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Familial Hypercholesterolemia: Advances in Understanding the Early Natural History

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Abstract Familial hypercholesterolemia (FH) is a very common inherited disorder of lipoprotein metabolism, associated with increased cholesterol levels from birth onwards and premature coronary artery disease. In order to prevent cardiovascular disease at a young age, children and young adults with FH should be identified and treated as early as possible. Nowadays, several different screening strategies have been developed, using either universal screening or case finding screening to search for children with FH. Currently, a number of treatment options for those children are available, and drugs of first choice are statins. However, there is still a need for long term follow up studies to answer the question whether it is justified to start treatment at a young age and prevents CVD later in life.

Keywords Familial hypercholesterolemia · FH · LDL-cholesterol · Cardiovascular disease · Lipid-lowering therapy · Statins · Screening strategy

Introduction on Familial Hypercholesterolemia

Familial hypercholesterolemia (FH) is an inherited disorder of lipoprotein metabolism, associated with increased cholesterol levels and premature coronary artery disease. FH affects 1:500 individuals among the general population, with an even higher prevalence in certain populations in Quebec (1:270), Lebanon (1:171) and South Africa (1:70) [1, 2]. The majority of FH is due to mutations in the LDL receptor (LDLR) gene, causing an absence of expression or loss of function of the LDLR. This limits the uptake of LDL-cholesterol (LDL-C) by the liver and subsequently leads to increased levels of plasma LDL-C from birth onwards. A similar phenotype can be caused by amino acid changes in the apolipoprotein B (apo-B) gene and gain of function mutations in the PCSK 9 gene [3]. Altogether, more than a thousand different mutations are known to underlie FH.

Clinical presentation of FH is characterized by two to three fold elevations in plasma LDL-C levels, a family history positive for CVD and physical symptoms of cholesterol deposits in the skin [1]. Hypercholesterolemia plays an important role in the development of atherosclerosis. Accumulation of cholesterol ester-enriched macrophages in the arterial wall leads to atherosclerotic plaques that can eventually occlude the arterial lumen. Two major pathological studies, The Pathological Determinants of Atherosclerosis in Youth Study (PDAY) and The Bogalusa Heart study, evaluated the relationship between cardiovascular risk factors and atherosclerosis after accidental death in children and young adults. Both studies showed a significant correlation between increased cholesterol levels and the extent of atherosclerotic lesions in the arteries of the young subjects [4, 5]. These data have also been supported with studies of non invasive measurements of early atherosclerosis in FH children. Despite any complaints or symptoms, impaired flow-mediated dilatation (FMD), increased intima media thickness (IMT), and abnormal levels of coronary calcium on CT, have already been observed in these subjects [6, 7, 8•]. Altogether, these findings have led to the hypothesis that early diagnosis and treatment of FH is important, in

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order to decrease atherosclerosis progression and reduce the risk of premature cardiovascular events. The last decade has brought more insight in the natural history of FH and advances in strategies for early diagnosis and treatment of this disorder. This article aims to provide an outline of the current screening and treatment options in FH.

Screening for FH

Who to Screen

The clinical diagnosis of FH in adults is based on personal and family history, in combination with physical examination findings and plasma cholesterol levels. Three clinical tools currently used are the Dutch Lipid Clinical Network Criteria (DLCNC), the Simon Broome Register criteria and the Make Early Diagnosis-Prevent Early Death (MED-PED) criteria [9, 10]. These criteria mainly differ in their need for DNA testing, but overall they have rather similar specificity and sensitivity comparing to molecular DNA diagnosis [11].

All currently used guidelines agree on the fact that once FH has been identified, or is suspected based on a genetic test or clinical criteria (including a positive family history of premature CVD) in one parent, screening for FH should be performed in their children. This can be done by either molecular genetic testing or taking a fasting lipid sample. Furthermore, specific conditions like diabetes, nephrotic syndrome or hypothyroidism can cause secondary hypercholesterolemia and should be early recognized.

