PANCREATITIS SECONDARY TO HYPERTRIGLYCERIDEMIA

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CLINICAL ASPECTS

After ethanol and gallstones hypertriglyceridemia is the third leading cause of acute pancreatitis causing between 5-25% of episodes. During pregnancy hypertriglyceridemia is the leading cause of acute pancreatitis accounting for up to 50% of cases. During pregnancy acute pancreatitis occurs most commonly in the third trimester but may occur in the first or second trimester. The frequency of acute pancreatitis due to hypertriglyceridemia during pregnancy is estimated to be between 1 in 1,000-12,000 pregnancies. Pancreatitis due to hypertriglyceridemia may also occur during infusion of lipid emulsions for parenteral feeding or with use of the anesthetic agent propofol, which is infused in a 10% fat emulsion.

Regardless of the cause of the hypertriglyceridemia the risk of acute pancreatitis increases the higher the triglyceride levels with the risk particularly elevated when triglyceride levels exceed 1,000-2,000mg/dL. In individuals with triglyceride levels between 1,000-1,999mg/dL the prevalence of acute pancreatitis is estimated to be approximately 10% and if the triglyceride levels are greater than 2,000mg/dL the prevalence is estimated to be approximately 20%. It should be noted that the susceptibility to acute pancreatitis is variable with some patients with very high triglyceride levels (>10,000mg/dL) not developing pancreatitis while some patients with lower triglyceride levels (400-1000mg/dL) develop pancreatitis. In some instances, the lower triglyceride levels may be due to a decrease in triglyceride levels secondary to the inability to eat prior to seeking medical attention. Individuals with familial hyperchylomicronemia syndrome are at greater risk of developing acute pancreatitis compared to individuals with multifactorial chylomicronemia syndrome (see discussion below describing these disorders).

The acute pancreatitis secondary to hypertriglyceridemia can be severe and life-threatening. Studies have suggested that the acute pancreatitis is more severe in patients with hypertriglyceridemia induced pancreatitis compared to patients with other causes of pancreatitis. If the hypertriglyceridemia is not treated recurrent episodes of pancreatitis can occur leading to chronic pancreatitis with associated exocrine pancreatic insufficiency resulting in malabsorption and endocrine pancreatic failure leading to diabetes.

The high levels of plasma triglycerides can interfere with assays of plasma pancreatic enzymes (lipase and amylase) resulting in inaccurate low levels and therefore the clinician should not eliminate the possibility of pancreatitis based on low amylase and lipase levels.

PATHOGENESIS

The mechanism by which elevated triglyceride levels lead to pancreatitis is not fully understood. A leading hypothesis is that the interaction of high levels of triglyceride rich lipoproteins with pancreatic lipase in the pancreatic capillaries leads to the breakdown of

triglycerides to free fatty acids and phospholipids to lysophosphatidylcholine. Both free fatty acids and lysophosphatidylcholine could induce pancreatic damage resulting in pancreatitis. Additionally, the elevated chylomicron levels increase plasma viscosity in the pancreatic capillaries resulting in stasis and hypoxia that can injure the pancreas.

Chylomicronemia may be due to a monogenic disorder (familial chylomicronemia syndrome; FCS) or due to multiple genes (polygenic) in association with other factors (multifactorial chylomicronemia syndrome; MFCS). Greater than 95% of patients with chylomicronemia have MFCS rather than FCS.

FCS is an autosomal recessive disorder that is very rare with an estimated prevalence of about 1 in 300,000. It may be due to biallelic pathogenic variants in lipoprotein lipase (LPL), Apo C-II, Apo A-5, glycosylphosphatidylinositol-anchored high-density lipoprotein–binding protein 1 (GPIHBP1), and lipase maturation factor 1 (LMF1) with abnormalities in LPL being the most common abnormality (either homozygous or compound heterozygous for two defective LPL alleles). Individuals who have a single allelic pathogenic variant may have moderately elevated triglyceride levels and in combination with other factors develop very high triglyceride levels (see below). Autoantibodies to LPL, Apo C-II, and GPIHBP1 has been reported to lead to chylomicronemia and mimic FCS. Patients with FCS primarily have chylomicrons contributing to the hypertriglyceridemia. Individuals with FCS usually present in childhood or early adolescence but can be first diagnosed in adults. Typical features are very high triglycerides, eruptive xanthomas, lipemia retinalis, hepatosplenomegaly, and pancreatitis. Individuals with FCS are not at a higher risk for atherosclerotic cardiovascular disease. The diagnosis of FCS should be considered in patients who are young, do not have secondary causes of hypertriglyceridemia, have a poor response to therapy, and no history of previous triglyceride levels less than 200mg/dL. Genetic studies if available can definitively diagnose FCS.

