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Short Communication

Familial Hypercholesterolemia - A Hidden Danger

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Familial Hypercholesterolemia (FH) is an inherited defect in the body where it cannot recycle LDL properly. FH is caused by mutations in the genes coding for the Low-Density Lipoprotein Receptor (LDLR), apolipoprotein B (ApoB) or Proprotein Convertase Subtilase/Kexin type 9 (PCSK9). This defect leads to severe elevations in total cholesterol (CH) and low-density lipoprotein cholesterol (LDLc) in the body. FH has a huge impact on molecular biology, clinical medicine and public health.

FH leads to increased risk for premature cardiovascular diseases (CVDs). Almost 34 million people are affected with FH worldwide and out of the total estimated cases almost 90% remain undiagnosed. Diagnosis of FH is generally made only after the irreversible consequences of atherosclerosis have been established in a patient. This generally occurs due to the lack of awareness amongst paediatricians and the general public.

Heterozygous FH (HeFH) is not an uncommon disorder. It has an estimated prevalence of 1 in 500. Homozygous FH (HoFH) is although uncommon and has prevalence of less than one per million in the general population. HoFH is a very serious condition if present affects the individual in first few years of life.

FH has detrimental cardiovascular consequences that start in childhood as early as in the 1st decade of life. Early treatment of FH is very important as it can reverse the atherosclerotic changes in the arterial system. FH was identified by Fagge more than a century ago as a skin ailment, but Norwegian physician Carl Muller recognized its correlation with atherosclerosis in 1939. Asia has the largest numbers of FH patients compared to Africans, Americans or Europeans. There is a major shortfall in the detection and treatment of FH. The affected individuals have a 10- to 20- fold increased risk of developing premature Coronary Artery Disease (CAD).

FH is characterized by elevated serum LDLc levels, which results in excess deposition of cholesterol in tissues resulting in cutaneous and tendinous xanthomas, valvular and supravalvular stenosis, and premature onset of atherosclerosis and cardiovascular disease (CVD).

Patients with HeFH are asymptomatic in childhood and adolescence. They are diagnosed typically by screening methods. HoFH patients are symptomatic and present in the 1st decade of life. These patients are found to have dermatological and ocular manifestations primarily in form of tendon xanthomas and interdigital xanthomas. These patients have severe atherosclerosis which involves multiple vascular beds, including coronary, cerebral, and peripheral vascular system. The premature cause of death in these patients is coronary atherosclerosis. These patients can also develop significant morbidity due to calcific aortic valve stenosis and aortic root disease, including supravalvular aortic stenosis due to cholesterol and inflammatory cell infiltration which may require aortic valve and root replacement.

Whenever FH is suspected, before arriving at the final diagnosis secondary dyslipidaemias due to diabetes, endocrine disorders including hypothyroidism, renal disorders, obesity and offending drugs must be ruled out.

Individuals with FH are diagnosed based upon the elevated levels of total-, LDL-, and non-HDL-cholesterol above the 95th centile recommended for the age and sex of the patient along with a positive family history or identification of genetic mutation by genetic testing.

There are different criteria for diagnosis of FH which includes Make Early Diagnosis to Prevent Early Deaths (MEDPED) criteria from the United States, the Dutch Lipid Network Clinic (DLNC) criteria and the British Simon Broome Registry (BSBR) criteria.

The MEDPED criteria is based solely on the age and the blood lipid levels of the patient. The DLNC and BSBR criteria require family history and clinical findings as well.

Cascade screening of the family members of the index FH patient using lipid profile is most effective way of preventing premature CAD in the population. EARLY diagnosis of FH is most important to prevent its consequences.

A late (or no) diagnosis and inadequate treatment of FH leads to uncontrolled lipid levels in an individual causing premature atherosclerosis and CVD which contributes to the pandemic of metabolic and cardiovascular diseases.

Many studies have been done in asymptomatic HeFH patients in the past. The Cardiac CT and MRI in these patients revealed greater coronary calcium score, greater prevalence, extension and severity of subclinical CAD, significantly higher number of plaques, stenosis and segments with plaques. Atherosclerotic plaques in descending aorta were also significantly higher in FH cases.

The diagnosis of FH in children is made if an LDLc level ≥ 190 mg/dL on two successive occasions after 3 months diet indicates a high probability of FH. A family history of premature CAD in close relative(s) and/or baseline high cholesterol in one parent, together with an LDLc ≥ 160 mg/dL indicates a high probability of FH. If the parent has a genetic diagnosis, an LDLc ≥ 130 mg/dL suggests FH in the child. If a parent died from CAD, a child even with moderate hypercholesterolemia should be tested genetically for FH and inherited elevation in Lp(a).

