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GENETIC DISORDERS CAUSING HYPERTRIGLYCERIDEMIA IN CHILDREN AND ADOLESCENTS

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ABSTRACT

Primary disorders of lipid metabolism causing hypertriglyceridemia (HTG) result from genetic defects in triglyceride synthesis and metabolism. These disorders, with the exception of mutations in the lipoprotein lipase complex, are often unmasked by precipitating factors including obesity, diabetes or medications. Physical findings can include eruptive, palmer, or tuberoeruptive xanthomas. Other lipid abnormalities may or may not be present. Each of the genetic causes of HTG is associated with an increased risk for develop recurrent pancreatitis; some may also increase the risk of premature cardiovascular disease. Appropriate management includes recognition of the disorder and adoption of a healthy lifestyle that includes a low-fat diet, optimizing body weight, smoking avoidance/cessation, and daily physical activity. Pharmacologic therapies are available and can be beneficial in select disorders. We review the genetic disorders causing HTG in children and adolescents, discuss their clinical presentation and associated complications. We conclude with management and novel therapies in development. For coverage of all related aeas of Endocrinology, please visit our on-line FREE web-text, WWW.ENDOTEXT.ORG.

INTRODUCTION

Triglycerides (TGs) constitute one of the major lipid groups. Accumulation of TG in the blood leads to hypertriglyceridemia (HTG). Causes of HTG can be categorized as either primary or secondary disorders. Secondary causes of HTG account for the majority of the cases of high TG in the pediatric age group and are often the result of unrecognized or poorly controlled diabetes, obesity, metabolic syndrome, and medications (including atypical antipsychotics and estrogens). See Table 1. Primary disorders are genetic defects in TG synthesis or metabolism but are rare. In fact, TG concentrations of > 500 mg/dL account for <0.2% of the HTG cases in

children but when encountered should prompt consideration of a primary disorder of TG metabolism (1). Our focus in here is to review pathogenesis, genetics, presentation and diagnosis of primary HTG disorders in children and adolescents.

Table 1. Secondary Causes Hypertriglyceridemia in Children and Adolescents

Uncontrolled type 1 or type 2 diabetes mellitus
Endocrine Disorders (obesity, metabolic syndrome, hypothyroidism, hypercortisolism)
Medications (steroids, estrogen, second generation antipsychotic, antidepressants, accutane, rosiglitazone, thiazides, beta-blockers, bile acid sequesterants, sirolimus, antiretroviral therapy)
Pregnancy
Renal disease (nephrotic syndrome, renal failure)
Liver disease (acute hepatitis)
Excessive alcohol intake

CLASSIFICATION OF HYPERTRIGLYCERIDEMIA

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

Table 2. Classification of Hypertriglyceridemia (mg/dL) in Children and Adolescents

Age	Normal	Borderline	High	Very high	Severe	Very Severe
0-9 yrs	<75	≥75-99	≥100-499	≥500-999	≥1000-1999	≥2000
10-19 yrs	<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.

Table 3. Summary of Primary Hypertriglyceridemia Disorders

Lipid Disorder	Molecular Defect	Incidence	Lipoprotein Abnormality	Lipid Profile	Presentation
Familial Chylomicronemia Syndrome (FCS)	**LPL deficiency, apo CII deficiency	1 per 1,000,000	↑↑ Chylomicrons,	↑↑ TG (>1000 mg/dL)	Early onset ↑↑ TG, eruptive xanthomas, recurrent pancreatitis
*Familial Combined Dyslipidemia	Unknown	1/200	↑ VLDL, ↑ LDL	↑ TG ↑ LDL-C, ↓HDL-C, ↑ small dense LDL	Often seen with obesity, insulin resistance, hypertension
*Familial Hypertriglyceridemia	Unknown	1/500	↑↑ VLDL	↑ TG (200-1000 mg/dL)	Family members usually affected
*Dysbeta-lipoproteinemia	Abnormal ApoE	1/5000	↑ Chylomicrons, ↑ VLDL remnants (IDL)	↑ TG (250-600mg/dL) ↑ Total cholesterol	Palmer and tuberoeruptive xanthomas

*Generally present in adulthood unless precipitated by a secondary cause (obesity, insulin resistance)
** Rare causes include mutations of apoA-V, glycosylphosphatidylinositol-anchored high-density lipoprotein-binding protein (GPIHBP1) or lipase maturation factor-1(LMF-1) or the presence of circulating inhibitors to LPL.

