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Primary hypertriglyceridemia in children and adolescents

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Abstract: Primary disorders of lipid metabolism causing hypertriglyceridemia (HyperTG) result from genetic defects in triglyceride synthesis and metabolism. With the exception of lipoprotein lipase deficiency, these primary HyperTG disorders usually present in adulthood. However, some are unmasked earlier by precipitating factors, such as obesity and insulin resistance, and can be diagnosed in adolescence. Physical findings may be present and can include eruptive, palmer, or tuberoeruptive xanthomas. Triglyceride levels are very high to severe and can occur in the absence or the presence of other lipid abnormalities. Each of the causes of HyperTG is associated with an increased risk to develop recurrent pancreatitis and some may increase the risk of premature cardiovascular disease. Adoption of a healthy lifestyle that includes a low-fat diet, optimizing body weight, smoking avoidance/cessation, and daily physical activity is the first line of therapy. Pharmacologic therapies are available and can be beneficial in select disorders. Here, we review the causes of primary HyperTG in children and adolescents, discuss their clinical presentation and associated complications including the risk of pancreatitis and premature cardiovascular disease, and conclude with management and novel therapies currently in development. The goal of this article is to provide a useful resource for clinicians who may encounter primary HyperTG in the pediatric population.

The prevalence of hypertriglyceridemia (HyperTG) defined as triglyceride (TG) concentrations >150 mg/dL[1] is estimated to be ~10.7% among US children and adolescents aged 12 to 19 y.[2] Secondary causes of high TG due to obesity and type II diabetes account for most cases of HyperTG in children and adolescents.[2] TG concentrations of >500 mg/dL are rare (<0.2%) but when encountered should prompt consideration of a primary TG metabolism. Here, we review the causes of primary HyperTG in children and adolescents and discuss their clinical presentation. We also discuss the associated risks of pancreatitis and cardiovascular disease (CVD). Finally, we conclude with treatment and novel therapies in development. The goal of this article is to provide a useful resource for clinicians who may encounter primary HyperTG in the pediatric population.

Definitions and classifications

TGs constitute one of the major lipid groups. Accumulation of TG in the blood leads to HyperTG. HyperTG can be categorized as primary or secondary. Primary HyperTG includes genetic defects in TG synthesis or metabolism,

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Table 1 Secondary causes of hypertriglyceridemia in children and adolescents

Uncontrolled diabetes mellitus (type I and type II)
Endocrine disorders (obesity, metabolic syndrome, hypothyroidism, hypercortisolism)
Medications*
Pregnancy
Renal disease (nephrotic syndrome, renal failure)
Liver disease (acute hepatitis)
Excessive alcohol intake

*Estrogen, second generation antipsychotic, antidepressants, isotretinoin, rosiglitazone, steroids, thiazides, beta-blockers, bile acid sequesterants, sirolimus, and antiretroviral therapy.

whereas secondary causes in the pediatric age group are often the result of unrecognized or poorly controlled diabetes, obesity, metabolic syndrome, and medications (including atypical antipsychotics and estrogens). Secondary causes of HyperTG are listed in Table 1. Our focus in this review is primary HyperTG with emphasis on the presentation and management in children and adolescents.

The classification of HyperTG in children and adolescents as published by the National Expert Panel on Cholesterol Levels in Children[3] and the Expert Panel on Cardiovascular Health Risk Reduction in Children[4] include definitions of borderline and high TG based on the 75th and 95th percentiles of TG in children, respectively.[4] Unfortunately, this classification does not emphasize the severe TG levels often seen in primary HyperTG. For that reason, we present (Table 2) a classification that combines the former recommendations with the 2010 Endocrine Society guidelines on HyperTG[5] to focus attention on the very high levels of TG seen primary HyperTG. The most common causes of primary HyperTG are discussed below and summarized in Table 3.

Lipoprotein lipase deficiency

Lipoprotein lipase (LPL) deficiency is a rare autosomal recessive disorder with an incidence of 1:500,000 to 1:1,000,000.[6,7] The LPL gene is composed of 10 exons and is located on chromosome 8p22. The first mutation was described in 1989, and since that time, hundreds of mutations have been identified.[8] Most mutations occur in exons 3, 5, and 6, which are responsible for the catalytic coding region of the LPL gene.[8]

The LPL enzyme and its cofactor, apolipoprotein (apo) C-II, act on the luminal surface of the capillary endothelium and are responsible for liberating free fatty acids from TG in dietary-derived chylomicrons and hepatic very low–density lipoprotein (VLDL). When LPL is defective, there is a massive accumulation of chylomicrons in the blood that results in profound fasting HyperTG with marked reductions in high-density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol concentrations.[6] As a result of the massive accumulation of chlomicrons, LPL deficiency is usually referred to as the familial chylomicronemia syndrome. Chylomicrons also accumulate in organs such as the liver and spleen causing organ enlargement and in the pancreas triggering inflammatory changes.

The presentation of LPL deficiency in infancy is suspected by a creamy appearance of the blood on routine blood draw or fingerstick that results from TG accumulation secondary to decreased clearance of chylomicrons from the plasma. If the diagnosis is not made earlier, the disease often presents as severe abdominal pain from acute pancreatitis.

Recurrent abdominal pain and pancreatitis are common. Physical signs can include lipemia retinalis and eruptive xanthomas generally located over the buttocks and extensor surfaces and hepatosplenomegaly.[9] Complications of LPL deficiency can include, pancreatic calcification, diabetes mellitus, and steatorrhea, especially in those who are unable to comply with a very low–fat diet.[10]

The diagnosis of LPL deficiency is supported by the presence of markedly elevated TG concentrations and chylomicrons, the latter, which are normally rapidly cleared from the plasma after a meal. Homozygous or compound heterozygous individuals have absent or markedly reduced LPL activity with serum TG concentrations that can reach 10,000 or higher.[8] In contrast, heterozygous carriers have normal to moderately reduced LPL activity, are usually asymptomatic, and may have mildly elevated fasting TG concentrations that can range from 200 to 750 mg/dL.

Reduction or absent LPL activity can be measured after intravenous heparin administration in the presence of normal apoC-II levels.[11] Heparin is a competitive agonist of LPL and absent LPL activity after an intravenous heparin bolus is diagnostic.[12] Molecular genetic analysis is also available but is not necessary for treatment.

Table 2 Classification of hypertriglyceridemia (mg/dL) in children and adolescents

Age, y	Normal	Borderline	High	Very high	Severe	Very severe
0–9	<75	≥75–99	≥100–499	≥500–999	≥1000–1999	≥2000
10–19	<90	≥90–129	≥130–499	≥500–999	≥1000–1999	≥2000

Definitions integrated from the National Expert Panel on Blood Cholesterol Levels in Children, Expert Panel on Cardiovascular Risk Reduction in Children, and the Endocrine Society Statement on Evaluation and Treatment of Hypertriglyceridemia.