

Minireview

Monogenic pediatric dyslipidemias: Classification, genetics and clinical spectrum

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Received 28 August 2007; received in revised form 9 October 2007; accepted 9 October 2007

Available online 26 November 2007

Abstract

Monogenic disorders that cause abnormal levels of plasma cholesterol and triglycerides have received much attention due to their role in metabolic dysfunction and cardiovascular disease. While these disorders often present clinically during adulthood, some present most commonly in the pediatric population and can have serious consequences if misdiagnosed or untreated. This review provides an overview of monogenic lipid disorders that present with unusually high or low levels of plasma cholesterol and/or triglycerides during infancy, childhood and adolescence. Biochemical and genetic findings, clinical presentation and treatment options are discussed with an emphasis upon recent advances in our understanding and management of these monogenic disorders.

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Keywords: Adolescence; Childhood; Dyslipidemia; Genetic; Hypercholesterolemia; Hypertriglyceridemia; Lipid disorder; Monogenic; Mutation; Pediatric

Introduction

Monogenic lipid disorders are lifelong conditions that often present during childhood and adolescence with clinically and biochemically extreme phenotypes. As with many other chronic conditions that present early in life, monogenic lipid disorders can require early and dramatic intervention as well as careful surveillance to maximize long-term symptom-free survival. Yet while some monogenic dyslipidemias present commonly in adulthood, those that present almost exclusively in the early years pose distinct challenges due to their more severe symptomatology and need for aggressive therapy. Furthermore, although dyslipidemias in adult populations are often multifactorial in etiology, those in the pediatric population are much more likely to have a monogenic cause and may be due to a variety of gain-of-function or loss-of-function mutations in a

range of candidate genes with important roles in normal lipid metabolism.

Detection and appropriate management of pediatric dyslipidemias can have a significant impact upon the disease course and can prevent complications. While coronary artery disease is a major cause of mortality and morbidity in adult-onset dyslipidemias of monogenic or multifactorial etiology, monogenic pediatric disorders such as homozygous familial hypercholesterolemia are also associated with cardiovascular disease and acute coronary events sometimes occurring as early as 3 years of age [1]. Lipid lowering treatments prevent such events when initiated early in life by reducing long-term complications and improving quality of life. The exact timing for initiation of these treatments is an evolving field of research. Genetic hypertriglyceridemia can result in recurrent pancreatitis which can be fatal if not properly diagnosed and treated.

This review will summarize the current understanding of genetic determinants, clinical manifestations and treatment modalities associated with monogenic lipid disorders presenting during childhood and adolescence. Although not

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a focus of the review, some aspects of lipid metabolism will be addressed; for an enhanced understanding of normal lipid metabolism, the authors suggest several current reviews found elsewhere [2–6]. Key points for each disorder have been summarized in Tables 1–3. The review will cover disorders of cholesterol (hyper- and hypocholesterolemia), triglycerides (hypertriglyceridemia), and other miscellaneous disorders.

Disorders resulting in elevated plasma LDL-cholesterol (Table 1)

Homozygous familial hypercholesterolemia (HoFH)

Familial hypercholesterolemia (MIM 143890) is a heritable disorder of cholesterol metabolism characterized by deficiency or defective function of low density lipoprotein (LDL) receptors [7]. These receptors are present on most cell surfaces and remove LDL particles from plasma. LDL particles are the cholesterol-rich remnants of very low density lipoprotein (VLDL) metabolism that deliver endogenously produced and exogenously acquired cholesterol to the periphery and to the liver [8]. Known as “bad” cholesterol [9], high levels of plasma LDL have a well-documented atherogenic potential [10]. Children with HoFH inherit two defective copies of the *LDLR* gene (MIM 606945) and thus lack functional low density lipoprotein receptors (LDLRs), resulting in plasma LDL concentrations elevated on average sixfold above the normal range [11]. Parents of HoFH children have heterozygous familial hypercholesterolemia (HeFH) with one defective and one wild-type *LDLR* allele each.

As of 2006, >800 mutations in the *LDLR* gene have been documented worldwide in familial hypercholesterolemia patients, and these mutations have been found in all functional domains of the LDLR protein [12]. The LDLR ligand, apolipoprotein B (apo B), is the protein component in LDL particles that facilitates LDL binding and internalization into hepatic and peripheral cells [13]. In addition to single nucleotide mutations, copy number variations [14,15] and splicing mutations [16,17] have also been reported throughout the *LDLR* gene in familial hypercholesterolemia patients. While the products of some mutant *LDLR* alleles are more functional than others, simple homozygotes and compound heterozygotes with different mutations tend to show similar early-onset clinical phenotypes [7]. HoFH has a prevalence of 1 in 1,000,000, while HeFH has a frequency of 1 in 500 [18].