FAMILIAL CHYLOMICRONEMIA SYNDROME (FCS)

Genetics and Pathogenesis

FCS is a rare monogenic disorder, with an estimated prevalence of about 1 in 500,000 to 1,000,000 (6, 7). FCS results from a mutation in one or more genes of the lipoprotein lipase (LPL) complex and affects chylomicron catabolism. The most common gene affected is in LPL itself, in which patients are homozygous or compound heterozygous for two defective LPL alleles. 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, over 100 mutations that result in LPL deficiency have been reported (8, 9). 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 any part of the LPL complex is defective, there is a massive accumulation of chylomicrons in the blood, hence the name FCS.

FCS can result from loss of function mutations in apoC-II, the cofactor for LPL. Mutations in glycosylphosphatidylinositol-anchored high density lipoprotein-binding protein (GPIHBP1) which helps to anchor chylomicrons to the endothelial surface (10) and mutations in LMF1 factor 1, an endoplasmic reticulum chaperone protein required for post-translational activation of LPL (11) also result in FCS. ApoA-V plays a role in stabilizing the lipoprotein–enzyme complex thereby enhancing lipolysis; thus, defective or absent apoA-V can result in reduced efficiency of LPL-mediated lipolysis (12, 13). Circulating inhibitors to the LPL enzyme (14) have also been

described. Each of the above has an indistinguishable clinical phenotype from LPL deficiency (15).

Presentation and Diagnosis

The presentation of FCS 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. The diagnosis of FCS 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. Laboratory data will also show marked reductions in high-density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol concentrations (7). Homozygous or compound heterozygous individuals who have absent or markedly reduced LPL activity typically have 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.

Physical signs can include lipemia retinalis and eruptive xanthomas generally located over the buttocks and extensor surfaces (9). Hepatosplenomegaly can occur from the accumulation of chylomicrons in the liver and spleen (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 (16).

Reduction or absent LPL activity can be measured after intravenous heparin administration in the presence of normal apoC-II levels (17). Heparin is a competitive agonist of LPL and absent LPL activity after an intravenous heparin bolus is diagnostic (18). Molecular genetic analysis is also available but is not necessary for treatment.

FAMILIAL COMBINED HYPERLIPIDEMIA (FCHL)

Genetics and Pathogenesis

FCHL is one the most common causes of genetic hyperlipidemia with a prevalence of 0.5% to 2% in the population (19, 20). In a pediatric clinic population, FCHL has been shown to be 3 times more prevalent than familial hypercholesterolemia (21). FCHL is a genetically complex disease and the phenotype is usually determined by the interaction of multiple susceptibility genes and the environment. Genome wide association studies (GWAS) and linkage approaches have been utilized to screen the genome in FCHL families from different populations to identify loci linked to the phenotype. At least 35 genes have been implicated in the development of FCHL. One chromosomal locus that has been consistently linked to FCHL is 1q21–23 (22). Another commonly linked gene in FCHL is the ubiquitous transcription factor upstream stimulatory factor 1 (USF1), which has numerous target genes related to lipid and glucose

metabolism (23). A detailed review of gene associations in FCHL is available (22). In general, implicated genes are primarily those involved in an overproduction of VLDL and apoB-100 by the liver, a reduction of fatty acid uptake by adipose tissue, and a decrease in clearance of chylomicron remnants.

Presentation and Diagnosis

The lipid profile in FCHL is variable but in addition to high TG concentrations can include normal or elevated LDL cholesterol and low HDL cholesterol levels. There is also an increase in small dense LDL particles, due to the delayed clearance of VLDL (24, 25). Elevated levels of apoB (> 90 percentile) and small dense LDL particles are now considered diagnostic criteria for FCHL in adults (24), although neither is routinely assessed in clinical practice. The presence of elevated TG and apoB levels in at least 2 family members is also considered necessary for a definitive diagnosis of FCHL (26).

