Original Research Article

Indian prevalence of familial hypercholesterolemia demystified by applying Dutch lipid clinic network criteria

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ABSTRACT

Background: Dyslipidemia is a growing problem in India, with familial hypercholesterolemia (FH) being an under diagnosed and under treated cause of the same. FH is a common genetic disorder associated with high LDL cholesterol, leading to premature CAD and peripheral vascular diseases. The prevalence of FH is 1 in 250 individuals. True global prevalence of FH is underestimated. The prevalence of FH in Indian population is still unknown.
Methods: A total 4000 patients who had tested their lipid profile at Max hospital, between Aug 2017-Aug 2019 were screened. Out of these we found 530 patients with LDL cholesterol ≥155 mg/dl. Amongst these, 90 patients consented for clinic visit and examination, and thus enrolled and assessed for FH using the Dutch lipid clinic network (DLCN) criteria. Based on scores, patients were diagnosed as definite, probable, possible, or no FH. Other risk factors known to cause dyslipidemia such as smoking, diabetes mellitus and hypertension were excluded.
Results: In a general population of 4000 patients, 4 individuals were detected with definite FH, showing a prevalence of 1 in 1000 (0.1%). Out of the enrolled 90 patients with high LDL cholesterol, 4 (4.44%) were diagnosed as definite, 14 (15.56%) as probable, 33 (36.67%) as possible, and 39 (43.33%) as unlikely FH.
Conclusions: Prevalence of FH appears to be much higher among Indians with high LDL cholesterol. Therefore, it should not be ignored in individuals with high LDL cholesterol. To detect patients with FH, routine screening with simple DLCN criteria may be effectively used.

Keywords: FH, High LDL cholesterol, Premature coronary artery disease, DLCN criteria, Arcus cornelis, Tendon xanthoma

INTRODUCTION

Familial hypercholesterolemia (FH) is an autosomal dominant disorder, characterized by very high levels of LDL cholesterol, tendon xanthoma (TX) and increased risk of premature cardiovascular diseases (CVD).[1] The lack of clinical suspicion of FH makes it a major under-diagnosed and under-treated problem. FH is one of the most common inherited condition, with a prevalence of 1 in 200-250 individuals in the general population and one baby being born with FH globally every minute.[2,3] Majority of heterozygous FH (HeFH) patients are detected only after an acute event.

FH is primarily caused by mutation in one of the three genes, i.e., LDL receptor gene, apolipoprotein B (apo-B) gene and gain-of-function mutations of the proprotein convertase subtilisinkexin 9 (PCSK9) gene. Out of these 3 mutations, LDL-R mutation is most common (85-90%), followed by apo-B (1-12%) and PCSK9 (2-4%).[4-8] Each of these three mutations impairs LDL receptor mediated catabolism of LDL-C.[9,10] Eighty percent (80%) patients with definite FH may have mutations in one of these genes, whereas this mutation would be found in only 20-30% people with possible FH.

Homozygous FH is a rare life-threatening disease characterized by markedly elevated LDL-C

levels and accelerated premature atherosclerotic CVD.[2] These individuals may have CV events as early as in the first decade of life. Historically, untreated HeFH begins to manifest its clinical consequences in the fourth decade of life in men and fifth decade in women. Patients with HoFH, however, may suffer significant cardiovascular (CV) events as early as in the first decade of life.

Prevalence of HeFH by WHO is estimated to be 1:250, whereas that of HoFH is 1:1,000,000. However, recent studies suggest the prevalence is vastly underestimated.[11] Information about prevalence of FH in India is very limited. Most of our current knowledge on FH stems from studies conducted in the West. Recent study conducted in India using DLCN criteria by Sawhney et al showed high prevalence of FH in patients with preexisting coronary artery disease.[12]

Therefore, there is a tremendous need for further research, to determine the true prevalence of FH in India. The aim of this study was to identify the prevalence of FH in individuals with high LDL-C using the DLCN criteria, which is a simple, practical, clinical tool approved by several international authorities. But unfortunately, due to lack of awareness, it is not used appropriately.

METHODS

This study was approved by the institutional ethics committee of Max hospital, Saket, New Delhi. We screened 4000 patients attending the outpatient or inpatient departments of our hospital, who had their lipid profile tested over the period of 2 years from August 2017 to Aug 2019. The data was extracted using the computerized patient record system (CPRS), the electronic data base used within the hospital. We found 530 patients out of the screened 4000, with LDL-C ≥155 mg/dl. Out of these we enrolled 90 patients, with age more than 18 years but <55

years for men and <60 years for women. We excluded all non-Indian patients and those who did not consent. Informed written consent was obtained from all these 90 patients. They were called for clinic visits for a detailed physical examination to look for cutaneous manifestations of FH i.e., TX and corneal arcus (CA). Detailed history, including family history (clinical history of the first degree relative) was obtained from the participant during clinic visits. Information regarding previous history of CAD, MI, cerebral and PVDs were established on the basis of data from the participants previous medical documents, provided during the visit. For CAD, patient's medical records and the data confirming the diagnosis i.e., a positive stress test, significant stenosis in coronary angiography, prior myocardial infarction, unstable angina, coronary artery revascularization were taken.