MFCS is a relatively common disorder (1:250 to 1:600 in the general population) that is due in most patients to polygenic hypertriglyceridemia (multiple genes that each have a small effect) or heterozygosity for a gene causing FCS (single gene that has large effect). These genetic abnormalities typically result in triglyceride levels between150mg/dL to 500mg/dL but in combination with secondary factors such as disorders or drugs that further elevate triglyceride levels can result in very high triglyceride levels. Common disorders that can elevate triglyceride levels include poorly controlled diabetes, obesity, pregnancy, renal disease, hypothyroidism, and HIV (Table 1) and common drugs that increase triglyceride levels are ethanol, oral estrogens, glucocorticoids, retinoids, beta blockers, thiazide and loop diuretics, protease inhibitors, and atypical anti-psychotics (Table 2). Individuals with MFCS have an increase in both VLDL and chylomicrons and are at a higher risk for atherosclerotic cardiovascular disease. If the secondary disorder is successfully treated or the drug discontinued the very high triglyceride levels typically return to the mild to moderately elevated range (150mg/dL to 500mg/dL).

Table 1. Disorders Associated with an Increase in Triglyceride Levels
Obesity
Alcohol intake
High simple carbohydrate diet; high fat diet
Diabetes
Metabolic syndrome
Polycystic ovary syndrome
Hypothyroidism
Chronic renal failure
Nephrotic syndrome
Pregnancy
Inflammatory diseases (Rheumatoid arthritis, Lupus, psoriasis, etc.)
Infections
Acute stress (myocardial infarctions, burns, etc.)
HIV
Cushing's syndrome
Growth hormone deficiency
Lipodystrophy
Glycogen Storage disease
Acute hepatitis
Monoclonal gammopathy

Table 2. Drugs That Increase Triglyceride Levels
Alcohol
Oral Estrogens
Tamoxifen/Raloxifene
Glucocorticoids
Retinoids
Beta blockers
Thiazide diuretics
Loop diuretics
Protease Inhibitors
Cyclosporine, sirolimus, and tacrolimus
Atypical anti-psychotics
Bile acid sequestrants
L-asparaginase
Androgen deprivation therapy
Cyclophosphamide
Alpha-interferon
Propofol

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

The diagnosis of acute pancreatitis secondary to hypertriglyceridemia is confirmed if the triglyceride levels are very high (>1,000mg/dL) and there is not another likely cause of the acute pancreatitis. Hypertriglyceridemia as a likely cause of acute pancreatitis can sometimes be suspected during the physical exam by detecting eruptive xanthomas or lipemia retinalis. As noted earlier marked elevations in triglyceride levels can result in falsely low serum amylase and lipase and therefore the diagnosis may be dependent on CT evaluation of the pancreas.

THERAPY DURING ACUTE PANCREATITIS

The management of acute pancreatitis secondary to hypertriglyceridemia is similar to the management of pancreatitis due to other causes except for the need to lower triglyceride levels as quickly as possible. Admission to the hospital, cessation of oral food intake, intravenous hydration, management of metabolic abnormalities, and pain management are routinely provided. With cessation of food intake plasma triglycerides usually decrease rapidly (approximately 50% decrease in 24 hours). Parenteral feeding with lipid emulsions should be avoided since they will delay the clearance of triglyceride rich lipoproteins and exacerbate the hypertriglyceridemia.