The classical clinical manifestations of HoFH include early appearance of corneal arcus, cutaneous planar xanthomata over hands and extremities, tuberous xanthomata over elbows and tendinous xanthomata in the hand extensor and Achilles tendons, although xanthelasmata are more common in HeFH patients [7,19]. These signs occur as a result of LDL-cholesterol deposition and foam cell formation in skin, tendons and corneae. In HoFH, these signs may become manifest in the first or second decade of life,

while in HeFH these signs appear in the third to fifth decades of life. The life-threatening effects of both HeFH and HoFH are related to foam cell accumulation within the vasculature that can progress to occlusive atherosclerosis. HoFH children are predisposed to early atherosclerosis, including arterial plaque formation and coronary ostial stenosis leading to cardiac ischemia [19]. Aortic valvular thickening and aortic root thickening can lead to aortic regurgitation [20] or stenosis [19] requiring valve replacement. Death from myocardial infarction occurs in untreated subjects before age 30 [7,21] although disease progression in individual patients is quite variable [1,22,23].

Numerous diagnostic criteria have been proposed for HeFH, but none have been proposed specifically for HoFH. Correct diagnosis of HoFH is based on a combination of physical and biochemical findings, family history and molecular genetic analysis [24,25]. Clinicians should suspect HoFH in children presenting with the physical signs listed above and with a positive family history of HeFH in one or both parents. Conversely, isolated pediatric HoFH may be an indicator of undiagnosed parental HeFH since heterozygote symptoms usually appear after childbearing age [26] so that serum lipid profiling for both parents and their children is indicated. Alternatively, children with the extremely rare disorder autosomal recessive hypercholesterolemia (ARH; see below) due to mutant *ARH* can appear to be phenotypically indistinguishable both clinically and biochemically from HoFH patients, with the exception that plasma lipid profiles in parents of a child with ARH are normal [27]. Evidence from a Canadian study indicates that HoFH children have plasma total cholesterol levels >10 mmol/L at a minimum (and usually >18 mmol/L), suggesting that HoFH should be suspected in children whose plasma cholesterol levels exceed this threshold [18]. Although the Simon Broome criteria for HeFH diagnosis [21] specify that patients under 16 must have total plasma cholesterol >6.7 mmol/L or plasma LDL-cholesterol >4.0 mmol/L for a positive HeFH diagnosis, specific diagnostic guidelines for HoFH have not been validated. Definitive diagnosis can be obtained through LDLR functional assays in cultured fibroblasts showing virtual absence of receptor function [7] or *LDLR* gene sequencing showing mutations on both alleles.

All patients with HoFH receive dietary counselling to reduce intake of exogenous cholesterol and saturated fats [28]. The current treatment of choice for HoFH is serial plasma exchange or plasma LDL apheresis, which has so far proven highly effective in prolonging endpoint free survival [29,30]. LDL apheresis has the advantages of reduced exposure to blood products, no significant changes in high density lipoprotein (HDL) cholesterol, and less dramatic volume shifts compared to straight plasma exchange [31]. Concurrent high-dose statin therapy may enhance LDL clearance by upregulating expression of partially functional LDLR, but patients whose mutations leave them with non-functional LDLR show little plasma LDL-cholesterol response [32]. Ezetimibe, a cholesterol absorption inhibitor

Table 1
Monogenic dyslipidemias causing increased LDL-cholesterol in the pediatric and adolescent population

Monogenic disorder	Affected gene	Gene product	Inheritance	Key biochemical features	Key clinical features	Typical age of presentation	Long-term cardiovascular and other risks
Homozygous familial hypercholesterolemia (HoFH)	<i>LDLR</i>	Low density lipoprotein receptor	Autosomal dominant	Very high plasma total cholesterol (>10 mmol/L) High plasma LDL-cholesterol (>8 mmol/L) Normal plasma triglycerides	Corneal arcus Tendon xanthomata of Achilles and hand extensors Tuberous and skin xanthomata over elbows and extremities	Childhood, adolescence	Premature atherosclerosis and cardiovascular disease
Heterozygous familial hypercholesterolemia (HeFH)	<i>LDLR</i>	Low density lipoprotein receptor	Autosomal dominant	Elevated plasma LDL-cholesterol (>4.9 mmol/L) Normal plasma triglycerides	Corneal arcus xanthelasmata Tendon xanthomata	Young adulthood	Premature atherosclerosis and cardiovascular disease during early to middle adulthood
Familial defective apolipoprotein B (FDB)	<i>APOB</i>	Apolipoprotein B-100	Autosomal dominant	Same as HeFH	Same as HeFH	Same as HeFH	Same as HeFH
PCSK9 gain-of-function	<i>PCSK9</i>	Proprotein convertase subtilisin/kexin 9	Autosomal dominant	Same as HeFH	Same as HeFH	Same as HeFH	Same as HeFH
Autosomal recessive hypercholesterolemia (ARH)	<i>ARH</i>	ARH adaptor protein	Autosomal recessive	Extremely high plasma total cholesterol (often >20 mmol/L)	Similar to HoFH above	Variable	Premature atherosclerosis and cardiovascular disease
Wolman disease	<i>LIPA</i>	Lysosomal acid lipase	Autosomal recessive	Normal lipid biochemistry	Anemia Failure to thrive Hepatosplenomegaly Jaundice Steatorrhea	Infancy	Death during first year
Phytosterolemia	<i>ABCG5</i> <i>ABCG8</i>	ATP-binding cassette G5, G8	Autosomal recessive ^a	Very high plasma sitosterol and campesterol (both >>0.1 mmol/L; normal <<0.1 mmol/L) Low to high plasma total cholesterol (<10 mmol/L)	Recurrent joint arthritis (knees and ankles) Splenomegaly Tendon xanthomata Tuberous xanthomata Premature atherosclerosis	Childhood	Premature coronary artery disease with highly variable progression and severity

