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Early Prevention of Atherosclerosis: Paediatric Aspects of Familial Hypercholesterolamia

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Abstract

Familial Hypercholesterolaemia (FH) is the most common primitive cause of hypercholesterolaemia, affecting 1: 200-250 individuals and characterized by lifelong elevation of low-density lipoprotein cholesterol (LDL-C) levels which significantly accelerate atherosclerosis. Early detection and treatment of hypercholesterolaemia in childhood can reduce the impact on the cumulative life-burden of LDL cholesterol. In the last ten years, many screening strategies involving the whole family have been carried out: selective screening, cascade screening, inverse screening, and universal screening. Blood lipid profile evaluation (total cholesterol, LDL-C, HDL-C and triglycerides) is the first step. It has to be ideally performed between 2 and 10 years of age. Hypercholesterolaemia has to be confirmed with a second sample and followed by the detection of family history for premature (before 55 y in men and 60 y in women) or subsequent cardio-vascular events and/or hypercholesterolaemia in 1st and 2nd degree relatives. The management of hypercholesterolaemia in childhood primarily involves healthy lifestyle and a prudent low-fat diet, emphasizing the benefits of the Mediterranean diet. Statins are the cornerstone of the drug therapy approved in USA and in Europe for use in children. Ezetimibe or bile acid sequestrants may be required to attain LDL-C goal in some patients. Early identification of children with severe hypercholesterolaemia or with FH is important to prevent atherosclerosis at the earliest stage of development, when maximum benefit can still be obtained via lifestyle adaptations and therapy.

Keywords: Hypercholesterolamia • Atherosclerosis • Paediatric • Prevention • Cholesterol • Cardiovascular • Coronary heart disease

Abbreviation

FH: Familial Hypercholesterolaemia; LDL-C: Low-Density Lipoprotein Cholesterol; HDL-C:High-Density Lipoprotein Cholesterol; CVDs: Cardiovascular diseases; CHD: Coronary Heart Disease; FFQ: Food Frequency Questionnaire; PCSK9: Proprotein Convertase Subtilisin Kexin Type 9; HeFH: Heterozygous Familial Hypercholesterolemia; HoFH: Homozygous Familial Hypercholesterolemia

Introduction

Cardiovascular diseases (CVDs) are still the leading cause of mortality and morbidity worldwide with atherosclerosis being a lifelong process starting from conception and increasing evidence that in utero exposure to maternal high cholesterol impacts on the arterial biology in the fetus [1]. Also autopsy and imaging studies demonstrate that the atherosclerotic process begins in childhood and progresses in direct proportion to plasma LDL cholesterol levels ultimately resulting in myocardial infarction and stroke in adults [2]. In the presence of Familial Hypercholesterolemia (FH), lifelong elevation of LDL cholesterol levels greatly accelerates atherosclerosis and early treatment of children with FH can reduce the impact on the cumulative life-burden of LDL cholesterol [3]. Efforts to prevent atherosclerosis at an early age are therefore justified to inhibit the establishment of cardiovascular risk factors.

Literature Review

Detection and diagnosis

Early detection of children with severe hypercholesterolaemia is an issue of utmost importance in order to identify subjects at high cardiovascular risk [4]. It is increasingly recognized that childhood and early adolescence offer the most favorable time-frame for diagnosing FH as well as introducing and maintaining lifelong treatment and management strategies. To achieve such radical care from a young age, a shift in community and health professional perceptions of FH and its effects is required, as little attention has been given to date for FH screening in general practice and by paediatricians who have the potential to identify most affected patients [5]. FH has to be suspected in children in at least three situations: a child from a family where FH has been identified or suspected (clinical/genetic criteria); a child from a family with a history of premature (before age 55 years in men and 60 years in women) CHD or a child from one or both parents displaying primary hypercholesterolaemia. This emphasizes the importance of assessing the family history regarding cholesterol levels, CHD and confirmed or suspected conditions in all children [3].

As a first screening test, a non-fasting lipid profile can be performed, but LDL-C levels should be measured at least twice over 3 months in a fasting state to confirm the diagnosis [6]; it is advisable to evaluate blood levels of total cholesterol, LDL-C, HDL-C and triglycerides. The optimal window for screening is between 2 and 10 years of age, in order to minimize the effect of pubertal activation and diet. Also, it has to be noted that, before two years of age, lipid values present an important intra and inter-individual variability and dietetic treatment is thus not advisable, as an unnecessary lipid restriction may lead to brain and development delay. Lipid profile evaluation prior to two years of age should be performed only in specific cases, for example if HoFH is suspected, and this decision must be taken by a specialized Lipid Centre. After ten years of age, lipid values might be altered by pubertal activation, therefore this is not an adequate age for screening [7]. Detection of a pathogenic mutation in a child is the gold standard for the diagnosis of FH. Sitosterolaemia, a very rare disorder, may mimic FH in childhood. Secondary causes of hypercholesterolaemia must be excluded [3].