Screening for FH is recommended in order to prevent early cardiovascular events due to atherosclerosis. It should be kept in mind that the extent of childhood atherosclerosis increases as the number of CVD risk factors present increases. Therefore, the recent US guidelines also pays special attention to children with significant tobacco smoke exposure, hypertension or elevated BMI and recommends screening of their lipid profiles [8•].

Screening Strategies

Several different screening strategies are currently used to identify patients with FH.

Screening should involve measuring lipid levels with total cholesterol (TC) en triglycerides (TG) in order to calculate LDL-C according to the Friedewald formula. Because this is dependent on TG levels, a fasting sample is required. If cholesterol levels are increased, another sample is required, to ensure that the mean measurement reflects the true value.

Two major strategies are case finding, aimed to search specifically for FH children, and universal screening, aimed to identify any dyslipidemia in childhood. In its recent guidelines on Cardiovascular Health and Risk Reduction in Children and Adolescents the National Heart, Lung and Blood Institute (NHLBI) recommends universal screening for lipid levels in all children at 9 to 11 years of age, and again at 17 to 21 years of age [8•]. This guideline is addressed to distinguish children at risk for cardiovascular events, not specifically to diagnose FH. Universal screening is based on the rationale that childhood hypercholesterolemia is correlated with presence and severity of atherosclerosis and subsequent CVD. Early identification and adequate treatment of those individuals at risk would delay the progression of atherosclerosis and decrease the incidence of cardiovascular events.

However, universal screening has also generated some controversy. Main concerns are about the false positives (children with dyslipidemia that will not develop premature heart diseases) and possibility that those false positives will be treated with statins with insufficient information of the long term effects of this treatment [12, 13].

Most European guidelines advocate the use of case finding, that involves the selective screening of children at high risk for FH. These guidelines are quite similar in that once FH has been diagnosed, or is suspected based on a genetic test or clinical criteria in one parent, screening for FH should be performed in children [14, 15•]. However, several studies have shown that self-reported parental history is not particularly useful when identifying children with elevated LDL-C [16, 17]. Furthermore, most parents of FH children are nowadays adequately treated and therefore, premature CVD in family will eventually vanish.

Most guidelines also propose the use of cascade screening. Cascade screening is a way of classifying people at risk for a genetic condition by a process of systematic family tracing. For example, in the Dutch cascade screening programme, all first degree family members of FH patients with a proven DNA diagnosis are identified and offered a DNA test. Subsequently, cascade screening continues to screen more distant relatives by using the inheritance pattern across the pedigree. Due to cascade screening the age at which FH is diagnosed is reduced, and the percentage of adult FH patients in the Netherlands on lipid lowering treatment has risen from 37.6 % at screening to 92.5 % one year later [18]. Follow up of children, who were diagnosed as having FH by means of the cascade program, merits further attention, since the majority, but not all children were seen by medical providers [19]. Although cascade screening is a cost effective option for detecting FH cases across the population, the main problem in almost every country is the lack of funding support for this program [20, 21].

When to Screen

It was recently shown in a meta-analysis that cholesterol levels discriminate best between children with and without

FH at the ages of 1–9 years [22]. Total cholesterol levels remain quite constant from the age of 2 years up to puberty, were levels tend to decrease concurrently with rapid growth and sexual maturation [22, 23]. Regarding treatment options for children with FH, dietary inventions are not recommended before the age of 2 years old and there are at yet no safety data for children younger than 8 years old on lipid-lowering therapy. Therefore, screening between the age of 2 years and at least before puberty should be advisable.

Universal screening according to NHLBI should be done twice during childhood: first screening performed between 9 and 11 years of age, so before puberty and second screening performed between 17 and 21 years of age, just after puberty, as lipid values normally vary during puberty [8•].

Treatment of Children with FH

Treatment of FH in childhood starts with lifestyle modification, in order to reduce cholesterol levels and other CVD risk factors. Life style interventions including dietary changes, eliminating smoke exposure and increased physical activity. In children with identified hypercholesterolemia a restricted fat and cholesterol diet is mandatory, in which saturated fat intake is limited to ≤7 % of total caloric intake, and cholesterol intake is reduced to <200 mg/day. Few data are available on the effectiveness of these diets in children, but in adults it appears to lower LDL-C levels by 9 to 12 % compared to a western diet [24]. More important, dietary modifications do not interfere with normal growth and development [25, 26].

