The Lipo- Phenotypic Screening Tool for Familial Hypercholesterolaemia

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Abstract

Familial hypercholesterolaemia (FH) is a common disorder of lipid metabolism. However, it is rarely diagnosed in time, leading to a high burden of preventable cardiovascular (CV) morbidity. The authors describe a lipo-phenotypic screening tool, which can be used by clinicians to screen for FH. This simple construct is based on history, physical examination, lipid profile and non-invasive cardio-imaging. Structured as a bidirectional three column rubric, this tool should be able to improve clinical skills and teaching related to FH.

Keywords: ASCVD, coronary artery diseases, dyslipidemia, LDL cholesterol, stroke

Introduction

FH is an autosomal dominant inherited condition that leads to premature cardio vascular disease (CVD).[1] One out of 250 individuals is thought to have heterozygous familial hypercholesterolaemia (HEFH) worldwide. This prevalence is higher in some populations such as French Canadians, Ashkenazi Jews, Lebanese and Afrikaners, where FH may occur as frequently as 1 in 67 people. Roughly 1 in 160,000 to 1 in 1000,000 persons has homozygous familial hypercholesterolaemia (Ho FH).[2] There are no national estimates of FH prevalence in India. However, a conservative estimate (1:1000) suggests that 1.3 million Indians live with HeFH. The rising trend of premature CVD in young adults with no other obvious CVD risk factors adds credence to the seriousness of this problem.[3]

One of the reasons for the low detection rate of FH is the lack of awareness amongst general physicians. This lack of awareness, and interest, seems to be pervasive across various medical super specialties.[4] Validated screening tools for FH do exist,[5-9] and have proven their utility in improving the diagnosis of FH. It is assumed (erroneously) that FH can be screened and diagnosed only by genetic markers, and not by simpler methods. While the Make early diagnosis prevent early death criteria are based upon a positive family history, the Dutch Lipid clinic network criteria are weighted towards genetic markers and extremely high LDL levels, with higher scores for these abnormalities. The Simon Broome criteria and Japanese criteria include history, examination, and lipid abnormalities. However, all available screening and diagnostic tools assume a high level of clinical skills among users, and do not prescribe basic exclusion criteria for the diagnosis of FH. The criteria also have scoring systems with which all clinicians may not be comfortable.

Screening

Based upon WHO criteria, FH meets criteria of a disease which deserves to be screened. According to recent guidelines, a screening programme should target a recognized need, and have well defined objectives and target population.[10] Scientifically proven effective measures should be used with quality control and evaluation systems, in -built in the strategy. Apart from 'testing', education and clinical services must be integrated in the programme.

Apart from the above principles of screening, the tool used for screening should meet certain requirements. Every screening technology should ensure informed choice, confidentiality, respect for autonomy and equitable access. A screening tool should be based on clinical features (history, physical examination), and easily available laboratory tests (lipid profile). It should be economical and easy to use. Screening should be such that

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Figure: Lipophenotypic Screening Tool for Familial Hypercholesterolaemia.

Exclusion Criteria		
Diabetes	Hypothyroidism	Renal/Hepatic Disease
History/Examination		
Patient History	Family History	Examination
Premature ASCVD* (Age <45 yrs)	ASCVD first degree relative <60 yrs ASCVD second degree relative <50 yrs	Tendinous Xanthoma in patient/first Degree relative
Poor response to high intensity statin therapy**	Poor response to high intensity statin therapy**	Arcus Senilus at <45 yrs in patient/first/second Degree relative
Lipidogram		
Total Cholesterol>290 mg/dl [7.5mmol/L] [>260 mg/dl in children <16 yrs]	LDL-C>190 mg/dl [4.9mmol/l] [>155 mg/dl in children <16 yrs]	Normal Triglycerides
Cardiac Imaging		
Ankle Brachial Index<0.9 at <45 yrs of age	Abnormal CT coronary angiography [CTA]<45 yr age	Non rheumatic/Non congenital supravalvular calcification on CTA/Echo
Genetic		
LDLR gene (low density lipoprotein receptor)	APOB gene (apoprotein B)	PCSK9 gene (proprotein convertase subtilisin kexin) LDL Receptor Associated Protein 1 gene

*Atherosclerotic Cardiovascular Disease[Include: Coronary/Stroke/Peripheral Artery Disease];
**Defined as <50% LDL reduction with 40mg of rosuvastatin- or 80 mg of atorvastatin.

confirmatory tests are able to offer high yield of diagnosis across ethnic groups. The screening tool should be such that it can be validated in observational trials.