^a Some heterozygotes with disease have been reported [70].

that operates on brush border cells of the small intestine, seems to have some efficacy in plasma LDL-cholesterol reduction among HoFH subjects [33,34]. Liver transplantation (sometimes together with heart and lung transplantation) and gene therapy have been attempted, with variable results [7,35]. A recent long-term study into liver transplantation has shown promise for this as a viable treatment modality [36]. Finally, the microsomal triglyceride transfer protein (see below) inhibitor class of medications has shown short term benefit in LDL-cholesterol reduction in HoFH [37]. These medications inhibit the production of VLDL thereby eliminating VLDL metabolites, including LDL, from the plasma.

Heterozygous familial hypercholesterolemia (HeFH) and familial defective apolipoprotein B (FDB)—A pediatric perspective

HeFH has been well-studied and reviewed [7,38,39]. Its frequency in the general population is 1 in 500, although this figure rises within certain ethnic subgroups [39]. While HeFH presents typically during adulthood and is both clinically and biochemically milder than its homozygous counterpart, it is clearly a potent risk factor for early cardiovascular disease and death if undetected and untreated [21]. A study of over 1000 pediatric HeFH patients found that 89% had a positive family history of premature cardiovascular disease [40]. FDB (MIM 144010) results from mutations in the LDLR-binding domain of apo B that reduce LDLR-binding affinity. Homozygous FDB presents with biochemical, clinical and CAD risk profiles similar to HeFH, while heterozygous FDB is generally less severe than HeFH in all of these respects [41]. In most instances the two disorders are clinically indistinguishable, and treatments used in HeFH discussed below are also effective in FDB [13,41]. A rare subtype of HeFH results from a gain-of-function mutation in the *PCSK9* gene, discussed in more detail below.

An open question in HeFH management has been “At what age should management begin?” In contrast to HoFH, plasma LDL-cholesterol in HeFH can usually be adequately managed using statin therapy, often in combination with other agents, to upregulate expression of the single functional LDL receptor [39]. Men with untreated HeFH have 5%, 20% and 50% risk of coronary artery disease at ages 30, 40 and 50 years, respectively [42]. The primary manifestation during the pediatric age range is marked hypercholesterolemia, due to elevated LDL-cholesterol usually elevated two to three times above the upper normal limit [7]. Corneal arcus, xanthelasmata and tendon xanthomata begin to appear in a majority of patients during the third decade of life [43]. However, long-term cardiovascular disease severity may correlate with parental disease severity, since evidence shows that HeFH parental event-free survival is significantly reduced when their children’s plasma LDL levels exceed 6.23 mmol/L [40]. This suggests that higher plasma LDL

levels in pediatric HeFH patients should prompt earlier and more intensive therapy.

Current guidelines dating from 1992 for management of HeFH indicate pharmacotherapy in addition to diet therapy in children age 10 years or older when plasma LDL exceeds 4.9 mmol/L, or when it exceeds 4.1 mmol/L in the presence of family history of premature cardiovascular disease or at least two other cardiac risk factors [44]. These same guidelines recommended that pharmacologic intervention be limited to the use of bile acid sequestrants, which are not systemically absorbed.

However, mounting evidence over recent years has shown statin drugs to be both effective and probably safe when used in pediatric HeFH patients. Two meta-analyses of clinical trials involving statin use by HeFH patients in their second decade of life showed plasma LDL reductions of 25% [45] and 32% [46] with no significant increase in adverse reaction rates compared to placebo, although none of the trials exceeded 3 years in duration. Early statin therapy initiation in HeFH children has recently been shown to slow the progression of carotid intima media thickening [47]. In the short term, statins have no effect on sexual development, while effect on growth is negligible [45–47].