Additional supplements containing omega 3 fatty acids, plant stanols and sterols, soy proteins and water-soluble fibers might be beneficial. However most studies in children are small and therefore more studies are warranted for general recommendation.

Dietary interventions are rarely sufficient in children with hereditary hypercholesterolemia. If cholesterol levels are not significantly reduced after 6 months of proper lifestyle, pharmacological treatment should be considered. NHLBI guidelines recommend initiation of statin therapy for children from the age of 10 years, if LDL-C is ≥190 mg/dL. However, if LDL-C is persistently ≥190 mg/dL, after 6 months of diet, together with a positive family history of premature CVD, or other additional risk factors, it might be initiated from the age of 8 years on. This is in line with most European guidelines that also advocate initiation of drug therapy from the age of 10 years on.

Statins are currently the preferred pharmacological treatment for children with FH. These drugs inhibit cholesterol synthesis in the hepatic cells and thereby increase LDL receptor expression and thus lower serum cholesterol levels. Several different statins are currently available in childhood and US Food and Drug Administration (FDA) has approval for lovastatin, pravastatin, simvastatin and atorvastatin. Trials of rosuvastatin and pitavastatin are currently conducted and have enrolled children from the age of 6 years on. In adults, statins have been proven effective in reducing both LDL-C levels and the incidence of coronary and other vascular events [27]. Intervention studies in children have shown to be well tolerated and efficacious in decreasing LDL- C, as well as in improving markers of early atherosclerosis, like vascular endothelial function and IMT of the carotid artery. These are however short term studies. Long term studies are needed to establish, whether early initiation of statin therapy in children is justified in order to prevent cardiovascular events.

A second class of drugs used in children to lower cholesterol levels are cholesterol absorption inhibitors. Because they work through a different mechanism of action than statins, they are frequently used in combination with statin therapy to provide additional LDL-C reduction [28, 29]. Ezetimibe, one of the most frequently used cholesterol absorption inhibitors, has been investigated in a small number of studies in children, and appears to be effective in lowering LDL-C, without significant side effects. In children, ezetimibe is mostly used on top of statin therapy. Its role as monotherapy remains to be established on clinical end points, but it comes in particular use in patients who are statin intolerant and in patients with sitosterolemia, a very rare lipid disorder.

In the early days of lipid lowering therapy bile acid sequestrants (BAS) were considered the only suitable drugs for children, because they act in the intestinal lumen and are not systemically absorbed. Treatment of hypercholesterolemia with BAS can lower LDL-C by 10-20 %. Long term adherence and tolerability of the classic BAS is however poor, due to its gastro-intestinal upset and gritty texture. Recently, a novel second-generation BAS, colesevelam, was evaluated in children. Because of its greater affinity for bile salts, it can be used in a lower dosage and is associated with less unpleasant side effects and therefore achieves better adherence to treatment [30]. The only known long term trial shows that early initiation of statin therapy in children with FH might be beneficial in prevention of atherosclerosis later in life and is safe [31].

Altogether, the initial step in treatment of childhood hypercholesterolemia is lifestyle modification. If this fails in sufficiently lowering LDL-C levels, statins are the drugs of first choice. Clinical evidence has indicated the beneficial effect of statins on decreasing LDL-C and early markers of premature atherosclerosis. However, long term follow up studies on safety are lacking.

Conclusion

Everything considered, in the last decades we have gained more insight in FH and have developed several screening

strategies to identify children at risk for premature cardiovascular events, and developed guidelines for initiation of adequate treatment. The main questions that need to be answered are the age at which treatment should be initiated and whether long term statin therapy is indeed justified in order to prevent cardiovascular events later in life. Follow up with early adaptors in statin trials will help us to find the right answers.

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