All patients were assessed for FH using the DLCN criteria. Diagnosis of FH is considered as definite FH (total score >8), probable FH (score is 6-8), possible FH (score is 3-5) and unlikely (score <3) (Table 1).

Further these patients were counselled about the risks and family impact and recommended to undergo genetic screening for establishing the more precise and accurate gene defect and confirmation of FH. The genetic testing (21 samples) was offered by med genome labs which was offered to patients on the basis of "first-come first-serve basis". Targeted gene sequencing method was used for the assessment of genetic mutation in which selective capturing and sequencing of the protein coding regions of the genome/genes was performed. This is a cost-effective approach to detect variants present in multiple/large genes in an individual.

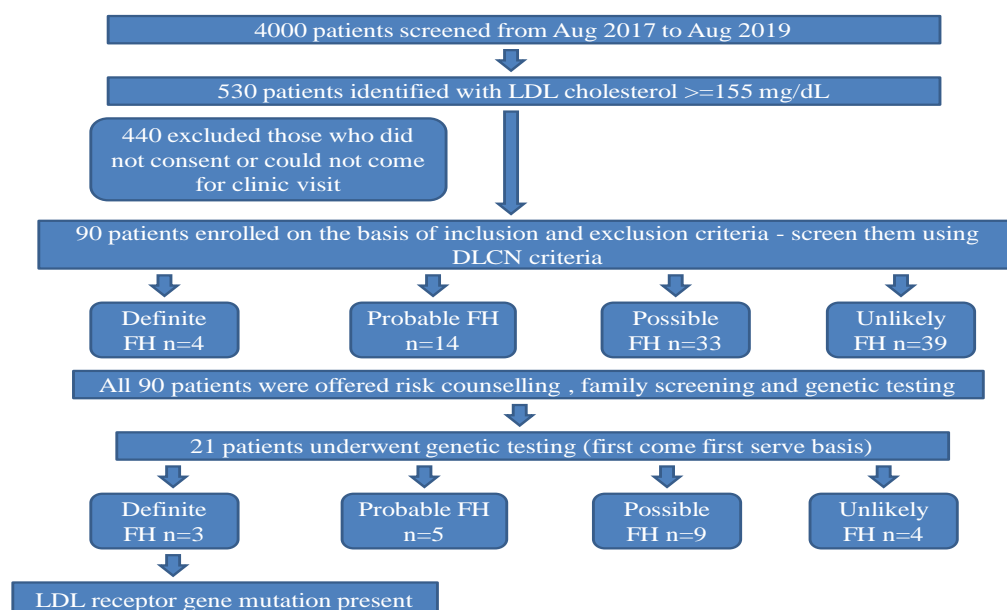Schematic representation of data collection shown in Figure 1.

Figure 1: Schematic representation of data collection.

Table 1: DLCN criteria.

Groups	Points
Group 1: Family history	
First degree relative with known premature CHD (<55 years in men, <60 years in women) or known LDL cholesterol >95th percentile by age and gender for country	1
First degree relative with TX and/or CA or children<18 years with LDL cholesterol >95th percentile by age and gender for country	2
Group 2: Clinical history	
Subject with-premature (<55 years, men; <60 years, women) CHD (as defined above)	2
Premature (<55 years, men; <60 years, women) cerebral or peripheral vascular disease (as defined above)	1
Group 3: Clinical examination	
TX	6
CA in a person<45 years	4
Group 4: Biochemistry (LDL cholesterol)	
>8.5 mmol/L (>325 mg/dL)	8
6.5-8.5 mmol/L (251-325 mg/dL)	5
5.0-6.4 mmol/L (191-250 mg/dL)	3
4.0-4.9 mmol/L (155-190 mg/dL)	1
Group 5: Molecular genetic testing	
Causative mutation in the LDLR, APOB, or PCSK9 genes	8
Diagnosis	**Score**
Definite FH	>8
Probable FH	6 to 8
Possible FH	3 to 5
Unlikely FH	0 to 2

Diagnosis of FH

DLCN criteria (Table 1) was used for diagnosis of FH.

Scores assigned in each group are then added.