A 2007 scientific statement from the American Heart Association acknowledges this evidence by adopting a much more permissive attitude towards the use of statins in children with HeFH and by providing a set of prescription and follow-up recommendations for clinicians [48]. This statement marks a significant departure from the previous 1992 guidelines in several respects: statins are now recommended as the first-line treatment in children requiring lipid management; treatment initiation may begin below the age of 10 years in children with certain high-risk conditions or risk factors; and obese children with dyslipidemias should receive additional screening for the metabolic syndrome [48]. This statement also reiterates the current lack of long-term safety data and encourages careful patient surveillance. Yet if any debate remains concerning the long-term benefits associated with starting statin therapy in the second decade of life versus the third decade, it will not be resolved until long-term data become available.

Autosomal recessive hypercholesterolemia

While autosomal recessive hypercholesterolemia (ARH; MIM 603813) is a monogenic lipid disorder most prevalent in people of Italian heritage, patients have been documented from many geographical ancestries [49]. ARH has a clinical presentation very similar to HoFH, with some key differences; for instance, physical signs are quite similar, but aortic valve stenosis is less common and aortic root disease shows slower progression [49]. Age of diagnosis can vary between the first and fifth decades of life, making ARH a potential diagnosis in both pediatric and adult populations. In reported patients, total plasma cholesterol levels have varied between 9.6 and 27.1 mmol/L, while LDL-

cholesterol levels have varied between 8.6 and 22.9 mmol/L [50]. Despite the large variability, these parameters are sufficiently abnormal in ARH patients to satisfy the Simon Broome criteria for HeFH diagnosis [39]; in the context of a pediatric clinical presentation ARH closely resembles HoFH. A recent study that directly compared the two conditions concluded that ARH most closely resembled receptor-defective HoFH, while receptor-negative HoFH patients have higher plasma LDL levels and a ninefold increased risk of CAD with earlier onset [51]. The two disorders may be distinguished through sequencing of the *ARH* and *LDLR* genes or through Western blotting of ARH protein in biopsy samples [52].

Treatment of ARH differs substantially from HoFH in that statins reduce plasma LDL-cholesterol by 30–60% [53]. ARH is an adapter protein that facilitates LDL uptake by hepatocytes by promoting clathrin-pit mediated LDLR clustering and internalization [54,55]. Evidence suggests that ARH fibroblasts could use a different mechanism of LDLR internalization independent of ARH protein [54,56], so that statin-induced LDLR upregulation enhances LDL clearance by these cells. Combination therapy including statins, ezetimibe and bile acid sequestrants (which sequester bile acids in the small intestine, causing upregulation of the LDL receptor which results in reduced plasma LDL-cholesterol) is typically indicated in these patients [57], rather than some of the more dramatic treatments used for HoFH.

Lysosomal acid lipase deficiency

Lysosomal acid lipase is the enzyme responsible for intracellular hydrolysis of triglycerides and cholesteryl esters by many tissues throughout the body [58]. Mutations in the *LIPA* gene encoding lysosomal acid lipase underlie lipid storage diseases characterized by intracellular accumulation of unhydrolyzed lipids [58]. The two autosomal recessive diseases associated with defective lysosomal acid lipase are Wolman disease (MIM 278000) and cholesteryl ester storage disease (CESD; MIM 278000), which are characterized by the production of non-functional and partially functional enzymes, respectively [59]. While CESD is a disease of adolescence and adulthood, Wolman disease is a neonatal disease often leading to death during the first year [60].

CESD is usually diagnosed during childhood or adolescence and typically presents with hypercholesterolemia and hepatomegaly, which eventually leads to hepatic fibrosis [60]. Wolman disease has a much more dramatic presentation during infancy, with clinical features that include hepatosplenomegaly, failure to thrive, steatorrhea, anemia, jaundice and an acutely ill appearance [60,61]. Pathological examination shows triglyceride and cholesterol accumulation in liver, spleen, intestinal lining, bone marrow and vasculature, as well as severe adrenal calcification [60,61]. Plasma cholesterol and triglyceride levels are low to normal [60]. While patients with CESD can have increased LDL-

cholesterol that responds to treatment with statins and ezetimibe [62], there is no specific treatment for Wolman disease and prognosis is sometimes unfavourable, although some remarkable results have been obtained showing the feasibility of bone marrow transplantation, enzyme therapy and gene therapy [63–65]. One recent report shows promise for early umbilical stem cell transplantation as a curative intervention [66]. Prenatal diagnosis can be performed when suspicion of the disease exists [67]. However, prognosis remains quite grim and children usually die within 1 year [60].