FCHL presents in childhood when unmasked by weight gain (27). FCHL is also influenced by age (27). As a result, in normal weight individuals, the presentation can be delayed. Thus, it is possible that children with normal lipid values but a family known to have FCHL should be retested as young adults (27). Physical examination findings in FCHL are lacking, but concurrent non-lipid CVD risk factors including obesity, insulin resistance, and hypertension are common (28). The diagnosis is made from a characteristic fasting lipid profile and, if available, a reliable family history of dyslipidemia and early CVD (29).

The association of FCHL with premature CVD is well established and CV cardiovascular risks such as visceral adiposity, insulin resistance, impaired glucose tolerance and hypertension are often present. (30, 31). Therefore, identifying this disorder is of particular importance for management of future cardiovascular health.

FAMILIAL HYPERTRIGLYCERIDEMIA (FHTG)

Pathogenesis and Genetics

Familial hypertriglyceridemia (FHTG) is an autosomal dominant disorder with a prevalence of approximately 1 per 500 (20). The genetic defect causing FHTG has not been identified, but studies in a Mexican-American cohort have identified genetic susceptibility loci on chromosomes 6, 7, and 15 that are linked to elevated TG levels (32, 33). The primary abnormality in FHTG is an overproduction of VLDL by the liver and impaired catabolism of TG-rich lipoproteins where normal numbers of very large triglyceride-enriched VLDL particles are secreted (28, 34). FHTG has also been associated with a defective regulation of bile acid synthesis, resulting in abnormally high production rate of bile acids, which associates with the subsequent development of HTG (35). Unlike FCHL, hepatic apoB-100 production is not increased and, as such, there is no overproduction of LDL. As a result prior work suggested no increased CVD risk (20), but recent data shows baseline TG levels predicted subsequent CVD mortality after 20 years of follow up among relatives in FHTG families (30).

Presentation and Diagnosis

TG levels are usually normal in childhood. Although FHTG is not usually expressed until adulthood, with the rise in childhood obesity FHTG has been diagnosed at an earlier age (36-38). The phenotype is usually asymptomatic HTG (36-38) with TG levels between 250 and 1000 mg/dL, normal-to-mildly elevated total cholesterol concentrations and low-to-normal LDL and HDL cholesterol levels (39). The diagnosis of FHTG is made by obtaining a detailed family history and examination of fasting lipoprotein profiles of the patient and relatives.

DYSBETALIPOPROTEINEMIA (REMNANT REMOVAL DISEASE)

Pathogenesis and Genetics

Dysbetalipoproteinemia is a rare autosomal disorder with an estimated genetic prevalence of 1% in Caucasian populations (40). It results from a homozygous apoE2 genotype or a dominant negative mutation in the apoE gene, which serves as a ligand for chylomicrons, intermediate-density lipoproteins, and VLDL receptors in the liver. In the presence of a secondary insult (genetic mutation, medication, or environment) there is abnormal uptake and metabolism of remnant particles (chylomicrons, intermediate-density lipoprotein, and VLDL) with subsequent accumulation of each in the blood. Clinically the disorder is relatively rare occurring in approximately 1 in 10,000 and illustrates the interaction of environment and genes in leading to dyslipidemia.

Presentation and Diagnosis

A secondary insult such as obesity, diabetes, or estrogen use is necessary for expression in childhood. The diagnosis of dysbetalipoproteinemia remnant removal disease should be suspected when total cholesterol and triglyceride levels (range from 300 to 1000 mg/dl) are roughly equal in magnitude (41).

Dysbetalipoproteinemia has been documented in the pediatric age group (38, 42, 43). A case series of 3 children from Vancouver, British Columbia, Canada demonstrated early presentation of the disorder (age range, 10–11 y) due to precipitating factors including hypothyroidism, partial LPL deficiency, and concurrent familial hypercholesterolemia (43). Each child presented with palmar and tuberoeruptive xanthomas.