There are a number of other therapies that have been proposed for the treatment of acute pancreatitis to rapidly lower triglyceride levels. Unfortunately, there are not carefully carried out randomized trials demonstrating the benefit of these treatments. Insulin stimulates LPL activity and therefore insulin administration has been proposed as a treatment. There is no evidence that in patients without diabetes that insulin improves the outcome in patients with pancreatitis and elevated triglycerides. Thus, insulin administration is not recommended for most patients. However, in patients with poorly controlled diabetes (i.e., elevated plasma glucose levels) insulin should be administered to both lower glucose levels and increase LPL activity thereby accelerating the clearance of triglyceride rich lipoproteins.

Heparin infusion transiently increases LPL activity by releasing LPL from the endothelium but over an extended period this results in a decrease in LPL activity. Therefore, most experts do not recommend the use of heparin to lower triglyceride levels. Additionally, heparin may increase the risk of hemorrhagic pancreatitis.

Lipoprotein apheresis, plasmapheresis, or plasma exchange have been employed in patients with pancreatitis secondary to hypertriglyceridemia. These procedures rapidly lower plasma triglyceride levels but studies have not definitively demonstrated a decrease in morbidity or mortality. These procedures are costly with the potential for adverse reactions (allergic reactions, infections, thrombosis, etc.) and therefore in the absence of evidence demonstrating benefit most experts do not recommend these procedures for most patients. Plasmapheresis or plasma exchange may be an option in patients with severe hypertriglyceridemia with persistent hypertriglyceridemia after the first 48-72 hours, pancreatitis secondary to hypertriglyceridemia during pregnancy, and patients with very severe pancreatitis (high levels of lipase, hypocalcemia, lactic acidosis, generalized organ dysfunction, etc.). Note that these recommendations are not evidence based but based on clinical experience.

FOLLOW-UP

The long-term treatment of patients with pancreatitis secondary to hypertriglyceridemia is essential to prevent recurrent episodes of pancreatitis. It is very important to recognize that the treatment of

hypertriglyceridemia is different in patients with familiar hyperchylomicronemia syndrome (FHS) and multifactorial chylomicronemia syndrome (MFCS).

The primary treatment of individuals with FHS is dietary therapy. Dietary fat calories need to be severely restricted to approximately 5-20% of calories. It is very difficult for most patients to follow such a fat restricted diet. Medium-chain triglycerides, which are not incorporated into chylomicrons and are delivered to the liver via the portal vein are a potential alternate fat source for these patients. One should monitor for deficiency of fat-soluble vitamins (A, D, E, K) and replace as necessary. Pregnancy in individuals with FCS need to be carefully planned with close monitoring to avoid acute pancreatitis. Similar, to the treatment of MFCS described below drugs that increase triglyceride levels should be discontinued if possible and conditions that raise triglyceride levels treated. Omega-3-fatty acids (fish oil) do not lower triglyceride levels in patients with FHS. Fibrates are also not effective but a few studies have suggested that orlistat may be beneficial. Volanesorsen (Waylivra), an antisense oligonucleotide inhibitor of apolipoprotein C-III mRNA, is approved in Europe but not the United States for the treatment of FCS. FCS patients treated with volanesorsen had a 77% decrease at 3 months in triglyceride levels (mean decrease of 1,712 mg/dl) whereas patients receiving placebo had an 18% increase in triglyceride levels. Volanesorsen can lead to thrombocytopenia and therefore was not approved in the US but it is hoped that second generation inhibitors of apolipoprotein C-III will not demonstrate this side effect.

In patients with MFCS one should try to reverse the secondary factors that are resulting in the marked hypertriglyceridemia. For example, improving diabetic control, eliminating ethanol intake, and discontinuing drugs that raise triglyceride levels. In patients with markedly elevated triglyceride levels (>1000mg/dL) initial dietary treatment should be a very low-fat diet until the triglyceride levels decrease. Once the triglycerides decrease a diet that reduces carbohydrate intake particularly simple sugars and minimizes alcohol intake is appropriate. Weight loss if appropriate can be helpful in lowering triglyceride levels. If triglycerides remain elevated after the above measures one can consider the use of drugs that lower triglyceride levels such as omega-3-fatty acids and fibrates. Many patients with MFCS are at high risk for atherosclerotic cardiovascular disease and therefore once the high triglyceride levels are lowered one needs repeat a lipid panel to determine whether treatment to reduce the risk of atherosclerotic cardiovascular disease is indicated (for example statin therapy).

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