Phytosterolemia

Patients with phytosterolemia (MIM 210250) can have some features in common with HoFH patients. Phytosterolemia, also known as sitosterolemia, is predominantly found in pediatric patients; the main defect involves a selective increase in plasma concentrations of plant sterols or phytosterols, including sitosterol and campesterol, which occur in concentrations of 100 and 10 times higher than normal, respectively [68]. One study found that normal and phytosterolemia patients had average plasma sitosterol concentrations of 0.3 and 3.5 mg/dL, respectively [69]. This condition results from mutations in the *ABCG5* (MIM 605459) and *ABCG8* (MIM 605460) genes [70,71], which together encode a heterodimeric G5G8 protein expressed by hepatocytes and enterocytes. In unaffected individuals, the G5G8 transporter in duodenal enterocytes rapidly returns most absorbed phytosterols back to the intestinal lumen before these sterols become incorporated into chylomicrons and reach the systemic circulation. Phytosterols that do enter the circulation are then secreted into the bile by hepatocytes using the same G5G8 transporter [2,72,73]. *ABCG5* and *ABCG8* mutations causing dysfunctional G5G8 transporters result in severely increased plasma phytosterol concentration; these sterols are incorporated into chylomicrons and other cholesterol-carrying lipoproteins.

Clinical similarities between phytosterolemia and HoFH include childhood presentation of tuberous and tendinous xanthomata, and early appearance of cardiovascular disease as a result of sterol deposition in the wall of the ascending aorta and coronary ostia [68]. Phytosterolemia may be distinguished from HoFH by a general absence of corneal arcus and by several additional key symptoms including recurrent joint arthritis often affecting knees and ankles, splenomegaly, hemolysis and platelet abnormalities [68]. Importantly, total plasma cholesterol levels may range from normal to moderately elevated, but are on average less than 10 mmol/L [69].

Treatment involves dietary elimination of all sources of non-cholesterol sterols, including such common foods as vegetable oils, margarine, nuts, olives, avocados and shellfish [68]. Bile acid sequestrants and ezetimibe effectively lower both plasma cholesterol and plant sterol levels, while statins produce minimal response due to their selective reduction in plasma cholesterol, [74,75].

Disorders resulting in depressed plasma LDL-cholesterol (Table 2)

Hypobetalipoproteinemia

Abnormally low levels of chylomicrons, VLDL and LDL particles in a child's plasma may be caused by several monogenic disorders that reduce the quantity or quality of apo B produced by the liver and small intestine. The two most well-studied are abetalipoproteinemia (ABL; MIM 200100) and familial hypobetalipoproteinemia (FHBL; MIM 107730), which result from mutations in the *MTP* (MIM 157147) and *APOB* (MIM 107730) genes, respectively [13]. A rare form of mild familial hypobetalipoproteinemia results from heterozygous loss-of-function mutations in the *PCSK9* gene, as discussed in detail below.

Microsomal triglyceride transfer protein, which is the product of the *MTP* gene, is indispensable for VLDL production; although many details remain unclear, it is likely that this protein stabilizes or chaperones nascent apo B early during VLDL synthesis while triglycerides are being added to the developing particle [76,77]. Missense and truncation mutations in *MTP* that result in non-functional protein products cause a near complete lack of circulating apo B containing lipoproteins in the plasma of homozygotes or compound heterozygotes [78]. In FHBL, almost 60 mutations have been documented in the *APOB* gene [79]. These are usually truncation mutations in contrast to missense mutations in the receptor-binding domain of apo B that cause familial defective apo B, a form of hypercholesterolemia (FDB, see above) [78]. Since apo B is the primary apolipoprotein in chylomicrons and VLDL, familial hypobetalipoproteinemia patients have persistently low plasma levels of these particles, even after a fatty meal.

The clinical pictures of ABL and homozygous FHBL are very similar, and both result from a lack of cholesterol, triglyceride and fat-soluble vitamin absorption and transport from the small intestine [13]. Children are normal at birth with both ABL and homozygous FHBL but soon develop steatorrhea, diarrhea and failure to thrive. Deficiency of vitamins A, E and K causes diverse symptoms such as retinitis pigmentosa, retinal structural degeneration, reduction in deep tendon reflexes and proprioception, and bleeding secondary to prothrombin deficiency [79]. Acanthocytosis of erythrocytes and fatty deposits in liver and intestinal epithelium are also observed [79]. Heterozygous FHBL patients may be asymptomatic or may experience some of the same symptoms as homozygous FHBL patients, although these symptoms usually appear during adulthood [78,79]. It should be noted that apo B truncations have a 3 in 10,000 frequency in the general population [80] while *MTP* mutations are also very rare; ABL appears to be more prevalent in contexts favouring parental consanguinity [79]. Family history is therefore an important factor for diagnosis of these conditions. A major biochemical differentiating factor is the presence of normal plasma