Palmer crease xanthomas (lipid deposits in the palmar creases) are pathognomonic for this condition, although eruptive xanthomas are possible on pressure sites like the elbows, knees, and buttocks (41). A 30-y retrospective review of lipid disorders from a single clinical practice identified 105 patients with dysbetalipoproteinemia. Palmar crease xanthomas occurred in 20% of patients, cutaneous xanthomas in 18%, and tendon xanthomas in 13% (41).

The diagnosis of dysbetalipoproteinemia is confirmed by documenting elevated remnant lipoproteins, abnormal gel electrophoresis mobility, or by identifying the genetic defect (Arg145 →Cys) in apoE2 (44). Despite having normal or low LDL cholesterol and apoB concentrations, individuals with dysbetalipoproteinemia often have an elevated CVD risk due to the increased remnant particles (45, 46). Affected individuals also are at increased risk for peripheral vascular disease (46).

COMPLICATIONS

Cardiovascular Disease

Children and adolescents with persistent moderate to high levels of TG may be at increased risk for premature cardiovascular disease during adulthood. However, the extent to which HTG independently contributes to CVD has long been debated and remains unknown (47). Few studies have shown an independent relationship between HTG and CVD, but effect sizes have been small (48, 49). In FCHL the increased CVD risk in probands and first degree relatives is largely attributed to the increase in apoB (30) and/or lipoprotein (a) (50). Likewise, in dysbetalipoproteinemia the increased CVD risk is attributed to increased remnant lipoprotein particles (45, 46). A recent systematic review and meta-analysis of observational studies evaluating HTG and CVD found that fasting HTG was associated with an increase in cardiovascular death (odds ratios (OR) 1.80; 95% confidence interval (CI) 1.31-2.49), cardiovascular events (OR, 1.37; 95% CI, 1.23-1.53) and myocardial infarction (OR, 1.31; 95% CI, 1.15-1.4 (51). However, recent statements by both the Endocrine Society and American Heart Association conclude that while there is growing evidence to support HTG is an independent CVD risk, the extent to which it is directly atherogenic remains unclear (4, 52).

Pancreatitis

FCS commonly presents with spontaneous pancreatitis in the first decade of life as a result of the degree of TG elevation, compliance with a low-fat diet is difficult and pharmacologic treatment is not always effective (see below). In contrast, FHTG and dysbetalipoproteinemia usually require a secondary risk factor to incite pancreatitis in adolescence (36, 43).

HTG accounts for 1-4% of cases of acute pancreatitis (53). Though the exact mechanism of inciting pancreatitis is unknown, TG-rich chylomicrons are thought to impair circulatory flow in capillary beds of the pancreas causing ischemia and triggering an inflammatory response (8, 9). HTG is the most common cause of pancreatitis not due to gallstones or alcohol abuse (1-3, 54).

Pancreatitis generally occurs when TG levels exceed 1000-1500 mg/dL (55, 56) but TG between 200-1000 mg/dL can be seen in the early stages of acute pancreatitis of any etiology (57, 58). The risk to develop acute pancreatitis in patients with serum TG >1000 and >2000 mg/dL is 5% and 10% to 20%, respectively (56). The presentation of pancreatitis usually includes abdominal pain, vomiting and ileus (59). When the diagnosis is suspected, serum TG levels should be measured because elevated concentrations in the blood can diminish rapidly.

Thus, a delay in obtaining TG concentration may lead to falsely low levels. Prevention of pancreatitis relies on TG lowering. Lowering levels to < 500 mg/dL effectively prevents recurrences of pancreatitis (56). Prevention of pancreatitis is crucial since mortality from pancreatitis can be as high as 20% (60).

SCREENING AND DIAGNOSIS

Primary disorder of HTG are diagnosed in childhood most often because a family member had experienced a premature cardiac event, because their siblings were known to have elevated triglyceride levels, or because abnormal test results were obtained during a routine examination (38).

Screening for dyslipidemia is recommended in children ≥ 2 years who have one of the following: (1) parents, aunts, uncles and/or grandparents (men ≤ 55 years old, women ≤ 65 years old) who have had a heart attack, treated angina, coronary artery bypass, graft/stent/angioplasty, stroke, or sudden cardiac death; (2) parents who have high blood cholesterol levels (>240 mg/dl); or (4) parental/grandparental family history is not known, and the patient has two or more other risk factors for CAD (including hypertension, cigarette smoking, low HDL cholesterol, obesity (>30% overweight), physical inactivity and diabetes mellitus (1, 2, 61).