RESULTS

We screened 4000 patients from hospital database who underwent lipid profile testing during the study period, of which 2622 were males and 1378 were females. Mean age of this population was 56.27±15.38. Mean LDL-C of this population that we screened was 109.9±39.31 mg/dL (Figure 2). Out of these 530 had LDL-C ≥155 mg/dl whom we approached, from which we enrolled 90 patients on the basis of inclusion and exclusion criteria.

The baseline characteristics of the enrolled patients are summarized in Table 2.

Amongst 90 patients, around two-third (n=59; 65.56%) were male and one-third were female (n=31; 34.44 %). Male to female ratio is 1.9:1. Around one-third (n=29; 32.2%) were up to 40 years of age while two-third (n=61; 67.8%) of study subjects were between 40 to less than 60 years of age. The mean age observed at the time of enrollment was 44±7.91 years. Mean LDLC level was 186.99±40.14 mg/dl. About 46.7% (n=42) of patients had premature CAD, and 83.3% (n=75) of patients reported family history of premature CAD. TX was observed in 4 patient (4.4%) and arcus Cornelis in one patient (1.1%). About 4.4% (n=4) of patients had premature Cerebral or Peripheral vascular disease. Around one-fourth (n=21; 23.33%) of study subjects were underwent genetic screening and 3 were found to be positive.

Table 2: Baseline characteristics of all patients enrolled, (n=90).

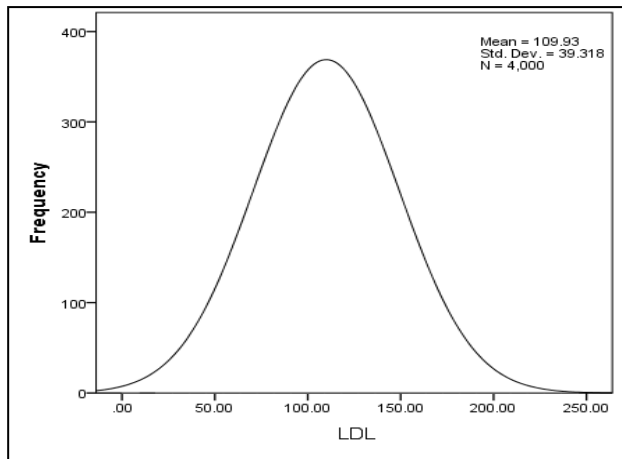| Baseline characteristics	Mean ± SD (%)
Gender	
Male	59 (65.56)
Female	31 (34.44)
Age (Years)	44±7.91
Mean LDL-C	186.99±40.14
Patients with h/o premature CAD	42 (46.7)
patients with h/o premature cerebral or peripheral vascular disease	4 (4.4)
Family history of premature CAD	75 (83.3)
TX	4 (4.4)
CA	1 (1.1)
Patients who underwent molecular genetic testing	21 (23.33)
Patients who underwent molecular genetic testing showing positive genetic mutation	3 (3.33)

Figure 2: Mean LDL cholesterol of general population is 109.9 mg/dl.

Amongst 4 Definite FH, 3 were confirmed by genetic study. Amongst the 3 genetically positive cases, all were positive for LDLR gene.

Four (4.44%) patients had definite FH, 15 (15.56%) had probable FH, 33 (36.67%) had possible FH and 39 (43.33%) patients unlikely have FH. TX is a relatively a specific diagnostic sign for definite FH because all 4 cases of TX were found in patient with definite FH. On contrary CA is a relatively nonspecific diagnostic sign as CA was present in only one (n=1.11%) patient with LDL-cholesterol ≥155 mg/dl (all below 45 years). History of premature CHD was found in all definite and probable FH patient (100%) and most of the possible (69.69%) FH patient, while it was rarely seen (2.56%) in patients with unlikely FH.

Table 3: The patient characteristics and prevalence of FH in different categories based on DLCN criteria score, (n=90).

Variables	Definite FH, n (%)	Probable FH, n (%)	Possible FH, n (%)	Unlikely FH, n (%)
Total patient	4 (4.44)	14 (15.56)	33 (36.67)	39 (43.33)
Gender				
Male	3 (3.33)	5 (5.55)	23 (25.55)	28 (31.11)
Female	1 (1.11)	9 (10)	10 (11.11)	11 (12.22)
Prevalence (%)	4.44	15.56	36.67	43.33
Mean LDL (mg/dl)	334±86	206±15	179±18	172±12
TX	4	0	0	0
CA	0	1	0	0
Patients with h/o premature CAD	4 (100)	14 (100)	23 (69.69)	1 (2.56)
Patients with h/o premature cerebral or PVDs	0	0	4	0
Patients showing positive genetic mutation	3	0	0	0

DISCUSSION

The present study showed a significant prevalence of FH in patients with high LDL Cholesterol (≥155 g/dl). To the best of our knowledge, not many studies have been done to assess the prevalence of FH in general population of India.