Table 2
Monogenic dyslipidemias causing decreased LDL-cholesterol in the pediatric and adolescent population

Monogenic disorder	Affected gene	Gene product	Inheritance	Key biochemical features	Key clinical features	Typical age of presentation	Long-term cardiovascular and other risks
Abetalipoproteinemia (ABL)	<i>MTP</i>	Microsomal triglyceride transfer protein	Autosomal recessive	Very low plasma total cholesterol	Acanthocytosis Diarrhea, steatorrhea Failure to thrive	Infancy	Degenerative demyelinating neuropathy with peripheral sensorimotor deficits Retinal degeneration with loss of colour vision and blindness
Familial hypobetalipoproteinemia (FHBL)	<i>APOB</i>	Apolipoprotein B (apo B)	Autosomal co-dominant	Near or complete absence of plasma apo B and LDL-cholesterol Persistently low plasma VLDLs and chylomicrons following fatty meal	Fatty liver Fat-soluble vitamin deficiency: Retinitis pigmentosa Neurological dysfunction Bleeding disorders		
Primary bile acid malabsorption	<i>SLC10A2</i>	Ileal apical sodium-dependent bile acid transporter (ASBT)	Autosomal recessive	Low plasma LDL-cholesterol Elevated fecal bile acid excretion	Diarrhea, steatorrhea Failure to thrive	Early infancy	Possible cardio-protective effects of low plasma LDL
<i>PCSK9</i> deficiency (loss-of-function)	<i>PCSK9</i>	Protein convertase subtilisin/kexin 9	Autosomal recessive	Extremely low plasma LDL-cholesterol (<1st percentile)	None	Variable	Possible cardio-protective effects of low plasma LDL

lipids in parents of ABL subjects but half-normal total and LDL-cholesterol in the heterozygous FHBL parents of homozygous FHBL children [81].

Treatment for both ABL and homozygous FHBL includes lifelong dietary supplementation with medium-chain triglycerides and massive amounts of fat-soluble vitamins A, E and K, given orally (absorbed through the portal circulation) to prevent the various symptoms that deficiencies can cause [79]. Due to malabsorption, long-chain triglyceride intake should be limited to less than 15 g per day and patients often become self-averse to these dietary constituents or conversely become relatively tolerant to them later in life [13].

Primary bile acid malabsorption

The *SLC10A2* gene (MIM 601295) encodes the apical sodium-dependent bile acid transporter (ASBT), which has an important role in bile acid reabsorption in the distal ileum [82]. Certain splicing and missense mutations in *SLC10A2* have reportedly caused primary bile acid malabsorption in children who are homozygotes or compound heterozygotes for these rare mutant *SLC10A2* alleles [83]. These children present with steatorrhea and diarrhea within the first few days of life, and failure to thrive becomes apparent after a few months [83–85]. Plasma LDL-cholesterol and the bile acid pool are markedly decreased, while fecal bile acid content and total stool output are markedly increased [83,86]. Although signs and symptoms tend to persist throughout life, steatorrhea and diarrhea have been improved dramatically through dietary therapy that is low in triglycerides and high in medium-chain fatty acids [83].

While patients with primary bile acid malabsorption and low serum LDL-cholesterol may benefit from long-term protection against cardiovascular disease, studies have not yet been performed to confirm this benefit. However, the reduction in LDL-cholesterol associated with ASBT dysfunction has made ASBT a potential pharmacological target in the treatment of cardiovascular disease, and several ASBT inactivators in mouse and guinea pig models have been shown to reduce plasma LDL-cholesterol and the progression of atherosclerosis [87–89].

Mutations in PCSK9

Mutations in the *PCSK9* gene (MIM 607786) have been implicated in both hypercholesterolemia (see above) and hypobetalipoproteinemia (see above) phenotypes, although prevalence of pediatric phenotypes due to mutations in this gene remains to be determined. Heterozygous gain-of-function missense and nonsense mutations have been associated with increased plasma LDL-cholesterol and early atherosclerosis [90–93], while loss-of-function mutations have been associated with extremely low plasma LDL-cholesterol and possible protection against early atherosclerosis [94–98]. The *PCSK9* gene encodes proprotein convertase

subtilisin/kexin 9, a serine protease that enhances LDLR degradation following both biosynthesis and LDL-mediated internalization, though these mechanisms have yet to be fully understood [99]. However, studies in mice have demonstrated that PCSK9 function negatively correlates with LDLR expression and positively correlates with plasma LDL concentration, while gain-of-function mutations can additionally increase VLDL apo B concentration [100–102].