Children affected with HoFH are at risk for early coronary events, and sudden death or heart attacks, which may occur as early as 1-2 years of age. A majority of patients affected with HoFH die before the age of 30. Initiating treatment, as early as possible, can significantly prolong an affected person's lifespan.

Recommendation for general target lipid levels vary in paediatric and adolescent patients. The recommendation is to have a target LDL level of < 130 mg/dl or > 50% reduction from baseline values.

Lipid association of India has guidelines for FH patients where an LDLc goal < 50 mg/dL in all patients in secondary prevention or very high-risk primary prevention but an optional goal ≤ 30 mg/dL in category A extreme-risk patients (e.g. CAD + FH) and a recommended goal ≤ 30 mg/dL in category B extreme-risk patients [CAD + (1) diabetes and polyvascular disease/≥ 3 major ASCVD risk factors/end organ damage, or (2) recurrent ACS within 12 months despite LDLc < 50 mg/dL, or (3) homozygous familial hypercholesterolemia].

A long-term cohort study revealed that if statins are initiated at a very early stage in such individuals, they do not have a risk of myocardial infarction that is significantly different from that of the general population.

Benefits of statins in FH includes: improved blood circulation, reduced red cell aggregation, whole blood viscosity, plasma viscosity, platelet aggregation. Significant lowering of LDLc with a statin can favorably affect kidney function and lowers microalbuminuria as a measure of endothelial function.

An effective statin treatment causes 32% reduction in total serum cholesterol (CH), 41% reduction in low density lipoprotein (LDL) CH, 16% reduction in triglycerides, 21% increase in high density lipoprotein CH. A statin improves myocardial and peripheral blood flow (PBF) in FH subjects even without the evidence of Coronary Atherosclerosis. PBF and MBF reserve were normalized after atorvastatin (ATV) treatment. In patients with HeFH, moderate- to high-intensity statin therapy lowered the risk for CAD and mortality by 44%. Rosuvastatin (RV) and ATV are 2 high-potency statins widely used in FH.

Early identification of children with FH ensures that adherence with lifestyle intervention is already established before puberty. Children with HeFH should be treated with a fat-modified, heart-healthy diet at diagnosis, and statins should be initiated as early as at the age of 8 - 10 years in them. In HoFH, pharmacologic treatment should start at diagnosis. Early initiation of lifestyle measures is essential for ensuring long-term adherence. Children diagnosed with FH should have lipoprotein(a) measured for risk stratification. For children aged 8 - 10 years, the Panel recommends that LDLc is ideally reduced by 50% from pre-treatment levels. For children aged ≥ 10 years, especially if there are additional cardiovascular risk factors, including elevated Lp(a), the target LDLc should be < 130 mg/dL. The benefits of LDLc reduction should be balanced against the long-term risk of treatment side effects.

Burden of LDLc is significantly reduced with early treatment of FH as statins also improve endothelial function, substantially attenuate the progression of atherosclerosis and improve coronary outcomes. The CHD free survival was 100% in the group of young adults who initiated statin therapy in childhood and 93% in the affected parents. Treatment with statins is an effective lipid-lowering therapy in children with FH. Few or no safety issues were identified in such patients with treatment. Treatment with statins seems to be safe in the short term, but long-term safety is yet to be established.

Children treated with statins should be carefully monitored and followed up by their pediatricians and their care transferred to an adult lipidologist once they reach 18 years of age. Large long-term randomized controlled trials are needed to establish the long-term safety issue of statins.

The advances and the future in FH lie with Microsomal triglyceride transfer protein inhibitors (lomitapide), Apo B synthesis inhibitors (mipomersen), PCSK9 inhibitors (PCSK9i) (alirocumab, evolocumab). Results from Phase 2 and Phase 3 trials for PCSK9i, in particular, hold hope for better results in FH care.

FH is a very serious condition. Early commencement of a therapy to reduce lipid levels and lifestyle modification may improve clinical outcomes in such individuals. FH starts in early childhood resulting in serious morbidities in later life. The need for a screening strategy to detect FH at an early age is recommended but there is no consensus regarding whom and when to screen. Most of FH cases are managed with a combination of statins and cholesterol absorption inhibitors but some will require more invasive therapies such as LDL apheresis. Even after having so many treatment options, a large majority of children fail to achieve target lipid levels due to improper diagnosis, inadequate monitoring and treatment. There is a need for a screening strategy that is effective along with initiation of established therapies at the right time. Only after this there will be reduction in burden of atherosclerosis in FH which is such a challenging condition and a hidden danger.