Review Article

Familial Hypercholesterolemia (FH) — Importance of General Awareness and Early Diagnosis

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Familial Hypercholesterolemia (FH) is an autosomal dominant disease characterized by severely elevated serum low-density lipoprotein cholesterol (LDL-C) leading to premature atherosclerotic cardiovascular disease (CVD). The homozygotes develop CVD in their teens. The contribution of FH to premature cardiovascular disease in India is unknown. The heterozygous (HeFH) phenotype is encountered most often (1 in 250-500) whilst the rarely encountered homozygous (HoFH) pheno-type has a worse prognosis (1 in million). Considering the Indian population of 1.32billion, approx-imately 2.6 million cases of HeFH and 2500 cases of HoFH are estimated to be present.

The diagnosis of FH is based on biochemical values of total cholesterol & LDL-C, clinical findings of lipid stigmata, family history, and genetic testing. Early diagnosis is important for the prognosis of the patient and it also has implications for the family members who may have inherited the same disorder. A child or adult with FH requires life long medications under medical supervision. Keeping in mind the lack of awareness of FH amongst the medical fraternity and the general population, creating a registry may be an eye-opener to the incidence and prevalence of this entity in the Indian Society. LAI has taken an initiative to offer genetic studies to cases registered with LAI FH Registry at concessional rates.

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One baby is born with familial hypercholesterolemia every minute. FH is underdiagnosed and undertreated globally. Over 90% of FH patients were characterized by the presence of cardiovascular disease at the time of death. Three out of four FH patients had experienced one or more myocardial infarctions prior to death. Classical risk factors were more prevalent in FH patients who died at a younger age.

What is FH ?

Familial hypercholesterolemia (FH) is an inherited condition leading to severely elevated serum low density lipoprotein cholesterol (LDL-C) that leads to premature atherosclerotic cardiovascular disease (ASCVD) and accounts for 2–3% of the cases of myocardial infarction in patients aged <60 years[1].

What is the Cause of FH ?

It is caused by mutations in the genes of the LDL-R (LDL receptor), Apo B (Apolipoprotein B) or PCSK-9 (Proprotein convertase subtilisin/kexin type 9) that interfere with clearance of LDL-C by the liver[2]. Elevated circulating markers of vascular inflammation and endothelial dysfunction are present in children with FH, reflecting early atherogenesis.

Editor's Comment :

- **FH is a highly atherogenic disorder increases risk of CHD by 10-20-fold.**
- **LAI recommendations will help in early diagnosis of FH.**
- **Early diagnosis and aggressive LDL-lowering treatment will prevent premature CHD and patients with FH can potentially live a full life.**
- **There is a need to increase awareness among doctors and public.**

What are the Types of FH and How Common are they ?

Clinically, the heterozygous (HeFH) phenotype is encountered most often (1 in 250-500) whilst the rarely encountered homozygous (HoFH) phenotype has much worse sequelae (1 in million)[3].

Considering the Indian population of 1.32 billion and the ratio of HeFH of 1 in 500 there will be approximately 2.6 million population of HeFH and 2500 cases of HoFh if the prevalence of 1 in one million is considered. Most of these patients are undiagnosed and are responsible for premature coronary artery disease in India.

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What are the Characteristics of Heterozygotes (HeFH) and Homozygotes (HoFH) ?

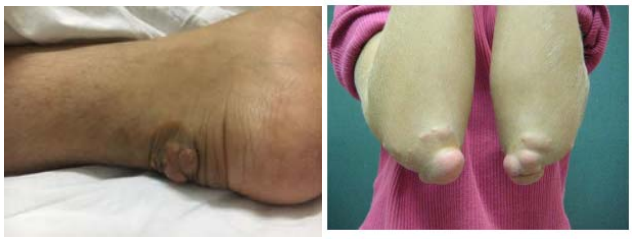
HeFH is seen when an individual inherits one mutant gene and is characterized by a 3–4-fold higher LDL-C concentration. Lipid stigmata including corneal arcus and tendon xanthomata can be seen and patients develop premature cardiovascular disease in their 4th decade, although women may develop these later. Untreated HeFH cases experience fatal or nonfatal coronary events in their 40s and 50s but can be readily treated with cholesterol-lowering medication in addition to lifestyle modifications[6]. In addition to statins, agents like bile acid sequestrants and cholesterol absorption inhibitors (eg, ezetimibe) may be required. In contrast, patients with HoFH inherit the defective genes from both the parents, have 4–8-fold higher LDL-C concentration as compared to the general population and they develop cutaneous stigmata and atherosclerotic cardiovascular disease in their teens[4]. LDL values in HeFH cases are generally between 350–550 mg/dl, whereas in HoFH, this value is between 650–1000 mg/dl. Ten-don Xanthomas are pathognomonic of FH, especially HoFH[5]. Accelerated atherosclerosis of the coronary, carotid, and lower limb arteries leading to cardiovascular diseases, recurrent transient ischemic attacks, strokes, intermittent claudication or gangrene is commonly seen at a younger age. Severe coronary artery disease requiring percutaneous interventions or coronary bypass sur-gery is common and the disease has high mortality in the second decade of life.