A patient with two loss-of-function *PCSK9* mutant alleles had extremely low but detectable plasma apo B and LDL-cholesterol [98], which contrasts with the absence of these analytes in ABL and homozygous FHBL. It is assumed that this biochemical phenotype would be associated with longevity and reduced long-term risk of cardiovascular disease, since evidence suggests that heterozygous nonsense mutations and non-synonymous sequence variations in *PCSK9* may reduce cardiovascular disease risk by up to 88% [96]. Meanwhile, patients heterozygous for a gain-of-function *PCSK9* allele (MIM 603776) share many of the clinical features of subjects with HeFH [90]; they should be managed in the same manner as patients with heterozygous *LDLR* mutations, with a combination of a statin and ezetimibe [12,91].

Other pediatric dyslipidemias (Table 3)

Hypoalphalipoproteinemia (decreased HDL-cholesterol)

There are several genetic disorders that can lead to reduced plasma high density lipoprotein (HDL) cholesterol concentration, some of which can present in childhood or adolescence. The most dramatic of these, namely Tangier disease (MIM 205400), is characterized by a near absence of HDL particles from the plasma [103]. The genetic defect lies in the *ABCA1* gene (MIM 600046), which encodes a cell membrane protein implicated in cholesterol efflux from tissues throughout the body [104–106]. As an important part of the reverse cholesterol transport pathway, *ABCA1* plays a focal role in cholesterol efflux from the cell interior onto nascent HDL particles via apo A-I [107]. Apo A-I (MIM 107680) is the main apolipoprotein component of HDL, which returns cholesterol from the periphery to the liver [5]. In the absence of functional *ABCA1*, plasma HDL levels rarely exceed 0.2 mmol/L and usually approach zero as apo A-I fails to bind and remove cholesterol from peripheral cells [103,108]. Some Tangier disease patients may also have mild to moderate hypertriglyceridemia.

For homozygous *ABCA1* mutations causing Tangier disease, the resulting clinical disease classically presents during childhood with enlarged orange or yellow adenoids and tonsils, hepatosplenomegaly and peripheral neuropathy that may be either transient and recurring or progressive and debilitating [103,108,109]. Accumulation of cholesterol in macrophages that cannot efflux cholesterol to HDL results in foam cell formation in the spleen, liver,

Table 3
Other monogenic dyslipidemias in the pediatric and adolescent population

Monogenic disorder	Affected gene	Gene product	Inheritance	Key biochemical features	Key clinical features	Typical age of presentation	Long-term cardiovascular and other risks
Tangier disease (TD)	<i>ABCA1</i>	ABCA1	Autosomal recessive	Extremely low plasma HDL-cholesterol (<0.2 mmol/L)	Enlarged yellow tonsils & adenoids Hepatosplenomegaly Peripheral neuropathy	Infancy, childhood	Increased lifetime cardiovascular risk, especially with other risk factors Corneal opacification Peripheral sensorimotor neuropathy with muscle weakness and atrophy
Hyperchylomicronemia	<i>LPL</i> <i>APOC2</i>	LPL Apo C-II	Autosomal recessive Autosomal recessive	Extremely high fasting plasma triglycerides (> 10 mmol/L, often >20)	Abdominal pain Failure to thrive Hepatosplenomegaly Lipemia retinalis Recurrent pancreatitis Nausea, vomiting Eruptive xanthomata over extensor surfaces and buttocks	Infancy, childhood	No increase in cardiovascular risk upon successful diet therapy

intestinal epithelium, bone marrow and other parts of the reticuloendothelial system; cholesterol deposition also occurs in fibroblasts, neurons and Schwann cells [103,108]. Despite also having low LDL levels, children with Tangier disease appear to have an increased risk of cardiovascular disease later during adulthood, which is likely related to the extremely low levels of plasma HDL [110,111]. Treatment of the metabolic disturbances in Tangier disease remains difficult using currently available HDL-increasing drugs due to the absent ABCA1 function [112]. Thus a reasonable treatment strategy later in life is to decrease the plasma LDL:HDL ratio using cholesterol-lowering pharmacotherapy in combination with cardiovascular risk factor reduction and prevention through lifestyle and diet modification [113]. Currently there is no consensus regarding the specific treatment of Tangier disease in children, and treatment courses are usually guided by the presence of secondary conditions and complications.

Other rare causes of depressed HDL-cholesterol are inherited deficiencies of lecithin cholesteryl acyltransferase (MIM 245900) or of apo A-I. These disorders do not present with the classical physical signs of tonsillar enlargement, hepatosplenomegaly or neuropathy associated with Tangier disease [103]. Although lecithin cholesteryl acyltransferase and apo A-I deficiency syndromes are characterized by extremely low plasma HDL-cholesterol, clinical presentation can be variable and signs such as corneal clouding, tendon or skin-fold xanthomata and, in some cases, premature cardiovascular disease, generally appear during adulthood [103,114–116].