Discussion

Management of hypercholesterolaemia in childhood

Management of children with hypercholesterolaemia can be divided into two intervention levels: First a general evaluation,aimed at detecting children at cardiovascular risk, carried out by family doctors and/or through screening programs, then a specific evaluation of children at high cardiovascular risk and/or with severe hypercholesterolaemia, carried out by specialized Lipid Centres. Collecting a problem-oriented family history, aimed at detecting cardiovascular events, is of utmost importance when approaching a child or adolescent

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with hypercholesterolaemia. A cardiovascular-disease-tailored family history collection is easy to do, easy to reproduce and must be carried out by any health professional dealing with children with hypercholesterolaemia. Cardiovascular events (angina, heart stroke, brain stroke) are considered premature if they occur before 55 years of age in men or before 60 years in women; later on, they cannot be considered as premature. The presence of dyslipidaemia in first and second degree relatives must be evaluated as well [8].

The single biochemical data of hypercholesterolaemia [6] must be confirmed with a second blood sample collected after a twelve-hour night fasting, which may be performed even after a few months. The result must always be analyzed taking into account age, sex and pubertal status of the subject [9]. Secondary causes of hypercholesterolaemia, such as hypothyroidism, kidney disease, liver disease, obesity, nervous anorexia, and/or pharmacological treatments, must be excluded. This first step management of children with hypercholesterolaemia is not expensive and it is an easy tool for family doctors, who can perform these analyses during routine medical controls. Hypercholesterolaemia in a subject with a positive family history for cardiovascular disease and/or hypercholesterolaemia must always be studied with further analysis [8].

Children with hypercholesterolaemia and positive family history for cardiovascular disease and/or positive family history for hypercholesterolaemia evaluated at the first visit in a specialized Lipid Centre, are administered a targeted CHD-oriented questionnaire. Written blood lipid profile of both parents is requested as relatives frequently report pathological lipidaemic values as normal, in this way the lipid profile is evaluated by the doctor of the Centre. Afterwards, blood analysis is performed including total cholesterol, LDL-C, HDL-C, tryglicerides, Apolipoprotein A1, Apolipoprotein B, lipoprotein (a), hepatic and renal function, thyroid markers, total homocystein and genetic analysis for mutations of LDL-R gene and other genes involved in FH phenotype [10].

Dietary habits are evaluated using a Food Frequency Questionnaire (FFQ), then specific and tailored nutritional and dietary advice is given. Six months later, the patient is usually re-evaluated. During this second visit the diagnosis is expressed more in detail and therapy and follow up managements are explained and discussed with the patient and his or her family. At least six months of dietary and lifestyle treatment are needed before starting any possible pharmacological treatment. Drug therapy must not substitute dietary and lifestyle recommendations; on the contrary, these two therapies are complementary [3].

Treatment of hypercholesterolaemia in childhood

Nutritional advice and promotion of a healthy life-style are the milestones and the first-step of the treatment of hypercholesterolaemia in childhood [11]. The aim of the nutritional intervention is to teach the child and his or her family correct nutritional habits that can last until adulthood and thereafter. The intake of saturated fatty acids rich foods has to be limited, as saturated fatty acids account for a possible increase in blood cholesterol levels. A low lipid diet is recommended, including less than 30% of total daily energy from lipids, less than 7% of total daily energy from saturated fatty acids and a daily cholesterol intake lower than 200 mg. An adequate intake of fruit and vegetables, fish and legumes is also recommended. Mediterranean Diet is an ideal model for children with hypercholesterolaemia, as it is based on high weekly intake of fish, legumes, fruits and vegetables, low intake of salt, and the use of olive oil. Steamed and baked preparations are preferred, putting a strong limitation to fried foods (10).

The promotion of an active life-style with adequate amount of physical activity and sport is another milestone of treatment for patients with hypercholesterolaemia. Possible secondary causes of CHD risk, such as cigarette smoke, obesity, diabetes and hypertension should be ruled out.