How do you Diagnose FH ?

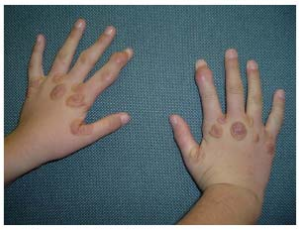
Lipid Association of India (LAI) recommends the Simon Broome criteria for the diagnosis of FH be-cause of ease of applying and diagnosing cases based on the criteria. The Simon Broome Criteria takes into consideration total cholesterol and LDL-C concentrations, presence of tendon xantho-mata, presence of the family history of premature vascular disease and the total cholesterol & LDL-cholesterol concentration in the family members[7].

Typical Physical Findings (Stigmata) of FH :

The clinical diagnosis of homozygous familial hypercholesterolemia is typically based on the pres-ence of cutaneous xanthomas before 10 years of age and an untreated low-density lipoprotein cholesterol >500 mg/dL. Interdigital xanthomas, particularly between the thumb and index finger, are pathognomonic for homozygous familial hypercholesterolemia.



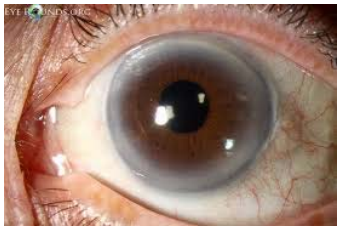
Tendon xanthoma over ankle and elbows



Interdigital Xanthoma.

Xanthelasmas

What is the Significance of Family History ?



Corneal Arcus

The family history of premature ischemic heart disease helps to identify an autosomal dominant mode of inheritance. If both parents have very high LDL-C (>190 mg/dL) and/or history of heart disease before age 55-65, this may suggest that they both have FH and can each pass a mutated gene to their children. When each parent has HeFH, by chance, 1 of 4 children will have a normal cholesterol level, 2 of 4 children will have HeFH and 1 of 4 children will have HoFH. LAI recom-mends Simon Broome criteria for the diagnosis of FH.

Simon Broome diagnostic criteria for Familial Hypercholesterolemia[8] :

Definite FH if the following are present —

• Total cholesterol > 260 mg/dL or LDL-C > 155 mg/dL in a child less than 16 years or total choles-terol > 300 mg/dL and LDL-C > 190 mg/dL in an adult with tendon xanthomas or evidence of these signs in a first- or second-degree relative

OR

• DNA-based evidence of an LDLR mutation, familial defective Apo B-100 or a PCSK9 mutation.

Possible FH if the following are present —

• Cholesterol concentrations defined as above and at least one of the following-

• Family history of MI in a first-degree relative younger than 60 years or a second-degree relative younger than 50 years, or

• Family history of raised total cholesterol >300 mg/dL in an adult first- or second-degree relative or >260 mg/dL in a child, brother or sister aged younger than 16 years.

The Dutch criteria use a point system for LDL-C concentration, presence of xanthomata and pres-ence of CVD and a total score of over 8 is considered as definite FH and 6–8 as probable FH[9]. The US Make Early Diagnosis to Prevent Early Deaths (MEDPED) criteria uses age and relative-specific LDL-C concentration for diagnosing FH[10].

What is Cascade Testing ?

It involves performing the lipid profiles on the relatives of the "Index" patient. It helps in the identification of new cases and also in the institution of early therapy[11]. The index patient is diagnosed either clinically through history, physical examination, and a lipid profile or by molecular diagnosis. Subsequently, the cascade testing of the family can be carried out similarly using lipid profiles followed by molecular testing in those meeting the criteria for FH. Training health professionals in the construction of the genetic tree is an important aspect of cascade testing[11].

What is the Significance of Molecular Diagnosis ?

A diagnosis of FH can be confirmed by genetic testing. However, it should be understood by health care providers that failure to detect a mutation does not exclude a diagnosis of FH and interven-tion with lipid-lowering therapy is required even if the diagnosis is clinical. Remember to "Treat the Phenotype and Counsel the Genotype"[12]. Financial restrictions due to the additional expense of genetic testing to family's needs to be kept in mind.