Hyperchylomicronemia

The hyperchylomicronemia syndrome seen in pediatric patients is usually attributable to one of two monogenic disorders affecting the peripheral metabolism of triglyceride-rich, intestinally derived chylomicron particles. Lipoprotein lipase (LPL; MIM 609708) is an enzyme of the vascular endothelium that hydrolyzes chylomicron triglycerides, making free fatty acids available for energy and storage needs of skeletal and cardiac muscle and of adipose tissue [117]. Apo C-II (MIM 608083) is incorporated into chylomicrons and VLDLs from HDLs as an LPL activator [118,119]. Homozygous or compound heterozygous mutations in either of these genes result in a hypertriglyceridemic syndrome that frequently manifests during infancy or childhood. LPL deficiency has a commonly cited prevalence estimate of one in one million and apo C-II deficiency is suspected to be even less common [120].

The most common symptom leading to referral is recurrent pancreatitis, which is thought to result from episodic pancreatic ischemia secondary to hyperchylomicronemia [121]. Patients usually complain of mild to severe abdominal pain with nausea and vomiting. Common physical signs during childhood include failure to thrive, hepatosplenomegaly, lipemia retinalis and eruptive xanthomata over extensor surfaces and buttocks [38]. However, evidence

suggests that presentations during infancy can be heterogeneous and may include other signs such as intestinal bleeding, pallor, anemia, irritability, diarrhea, seizures and encephalopathy [122,123]. Plasma lipid profiling typically shows extremely elevated fasting triglyceride levels above 10 mmol/L [124], although symptoms associated with hyperchylomicronemia syndrome such as pancreatitis usually occur when triglycerides exceed 20 mmol/L [125]. LDL and HDL levels are usually below normal [120]. Plasma appears milky and turbid, or lipemic, due to its high triglyceride content [124].

Early diagnosis is important to prevent such complications as chronic pancreatitis and pancreatic necrosis [117,126], although often pancreatic function deteriorates very slowly [127]. Cardiovascular risk may also be increased in these patients, though evidence has been inconclusive [121,128]. An infant or child presenting with hyperchylomicronemia syndrome can be tested for LPL deficiency by performing an LPL assay using postheparin plasma, which will demonstrate reduced LPL activity in a deficient patient; apo C-II deficiency can be diagnosed if this reduced LPL activity normalizes upon addition of exogenous apo C-II [129]. However, as with many other monogenic disorders, direct gene sequencing has now become the more expedient diagnostic method.

Unfortunately, hyperchylomicronemia resulting from deficiency in LPL or apo C-II is very difficult to treat with existing pharmacologic agents. Fibrates treat hypertriglyceridemia partially by upregulating LPL activity, making them unsuitable for these patients. Niacin reduces VLDL secretion by hepatocytes, which is only marginally useful since chylomicrons have an intestinal origin [121]. The most effective treatment modality is severe dietary triglyceride restriction, although recommended targets vary from less than 50 g per day, or under 25% of total daily caloric intake [121] to less than 20 g per day, or under 15% [130]. However, such a dietary regime is often very difficult for patients to follow. Recent efforts have focussed on the potential for gene therapy as a long-term cure, and expression of virus-recombinant human gain-of-function mutant LPLS447X in murine models has shown strongly favourable results when injected intramuscularly [131,132]. A clinical trial is currently under way to examine the feasibility of gene therapy in human LPL deficient patients [133].

Conclusions

There has been considerable recent progress in understanding at least a portion of the molecular bases for severe dyslipidemias of childhood. Clear distinctions at the molecular and clinical levels are emerging between lipid disorders that manifest during adulthood and those that present in children. Clinicians must adjust their perspective and goals when dealing with monogenic disorders of lipoprotein metabolism in the pediatric population. Monogenic disorders may be suspected in children who present with markedly deviated levels of plasma LDL-cholesterol, HDL-

cholesterol or triglycerides or with the signs and symptoms of syndromes described in this review. Genetic analysis is becoming more practical and useful in the diagnosis and management of these patients. Since the molecular genetic bases for some extreme pediatric lipid disorders are being increasingly well-understood, there is some hope for future treatments that take advantage of this understanding.

Acknowledgments

Supported by the Jacob J. Wolfe Distinguished Medical Research Chair, the Edith Schulich Vinet Canada Research Chair (Tier I) in Human Genetics, a Career Investigator award from the Heart and Stroke Foundation of Ontario, operating grants from the Canadian Institutes for Health Research (MOP-13430, MT-8014), the Heart and Stroke Foundation of Ontario (NA-5320, T-5603, PRG-5967 and the Irwin Bernick Summer Student Fellowship through the University of Western Ontario) and by Genome Canada through the Ontario Genomics Institute.

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