rare, autosomal recessive disorder of chylomicron metabolism characterized by extremely high serum concentrations of triglycerides. An important role is played by the hepatic enzyme Lipoprotein Lipase (LPL), which is involved in the breakdown of triglyceride-rich lipoproteins. Pathogenic variants in the LPL gene are causative for FCS. Additionally, LPL deficiency can also be caused by pathogenic variants in the APOC2 gene. Variants in the GPIHBP1 gene and the LMF1 gene have also been described. On the other hand, multifactorial chylomicronemia syndrome is a polygenic disease primarily found in adults and a late-onset form. A pan-elevation of TG-rich lipoproteins and elevated chylomicrons, VLDL and degressed HDL are present. Diagnosis is made by DNA sequencing and lipid electrophoresis. Lifetime pancreatitis risk differs between both types of 20-90%. Cardiovascular disease risk ranges between 5-40%. FCS is refractory to conventional therapies due to compromise of lipolytic reserve, whereas in MCS more responsiveness is found to drug therapy then FCS. Pediatricians should be aware of chylomicronemia in severe cases of hypertriglyceridemia in children.

Keywords: Chylomicronemia, Children, Hypertriglyceridemia, Treatment

Introduction

The Chylomicronemia Syndrome is characterized by severe hypertriglyceridemia (triglycerides in the blood >16.95 mmol/L or >1500mg/dL // >10 mmol/L or >885mg/dL) and clinical symptoms such as abdominal pain, acute inflammation of the pancreas, and eruptive xanthomas. Fats serve as an important source of energy, building blocks of cell walls, and components of hormones in the body. During digestion, fats are absorbed in the form of triglycerides in the small intestine and transported as fat molecules, called chylomicrons. In the further metabolism of these fat molecules, triglycerides are broken down by an enzyme called Lipoprotein Lipase (LPL). If there is inadequate breakdown or insufficient storage of triglycerides, the levels in the blood increase. There are two main forms of Chylomicronemia Syndrome: the more common Multifactorial Chylomicronemia Syndrome (MFCS) and the rare familial Chylomicronemia Syndrome (FCS). Multifactorial Chylomicronemia Syndrome (MFCS) occurs in about one in

600 individuals. It involves a predisposition from a collection of minor genetic variants that, in combination with lifestyle factors, comorbidities, or medications, can lead to an increase in fat levels. Non-genetic, or secondary factors that can contribute to an increase in triglycerides in the context of MFCS include alcohol consumption, obesity, undiagnosed or inadequately treated diabetes mellitus, as well as the use of medications such as estrogens, diuretics, and beta-blockers. However, there are many other medications that can interact with genetic forms of hypertriglyceridemia and lead to MFCS. Familial Chylomicronemia Syndrome (FCS) is a rare genetic disorder that occurs early and in about one in a million people. It is characterized by a deficiency or dysfunction of the enzyme Lipoprotein Lipase (LPL) and some associated proteins, leading to impaired breakdown of triglyceride-rich lipoproteins. Severe hypertriglyceridemia can cause recurrent abdominal pain and is the third most common cause of acute pancreatitis after alcohol and gallstones. Recurrent pancreatitis can lead to pancreatic dysfunction and the development of digestive problems and diabetes mellitus. Other symptoms include nausea, vomiting, fat deposits in the eye (lipemia retinalis) and skin (eruptive xanthomas), joint pain, as well as hepatosplenomegaly. Cognitive impairments or psychiatric disorders such as anxiety and depression may also occur. Initially, multiple triglyceride measurements are taken from the blood. A visible milky, fatty deposit may form during blood collection. The disease is diagnosed through a genetic examination of the blood.