What is the Management of FH ?

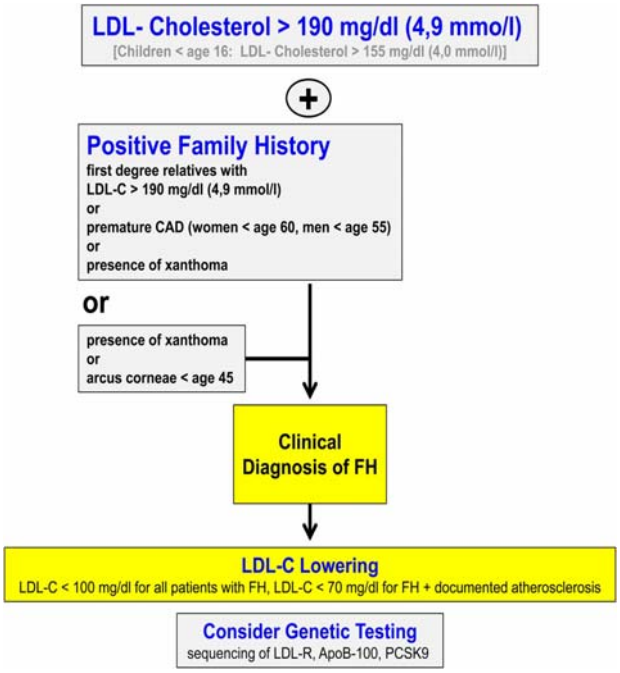
Lifestyle issues such as physical activities, dietary modifications, smoking cessation, alcohol restriction and stress management should be addressed and other ASCVD risk factors should be meticulously looked for and treated.

Statins at high doses is the mainstay of therapy. Other drugs like Ezetimibe may need to be added[4]. Bile acid resins are now available in India. Both mipomersen and lomitapide have the potential for use in HoFH[13]. Apheresis, a standard therapy in other countries is not easily available in India. PCSK-9 inhibitors lower LDL-C levels by up to 60% in patients already on statins and have been recommended in heterozygotes. Evolocumab (Repatha) is presently available in India though cost remains a constraint[14].

What are the Implications of Early Diagnosis ?

The diagnosis of FH is important not only for the prognosis of the patient but also has implications for the family members who may have inherited the same disorder. The contribution of FH to premature CVD in Indians is unknown, mainly due to the lack of awareness of this condition among both health care providers and the general population.

Simplified Algorithm to Detect and Treat Individuals with high LDL-associated Genetic Risk



Ulrich Laufs, and Klaus G — Parhofer Eur Heart J 2015; ***36:*** *3004-3006*

Homozygous FH is a serious medical condition and is life-threatening if not treated at a young age, preferably beginning in early childhood. A child or adult with HoFH needs life-long medications and other specialized treatments to lower the LDL-C and prevent heart attacks. This requires the expertise of a lipid specialist.

What is the need for the Maintenance of a Registry ?

Keeping in mind the lack of awareness of the seriousness of FH amongst the medical fraternity and the general population, creating a registry may be an eye-opener to the incidence and prevalence of this entity in the Indian Society. We need to remember that FH contributes to premature coronary events. Timely intervention may help to reduce the existing and ever-expanding trend of cardiovascular disease amongst Indians.

LAI has taken the initiative to offer genetic studies to cases registered with LAI FH Registry at INR 5200 (Courier

charges extra).

The year 2020 will be dedicated to the FH awareness India campaign by the Lipid Association of India.

For further information or to join FH registry log on to lipid .net. in / call on 9871071919 or email at lipidaoi@gmail.com

LAI Recommendations :

- Lipid profile estimation of children to be done at 2 years of age in those with a family history of FH and premature ASCVD.
- Universal screening of lipids to be carried out at age 20 years or at the time of college ad-mission.
- LAI recommends the Simon Broome criteria for the diagnosis of FH.
- In an established case of FH, LAI recommends the estimation of Lp(a) levels.
- Genetic testing and cascade screening should be performed wherever feasible.
- Look for other ASCVD risk factors and manage them appropriately.
- Strict dietary recommendations and lifestyle modifications as advised.
- Drug therapy to be started at age 8 years or earlier in individualized cases.
- LDL-C targets to be achieved :<70 mg/dL for HoFH and <100 mg/dL for HeFH in children and in adults <50 mg/dL in HoFH and 70 mg/dL in HeFH or at least 50% reduction in LDL-C from the baseline.

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