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Minireview

Monogenic pediatric dyslipidemias: Classification, genetics and clinical spectrum

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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.

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 nonfunctional LDLR show little plasma LDL-cholesterol response [32]. Ezetimibe, a cholesterol absorption inhibitor