With newer recommendations of universal lipid screening between 9-11 years (3), it is likely that FCHL, FHTG or dysbetalipoproteinemia may be detected more often in childhood. Any presentation of acute pancreatitis should prompt the need for a lipid profile. A fasting lipid profile (>12hours) should be obtained when TG are elevated in the non-fasting state. Cut points for normal and elevated TG levels are listed in Table 2.

Primary HyperTG disorders are diagnosed based upon the degree of TG elevation and associated lipoprotein abnormalities (if any), the clinical features (if present) and a reliable family history, when available. Patients can also be clinically classified according to the Fredrickson classification (15). See Table 4. The Fredrickson classification does not distinguish amongst the genes that may be responsible for the disorder. Genetic testing is available for suspected cases of FCS and dysbetalipoproteinemia, but is not necessary for treatment.

Table 4: Fredrickson Classifications of Dyslipidemia

Diagnosis	Fredrickson classification	Lipids	Lipoproteins	Genetics
Familial Hyperchylomicronemia	Type 1	↑TG	↑Chylomicrons	Autosomal recessive due to 2 mutant alleles of *LPL, ApoC2, ApoA-V, LMF-1, GPIHBP1*
Familial Hypercholesterolemia	Type 2A	↑TC	↑LDL	Autosomal codominant; heterozygous form results from 1 mutant allele of LDL receptor, ApoB, or PCSK9; homozygous form results

				from 2 mutant alleles of these genes.
Familial Combined Hyperlipoproteinemia	Type 2B	↑TC, ↑TG	↑VLDL, ↑LDL	Polygenic
Dysbetalipoproteinemia	Type 3	↑TC, ↑TG	↑IDL	Apo E2/E2 homozygosity; or heterozygous rare mutations in ApoE.
Primary Hypertriglyceridemia	Type 4	↑TG	↑VLDL	Unknown
Mixed Hypertriglyceridemia	Type 5	↑TC, ↑TG	↑VLDL, ↑Chylomicrons	Polygenic
Adapted from: Hegele RA. Plasma lipoproteins: genetic influences and clinical implications. Nat Rev Genet 2009; 10:109-21.				

MANAGEMENT

Lifestyle Intervention

Adoption of a healthy lifestyle, including dietary modification, optimizing body weight, smoking avoidance/cessation, and 30-60 minutes of moderate to vigorous physical activity daily, is the primary strategy for managing all HTG in youth (3). Diet changes associated with TG lowering effects include decreasing total, saturated and trans fats (62). Primary HyperTG defects, especially those with TG >1000 mg/dL, often require restriction of dietary fat to 10-15% of total calories with a reduction of both saturated and non-saturated fat to 10-25 grams (62), though this is often difficult to maintain. Other dietary recommendations include reducing simple carbohydrates including sugar sweetened beverages (61), substituting monounsaturated and n-6 polyunsaturated fatty acids for carbohydrate (63), and decreasing carbohydrate rich foods like white bread, rice and pasta (64). Thirty- sixty minutes of daily vigorous activity is also recommended for children between 2-21 years of age with TG elevations (3) as this degree of activity effectively reduces TG (65). Lifestyle recommendations for TG lowering are summarized in Table 5.

Table 5: Lifestyle Recommendations for Triglyceride Lowering in Children and Adolescents

Daily caloric intake should be < 25%–30% of calories from fat, <7% from saturated fat, <200 mg/d of cholesterol*, decrease trans fat
Avoid sugar intake (ice cream, candy, baked goods) and sugar sweetened beverages (pop, juice, sports drinks)
Replace simple carbohydrates (white bread, white pasta, white rice) with complex carbohydrates (wheat bread, whole grain pasta, brown rice)
Replace carbohydrates with monounsaturated fat (olive oil, canola oil, nuts, seeds)

Increase omega 3 fatty acids (fish)
30-60 minutes of vigorous exercise daily

* More severe elevations of TG may require reduction of fat to 10-15% of daily calories

Medium chain triglycerides (MCTs), e.g. chain length of 10 and 12 carbons, can be considered for cases of FCS. MCTs can be either added to infant formula or given as an oral solution to supplement fat calories. Dietary MCTs are directly absorbed into the portal vein and do not require transport on chylomicrons and as a result do not increase TG concentrations. Rouis et al. describe a unique patient with clinical features of LPL deficiency with a complete resolution of clinical symptoms with MCT oil and omega 3 fatty-acid therapy (66).