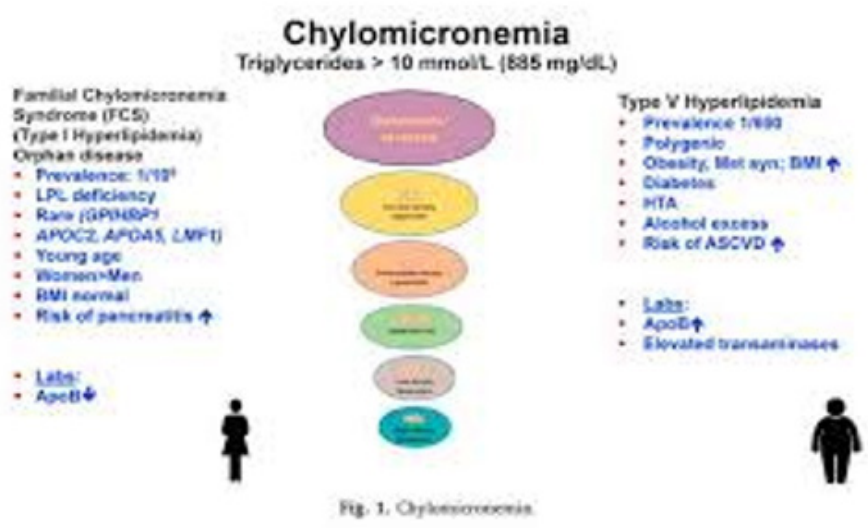

Fig. 1. Chylomicronemia

Table 1: Types of Chylomicronemia. Alothman L et al. Atherosclerosis. 2019 Apr: 283: 121-123.

The goal of treating Chylomicronemia Syndrome is to lower triglycerides in the blood, particularly to prevent potentially life-threatening acute pancreatitis. A low-fat and low-sugar diet is generally recommended, as well as avoiding alcohol. Physical activity can positively influence triglyceride levels. For MFCS, it is important to identify and treat identifiable causes of secondary hypertriglyceridemia and replace medications if necessary. This form of hypertriglyceridemia also responds well to treatment with fibrates, statins, and omega-3 fatty acids, which can usually sufficiently reduce the risk of pancreatitis. Many patients with MFCS have multiple gene mutations that cause not only hypertriglyceridemia but also other cardiovascular risk factors such as diabetes mellitus and hypertension, which also play a significant role in treatment. Due to the impaired breakdown of lipoproteins, it is particularly important to limit their intake through diet. In healthy individuals, about 30% of daily energy intake should come from fats. Patients with FCS are recommended to reduce fats to 10-15% and consume medium-chain triglycerides (e.g., in butter, coconut oil) in favor of increased calorie intake from carbohydrates. However, these should be complex carbohydrates and preferably not sugars. The lipid-lowering drug therapy with fibrates or statins, commonly used in the treatment of elevated triglycerides, is not sufficiently effective in patients with FCS. Volanesorsen, an antisense oligonucleotide, is used instead. It reduces the production of a protein, apolipoprotein CIII (ApoC-III), which inhibits the breakdown of lipoproteins in the cell, thereby reducing blood triglycerides by up to 77%. The medication is administered weekly as an injection. Side effects may include local skin reactions at the injection site and a decrease in platelets, which should be monitored during therapy.

Discussion

The two major goals of the treatment of hypertriglyceridemia are the prevention of cardiovascular disease and pancreatitis) [1-41]. Here we discuss the drugs used for the treatment of hypertriglyceridemia: (niacin, fibrates, omega-3-fatty acids, and

