Familial Hypercholesterolemia: Nip the Evil in the Bud

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Received: 14 March 2018 / Accepted: 14 March 2018 / Published online: 29 March 2018
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Familial Hypercholesterolemia (FH) is an autosomal dominant monogenic disorder characterised by lifetime elevation in plasma concentration of low density lipoprotein (LDL) cholesterol levels owing to impaired hepatic clearance of LDL cholesterol particles and the family history of dyslipidemia and cardiovascular disease (CVD). Various external manifestations including tendinous xanthoma, xanthelasma and corneal arcus result from deposition of low density lipoprotein-cholesterol (LDL-C) in tissues, whereas deposition in the blood vessels leads to the most dreaded complication of premature CVD.

Despite having life threatening implications and the availability of a simple biomarker (LDL-cholesterol), majority of people with FH remain underdiagnosed and hence, untreated [1, 2]. Recent work shows a prevalence of FH to be 1 in 250 against the previous estimates of 1 in 500, emphasizing the significant role of increased use of genetic testing for the diagnosis of FH [1]. Early identification and aggressive treatment of people with FH can minimize the significant burden of premature CVD, imposed by FH. FH satisfies World Health Organisation (WHO) guidelines for screening as it is a public health problem, has an appropriate treatment available and also the diagnosis can be made in the latent phase of the disease.

The diagnosis of FH can be made based on clinical criteria or genetic testing. Among the several clinical criteria proposed for the diagnosis of FH, the three most commonly employed are Simons Broome, Dutch Lipid Clinic Network (DLCN) and the Make Early Diagnosis to Prevent Early Disease (MEDPED) criteria. They are based on LDL-C levels, physical findings and family history.

The condition arises from genetic defects mainly in the LDL receptor; less commonly in apoprotein B, and rarely in Proprotein convertase subtilisin/kexin type 9 (*PCSK9*) genes.

About 15% of FH cases are either polygenic or are caused by other rarer monogenic mutations [2]. About 20% of FH cases can be missed by screening for the three most common genes mutations, and use of the NGS methodologies may improve the detection rate of the mutations causing FH [3].

Cascade genetic screening helps in early identification of asymptomatic carrier relatives of an affected individual and helps in timely initiation of vigilant screening for them. It will diagnose a large proportion of asymptomatic patients who will manifest signs in late adulthood, patients with milder phenotype and also the ones with equivocal diagnosis due to overlapping LDL values; all of which may be missed if we solely rely on clinical screening. Moreover, genetic diagnosis helps us better understand the genotype- phenotype correlations that can be used to modulate treatment and also has prognostic significance [4].

In the article by Setia et al. [5] in this issue of the journal, the authors have described the effectiveness of cascade screening for FH case identification, owing to the autosomal dominant inheritance of the disease. It involves screening every first degree relative of a proband with FH, and repeating the cycle iterative for each newly diagnosed individual. This study is important as it emphasizes that early diagnosis of FH allows prompt treatment and minimizes the associated complications. The authors have applied the Modified Dutch Lipid Clinic Network criteria for screening of probands and conducted cascade screening by mutation studies in 133 members of 33 probands recruited. About 66% were found to have the mutation positive and hence confirming their FH status. Also, this proved to be a strategy for primary prevention as 46 new cases were detected who were previously asymptomatic and subsequently started on lipid lowering agents. This subsequent benefit of treatment of those identified with FH has been shown to be highly cost-effective [6]. Health care systems utilizing cascade screening for the identification of patients with FH based on index case identification of middle-aged adults have shown promising results and cost-effectiveness [7].

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Selective screening of children when there is parental affection with hypercholesterolemia or family history of premature CVD carries unacceptably low yield. In contrast, universal screening at 9–11 y of age will detect 96% of FH children [8]. Implementation of lifestyle interventions alone rarely achieves the target treatment goals in children with FH. The efficacy and safety of pharmacological agents mainly statins have already been established [9] and they remain the cornerstones of FH treatment. In majority of FH heterozygotes, satisfactory control can be obtained with statin monotherapy or combination pharmacotherapy including statin and ezetimibe. Various studies have proved lipoprotein apheresis as an important adjunctive treatment in FH management and currently it is the treatment of choice for FH homozygotes [10, 11]. Although the long term efficacy and safety of novel lipid lowering agents including microsomal triglyceride transfer protein (MTP) inhibitors, antisense oligonucleotide to apolipoprotein B and monoclonal antibodies to PCSK9 need to be established, the initial trial reports are promising [12, 13].

To summarize, it is imperative to increase the awareness of FH at both the clinical and community levels. With the advent of improved diagnostics and therapeutics, early recognition and care of FH from childhood is critical to combat the increased morbidity and mortality in children and adolescents with this common inherited disorder.

Compliance with Ethical Standards

Conflict of Interest None.

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