Screening for FH

Various criteria are available to facilitate screening and diagnosis of FH.[5,9] However, none of these are used in routine clinical practice in South Asia. There is scope for a new screening model, which serves as an aid to clinical decision making, as well as a pedagogic tool. The lipo - phenotypic screening tool that we propose (Figure) follows a vertical framework, which reflects the hierarchy taught in clinical medicine. A medical and family history, as well as physical examination, precede biochemical investigations, which in turn are followed by imaging and genetic tests. However, initial suspicion can occur at any level of the screening framework, which is why a bidirectional flow chart is suggested.

The three column design, and the 3x3 clinical assessment framework enhances simplicity and increases appeal. The lipo-phenotypic character is reflected in the inclusion of lipid profile as a screening investigation. The word 'lipo-phenotype' implies an analysis of all lipid parameters and their abnormalities. It suggests an assessment of all lipid values, in conjunction with the phenotypic makeup of the affected individual (i.e., markers of hyperlipidaemia such as xanthomas, and arcus senilis). The use of this adjective fosters a better understanding of lipid metabolism amongst students and physicians as well.

Our rubric is unique as it includes poor response to high intensity statin therapy, and abnormal cardiovascular imaging (ankle brachial index, coronary angiography and supravalvular calcification) in the list of markers which should prompt a high index of suspicion for FH. Thus, it encourages good history taking, monitoring of drug therapy, and rational investigations, in the work-up of refractory dyslipidaemia. The differences and similarities between earlier criteria and the proposed lipo-phenotypic criteria are detailed in Table .

Pedagogic construct

The lipo phenotypic tool can be used in all medical settings, irrespective of resource limitations. This bidirectional tool is structured in a three column rubric, allowing for ease of understanding and reading. It pays equal emphasis to history, family history and general examination, and follow the basic tenets of good clinical medicine.[11] The chart also lists common differential diagnoses of dyslipidaemia, and reminds the reader to exclude them before labeling FH. Thus, it respects the philosophy of quaternary prevention,[12,13] which enjoins us to avoid over- investigation and over-diagnosis.

Table: Comparison between various screening criteria for familial hypercholesterolaemia (FH).

Criteria	Simon Broome	Dutch Lipid Clinic Network	MED PED	Japan	Lipo- phenotypic tool(India)
History					
Personal history	No	Yes	No	Yes	Yes
Drug history	No	No	No	No	Yes
Family history	Yes -high cholesterol, MI, tendon xanthomas	Yes-high LDL, premature CVD	Yes -FH	No	Yes
Examination					
Xanthomas	Yes	Yes	No	Yes	Yes
Arcus senilis	No	Yes	No	Yes	Yes
Lipid profile					
Total cholesterol	Yes	No	Yes	Yes	Yes
LDL cholesterol	Yes	Yes	No		Yes
Cardiac imaging	No	No	No	No	Yes
Exclusion criteria	No	No	No	No	Yes
Genetic markers	Yes	Yes	No	Yes	Yes
Scoring	Stratification as definite, probable	Yes	None	Major/ Minor items	None

CVD= cardiovascular disease, LDL=low density lipoprotein, MI=myocardial infarction

Any abnormality, identified on history, family history, drug response history, examination, lipid profile or cardiac imaging, should prompt a high index of suspicion for both HoHF and HEHF. Though three exclusion criteria (common causes of secondary dyslipidaemia) are listed, this does not mean that HF cannot coexist with diabetes, hypothyroidism or renal/hepatic illness.

Universal appeal

The biggest strength of the lipo-phenotypic screening tool is its universal applicability. The construct appeals to cardiologists, endocrinologists, nephrologists and neurologists on one hand, and general physicians on the other. It satisfies the needs of 'purists', by including genetic testing, and retains its pragmatism, by focusing on readily available clinical, as well as biochemical assessment. Thus, it should live up to its aim of improving the diagnosis, and thereby the management, of FH.

Limitations

Research is required to validate this tool, and to assess lipo-phenotypic patterns encountered in various clinical situations. Interesting questions would include how patients with FH are picked up, what phenotypic and lipotypic abnormalities predominate, and whether the natural history of the condition differs among various ethnicities. This may help us determine whether our policy of using ethno-specific cut offs for the diagnosis of "prematurity" of CVD is appropriate or not.

Summary

This simple clinical model works as a teaching tool and as an aid to clinical decision making. It creates a high index of suspicion in persons with history, physical findings or lab anomalies suggestive of FH. Thus, it may help improve the detection rate of FH in communities across the world.

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