apo CIII inhibitors. Niacin decreases total cholesterol, TGs (20-50% decrease), LDL-C, and Lp(a) [2,7,12]. Additionally, niacin decreases small dense LDL resulting in a shift to large, buoyant LDL particles. Moreover, niacin increases HDL-C. Skin flushing, insulin resistance, and other side effects have limited the use of niacin. The enthusiasm for niacin has greatly decreased with the failure of AIM-HIGH and HPS-2 Thrive to decrease cardiovascular events when niacin was added to statin therapy. The omega-3-fatty acids eicosapentaenoic acid (C20:5n-3) (EPA) and docosahexaenoic acid (C22:6n-3) (DHA) lower TGs by 10-50% but do not affect total cholesterol, HDL-C, or Lp(a). LDL-C may increase with EPA + DHA when the TG levels are markedly elevated (>500mg/dL). EPA alone does not increase LDL-C. Omega-3-fatty acids have few side effects, drug interactions, or contraindications. Numerous studies of low dose omega-3-fatty acids on cardiovascular outcomes have failed to demonstrate a benefit. However, in the JELIS, REDUCE-IT, and RESPECT-EPA trials high doses of EPA alone reduced cardiovascular events while in the STRENGTH and OMEMI trials high doses of EPA+DHA did not reduce cardiovascular events. Fibrates reduce TG levels by 25-50% and increase HDL-C by 5-20%. The effect on LDL-C is variable. If the TG levels are very high (>500mg/dL), fibrate therapy may result in an increase in LDL-C, whereas if TGs are not markedly elevated fibrates decrease LDL-C by 10-30%. Fibrates also reduce apolipoprotein B, LDL particle number, and non-HDL-C and there may be a shift from small dense LDL towards large LDL particles. Fibrates do not have any major effects on Lp(a). Monotherapy with fibrates appears to reduce cardiovascular events particularly in patients with high TG and low HDL-C levels. In contrast, in the ACCORD LIPID and PROMINENT trials the addition of fibrates to statin therapy did not reduce cardiovascular disease, which has reduced the enthusiasm for using fibrates to reduce cardiovascular disease. In patients with diabetes fibrates appear to slow the progression of microvascular disease (retinopathy, nephropathy, and amputations, ulcers, and gangrene. Antisense oligonucleotides, volanesorsen and olezarsen, inhibit the production of apolipoprotein C-III and decrease TG levels in patients with severe hypertriglyceridemia including patients with the Familial Chylomicronemia Syndrome (FCS). Studies also suggest that apo CIII inhibitors reduce episodes of pancreatitis in patients with severe hypertriglyceridemia. Patients with FCS have also reported that apo C-III inhibitors improved symptoms and reduced interference of FCS with work/school responsibilities. Of concern has been decreases in platelet levels with 47% of patients treated with volanesorsen developing platelet counts below100 x 109/L, a side effect that is not observed with olezarsen. Thus, a number of drugs are available for the treatment of hypertriglyceridemia and may be employed when lifestyle changes are not sufficient. Familial Chylomicronemia Syndrome (FCS) is a rare inherited disease, mainly due to Lipoprotein Lipase (LPL) gene mutations, leading to lipid abnormalities. Volanesorsen, a second-generation 2'-O-methoxyethyl (2'-MOE) chimeric antisense therapeutic oligonucleotide, can decrease plasma apolipoprotein C3 and triglycerides (TG) levels through LPL-independent pathways. The European Medicines Agency has approved volanesorsen as an adjunct to diet in adult FCS patients with an inadequate response to TG-lowering therapy. Areas covered: Available clinical data on volanesorsen efficacy and safety are presented. Furthermore, we discuss the yearly treatment with volanesorsen of a 21-year-old female FCS patient with LPL mutation. Volanesorsen was well-tolerated and decreased patient's TG levels (from >5000 mg/dL (56 mmol/L) to 350-500 mg/dL (4-5.6 mmol/L)) at 12 months. Lipoprotein Apheresis (LA) was stopped and there were no episodes of pancreatitis or abdominal pain. Expert opinion: Severe hypertriglyceridemia can potentially be fatal. Until recently, there was no specific treatment for FCS, apart from hypotriglyceridemic diet, fibrates, omega-3 fatty acids, and LA sessions [21,33]. Therefore, volanesorsen represents a promising therapeutic solution for these patients. The main side effect of volanesorsen therapy is thrombocytopenia, which should be monitored and treated accordingly. Increasing evidence will further elucidate the clinical implications of volanesorsen use in daily practice. Volanesorsen, an ASO targeting APOC3, has shown effectiveness in managing FCS, multifactorial chylomicronemia, and familial partial lipodystrophy, but its use is limited by thrombocytopenia. Emerging therapies, Olezarsen (ASO anti-APOC3) and Plozasiran (siRNA anti-APOC3), both conjugated with GalNAc, show promise in reducing acute pancreatitis risk without platelet concerns. ANGPTL3 inhibition requires residual lipoprotein lipase (LPL) activity, with only siRNA-based therapies-zodasiran and solbinsiran-under investigation. Suppressing APOC3 expression and targeting ANGPTL3 via siRNA offer significant potential, but long-term studies are needed to confirm their efficacy and safety. Future research may explore gene-editing strategies using lipid nanoparticle-based CRISPR-Cas9 delivery for more durable treatment outcomes [24,28,33]. Olezarsen is an antisense oligonucleotide targeting APOC3 mRNA, a key regulator of plasma triglyceride levels. It has been shown to significantly reduce triglyceride levels via APOC3 protein degradation. Clinical trials have demonstrated substantial reductions in triglyceride levels and APOC3, with minimal adverse events. Phase 2 and 3 trials showed consistent efficacy and safety profiles, with common adverse events including COVID-19 infection, abdominal pain, and diarrhoea. Relevance to Patient Care and Clinical Practice in Comparison to Existing Drugs: Olezarsen offers a targeted and effective treatment for FCS, addressing limitations of traditional therapies such as fibrates, omega-3 fatty acids, and statins. Its novel mechanism of action and once-monthly dosing regimen may improve patient adherence, providing significant advancement in FCS management.

Acknowledgement

None.

Conflict of Interest

None.

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