Bile acid sequestrants, such as cholestyramine, have been the only possible pharmacological treatment for hypercholesterolaemia in childhood for many years. Nowadays, statins are the most commonly used as first line agents. Statin therapy should be initiated with the lowest recommended dose, and then the dose should be up-titrated according to LDL cholesterol levels and patient's therapy tolerance. LDL cholesterol levels ≤ 130 mg/dl from ten years of age or a reduction of 50% of pre-treatment cholesterol levels in children of age between 8 and 10 years are recommended as a target. Reaching this target is not always possible, thus in some cases ezetimibe or bile acid sequestrants may be associated with statin therapy [12].

In current clinical practice, pharmacological therapy for hypercholesterolaemia for paediatric patients must always be well evaluated and discussed with the patient and his or her family. Parents often find it difficult to accept a pharmacological therapy, especially in young children. On the other hand, adolescents might not be interested in their pathology and therefore their compliance to the therapy can be very low [12, 13]. In severe cases, especially in HoFH, LDL-apheresis can be necessary. LDL-apheresis can be started from two years of age and has to be performed in specialized Centres. Lomitapide and mipomersen are two new drugs that have been recently approved for HoFH therapy. Human monoclonal antibodies known as PCSK9 inhibitors (alirocumab, evolocumab and bococizumab) represent a novel group of anti-cholesterol drugs. PCSK9 inhibitors have been proven to lower both LDL and Lp(a) levels [3].

Follow up and transition

Patients' follow up should include paediatric clinical evaluation every other six or twelve months, in order to monitor patient's growth and adherence to nutritional, lifestyle and pharmacological intervention. Statin adverse effects are rare in paediatric age, the more common being myopathies and hepatotoxicity. Therefore, liver (hepatic aminotransferases) and muscle (creatine kinase) enzymes should be measured before starting treatment and then periodically monitored [13]. When using recommended dose, the dose-response effect of statin therapy is not linear: the highest reduction in LDL cholesterol levels occurs at low dosage; afterwards, even when dose is doubled, a maximum reduction of 6%-7% of LDL cholesterol may be obtained [14]. Therefore, the use of high dose of statins in children should be strictly evaluated, taking into account the possible adverse effects caused by a prolonged drug exposure. When targeted levels of LDL are not reached even at high dose of statins and/or on multi drug treatment, therapy adherence and response should be rechecked more carefully. Paediatric patients with non-complicated and well controlled HeFH can be monitored by family doctors after having been diagnosed and screened in a specialized Lipid Centre. On the other hand, paediatric patients with very high LDL cholesterol levels, with multiple CVD risk factors and with adverse effects related to pharmacological therapy and/or with HoFH, should be followed up in a specialized Lipid Centre, with a multi-professional team including paediatricians and cardiologists [15].

Transition from adolescence to adulthood is a very delicate period in terms of therapy compliance. A good and steady nutritional lifestyle education starting from early stages of childhood is thus of utmost importance in order to obtain a long-lasting compliance. Female adolescent patients must also be advised that statins can be teratogenic, therefore a gynecological consultation should be provided and, when necessary, specific contraception should be prescribed. If oral contraceptives are prescribed, lipid levels should be carefully monitored, as oral contraceptives can cause an increase in LDL-C and triglyceride levels and can have a pro-thrombotic action. When planning a pregnancy, statin therapy should be ideally stopped at least three months before conception, and then stopped during pregnancy and lactation [16]. Taking into account the therapy stop due to a possible pregnancy or lactation, statin therapy should not be delayed in female patients. Transition from paediatric to general lipidologist should be started at 16-18 years of age, ideally when puberty is completed. Sometimes this transition can be seen as "childhood end" by parents, who often ask to keep on to be followed up by paediatric lipidologists. On the other hand, when parents with hypercholesterolaemia are followed up in a specialized Lipid Centre, they are more prone to let their children be followed up by a general lipidologist. In this context, a network connecting all professional figures involved in the management and treatment of patients with hypercholesterolaemia is essential [17, 18].

Conclusion

Early detection and treatment of patients at high CHD risk and/or with hypercholesterolaemia is a fundamental milestone in the atherosclerosis prevention pathway. In the last ten years, many screening strategies involving the whole family have been carried out with the aim of identifying and treating these patients. Unfortunately, the knowledge of the epidemiological and clinical importance of atherosclerosis and its implication is still low, especially when dealing with paediatric patients. Paediatricians, general lipidologists, patients' organizations and politicians must strictly collaborate in order to develop a health standard policy for children and adolescents at high CHD risk and for their families.

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