We screened 4000 patients who underwent lipid profile testing out of which 530 had high LDL cholesterol (≥155 mg/dl), from which we enrolled 90 patients on the basis of inclusion and exclusion criteria. Based on the DLCN criteria scoring, Definite FH was found in approximately 4 (4.4%) in 90 people with high LDL-C (≥155 mg/dl), i.e., 4 in a sub-set population of 4000. The frequency of FH found in our study is 0.45% (i.e., Definite and Probable FH. Advantages of our study are face-to-face examination of each participant, to establish the presence of TXta, CA, and secondly genetic screening.

In the Copenhagen general population study, 98,098 individuals were genotyped for LDLR and ApoB mutations and it was found that FH causing mutations estimated to occur in 1:217 in the general population and are identified by definite or probable phenotypic diagnosis of FH based on the DLCN criteria.[13]

The national health and nutrition examination survey (NHANES) conducted a study between 1999 to 2012 among participants ≥20 years of age (n=36949) to estimate the prevalence of FH by using DLCN criteria, including LDL cholesterol and personal and family history of premature atherosclerotic cardiovascular disease. Prevalence of probable/definite FH were calculated for the overall population. Results were extrapolated to the 210 million US adults ≥20 years of age. The estimated overall US prevalence of probable/definite FH was 0.40% or 1 in 250.[14]

Recent study conducted in India using DLCN criteria by Sawhney et al among patients with pre-existing coronary

artery disease.[12] Total of 635 patients with premature CAD were assessed for FH using DLCN criteria. Other CV risk factors known to cause CAD such as smoking, diabetes mellitus, and hypertension were also recorded. Of total 635 patients, 25 (4%) were diagnosed as definite, 70 (11%) as probable, 238 (37%) as possible, and 302 (48%) without FH, suggesting the prevalence of potential (definite and probable) FH of about 15% in the North Indian population. They also concluded that FH is more common in younger patients, and they have lesser incidence of common CV risk factors such as diabetes, hypertension, and smoking than the younger MI patients without FH (26.32% vs. 42.59%; 17.89% vs. 29.44%; 22.11% vs. 40.74%)

Amongst the 90 patients we screened, around two-third (n=59; 65.56%) were male while one-third were female (n=31; 34.44 %). Male to female ratio is 1.9:1. We found that around one-third (n=29; 32.2%) were up to 40 years of age while two-third (n=61; 67.8%) were between 40 to 60 years of age with mean age of study subjects was 44±7.91 years.

We found higher prevalence of premature CAD (n=42; 46.7%) amongst study subjects. Premature CHD was found in all definite, probable FH (100%) and most of the possible (69.69%) FH patient, while rarely seen (2.56) in patients with unlikely FH. We also found premature cerebral or PVDs (n=4; 4.4%), TX (n=4; 4.4%) and CA (n=1; 1.1%) in few patients.

Around one-fourth (n=21; 23.33%) of study subjects underwent genetic screening and 3 were found to be positive. Amongst 4 definite FH, 3 were confirmed by genetic study. All 3 were positive for LDLR gene mutation.

Therefore, DLCN criteria can be used as a simple, economical tool in screening of FH. Although we need further large population-based studies to estimate the prevalence.

Therefore, considering the high prevalence of FH in patients with high LDL cholesterol, we conclude that FH is an under-diagnosed disease. All these patients were newly diagnosed cases. We therefore, recommend the application of DLCN criteria for all dyslipidemic patients to cautiously look for FH, in order to detect and prevent premature CAD, cerebral vascular or PVD in individuals and their generations to come. We also recommend larger studies with more genetic testing, to assess the burden of this disease.

Limitations

The sample size of our study was limited as duration of our study was short, therefore further large population-based studies are required to assess the prevalence of FH in general population across the country. Secondly, the molecular genetic testing (DNA analysis) was not possible in all cases due to financial constraints, therefore scoring might be underrated.

CONCLUSION

It is concluded that the prevalence of FH is high amongst the patients with high LDL cholesterol. To detect the FH among patients with high LDL cholesterol, routine screening with DLCN criteria may be effectively used. Those with definite FH, estimated by DLCN criteria, also proven by genetic testing. Thus, re-establishing that the DLCN criteria as a simple, economical screening tool which can be used at the PHC level for the detection of FH and assist appropriate referral. Underdiagnosis of FH in India underlines the need for the intensification of FH detection so as to start early and aggressive case-specific treatment.

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