Drug Treatment

Pharmacological management is sometimes needed in disorders of primary HTG to prevent pancreatitis and/or reduce risk of CVD. Medications commonly used for TG lowering are presented in Table 6. It should be noted that although prescribed (1, 67-69), none are FDA approved for use in children and adolescents (<18 years of age).

Table 6. Medications used for Triglyceride Lowering

Medication	Mechanism of Action	Lipoprotein Effects	Side Effects
Fibric Acid Derivatives*	Agonist for PPAR-nuclear receptors that upregulate LPL and down regulate apoC-III causing ↑degradation of VLDL and TG	↓ TG (30-60%), ↑ HDL-C	Cholesterol gallstones. Contraindicated in liver and gall bladder disease. Use caution in renal disease
Nicotinic Acid*	↓ VLDL and LDL production and HDL degradation	↓ TG (10-40%), ↓ LDL-C, ↑ HDL-C, ↓ lipoprotein (a)	Dose dependent hepatotoxicity, worsening glucose metabolism and hyperuricemia.
Omega 3 fatty acids (fish oil) *	Decreases hepatic fatty acid and TG synthesis and VLDL release	↓ TG (20-50%), ↑ HDL-C, ↑ LDL-C, ↑ LDL particle size.	Fishy taste and burping

*Not FDA approved for <18 years of age

Fibric acid derivatives (fenofibrate, gemfibrozil) lower TG concentrations by 30-60% (70, 71). Patients with LPL deficiency can be offered a trial of fibric acid derivatives but the response is quite variable since these agents work to lower plasma TG primarily by upregulating LPL activity which is often deficient in this condition (72).

Niacin lowers TGs 10-30%, increases HDL cholesterol by 10-40% and lowers LDL cholesterol by 5-20%. The most common complaint is flushing due to the release of prostaglandin E2 in the skin. Flushing typically occurs 15-60 minutes after ingestion and can last up to 30 minutes. Aspirin 30 minutes before niacin can reduce flushing.

Long chain omega 3 fatty acids lower TG levels by 20-50% (73). These effects are primarily seen with prescription fish oils which contain approximately 465 mg of eicosapentaenoic acid (EPA) and 375 mg of docosahexaenoic acid (DHA). Over the counter preparations have variable quantities of EPA and DHA resulting in variable TG lowering effects. While omega 3 fatty acids lower plasma TGs in FCHL, they may actually aggravate the severe HTG of FCS and are therefore contraindicated in LPL deficiency (66).

In individuals with primary HTG who are unresponsive to treatment, plasmapharesis has been utilized. In this procedure plasma is separated from the blood and processed to eliminate selective components. The plasma is then reinfused, though on occasions it may be completely eliminated and replaced by an isovolumetric solution. Plasmapheresis can be carried out as either an emergency or a scheduled procedure. In situations where urgent, rapid and efficient reduction in TG levels are needed such as in pancreatitis, plasmapheresis has proven a valid and safe technique and results in drastic reductions in TG of as much as 60% (74). A multicenter study recently published data demonstrating success using plasmapheresis to prevent pancreatitis in those who fail medical therapy (75).

CONCLUSIONS

While genetic disorders of TG metabolism and synthesis are rare, they are observed in the pediatric population. Identification of these disorders is important given the risk for pancreatitis and/or early CVD. Lifestyle modification is central to prevention, but often is not sufficient. While medications can be helpful in lowering TG, in some disorders they have no benefit. Novel therapies are on the horizon. Whether these therapies will be beneficial in treating primary disorders of HTG in children and adolescents and their associated complications remains to be seen.

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