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The tertiary hospital laboratory; a novel avenue of opportunistic screening of familial hypercholesterolemia

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ABSTRACT

Background: Familial hypercholesterolemia (FH) is a common monogenic hereditary lipid disorder characterised by increased serum low-density lipoprotein cholesterol (LDL-cholesterol) concentrations and high risk of premature atherosclerotic cardiovascular disease. The prevalence of FH identified in a tertiary hospital laboratory was investigated by performing an opportunistic screen for index cases.
Methods: The prevalence of likely FH based on LDL-cholesterol thresholds >4.9 mmol/L as employed by the Dutch Lipid Clinic Network Criteria (DLCNC) score was evaluated retrospectively in a single tertiary hospital laboratory over a six-month period (July to December 2016).
Results: 4943 lipid profiles screened, 106 patients (mean age 53.2 ± 12.9 and 41% male) had LDL-cholesterol of >4.9 mmol/L after exclusion of 5 patients (0.1%) with secondary causes. Possible (n = 90) and probable/definite (n = 16) FH according to DLCNC score was seen in 1.8% and 0.4% of the overall screened population, respectively.
Conclusions: Point prevalence of screening for FH in patients undergoing lipid profile testing in a tertiary hospital laboratory was comparable with prevalence of FH in general population (based on 1 in 200–250). This supports the benefit of establishing an efficient "alert system" in conjunction with a trigger "reflex testing" to facilitate further formal FH scoring and exclusion of possible secondary causes of hyperlipidemia in potential index FH.

1. Introduction

Familial hypercholesterolemia (FH) is a hereditary lipid disorder characterised by increased serum low-density lipoprotein cholesterol (LDL-cholesterol) concentrations and premature atherosclerotic cardiovascular disease (ASCVD) [1]. It is an autosomal dominant condition frequently caused by mutations in the gene coding for the LDL-receptor (LDL-R) and, less commonly, mutations in the genes coding for Apolipoprotein-B (APO-B) and proprotein convertase subtilisin/kexin type 9 (PCSK9) [2].

The prevalence of FH has previously been reported as 1 in 500 in the general population [3–5]. However, emerging evidence suggests that FH is potentially more common than and possibly as high as 1 in 200–250 in the general population, and is often both underdiagnosed and undertreated by health care providers [6,7]. The risk of early-onset ASCVD is increased tenfold among untreated individuals with FH. Statin therapies have been demonstrated to improve the prognosis of patients with FH [8]. Hence, FH guidelines focus on early identification and management of index cases as well as cascade screening to prevent further cardiovascular events [9]. The key role of biochemistry laboratories and chemical pathology in detecting index cases of FH has been pointed out in an Australasian model of care for FH [10]; however, there is no existing data to support this proposed role.

There are several published criteria for the diagnosis of phenotypical FH, with the Dutch Lipid Clinic Network Criteria (DLCNC) score appearing to have more comprehensive stratification criteria and higher sensitivity for identifying screened individuals with FH [11]. On the basis of LDL-cholesterol level, clinical examination, family history, and genetic testing the odds of having FH can be assessed via DLCNC: definite FH >8, probable FH 6–8, possible FH 3–5 and unlikely FH <3 [12]. As universal screening for FH is economically prohibitive, every opportunity to screen patients for FH should be utilised. The feasibility of community laboratories to screen for individuals with potential FH has been formerly studied and described [1]. We studied the potential viability of a tertiary hospital laboratory as a novel avenue to opportunistically screen for patients with FH. This avenue of identification has not been previously evaluated.

Abbreviations: AHA, American Heart Association; ASCVD, Atherosclerotic cardiovascular disease; APO-B, Apolipoprotein-B; CAD, Coronary artery disease; DLCNC, Dutch Lipid Clinic Network Criteria; FH, Familial hypercholesterolemia; HDL-C, High density lipoprotein cholesterol; HIV, Human immunodeficiency virus; LDL-cholesterol, Low-density lipoprotein cholesterol; LDL-R, Low density lipoprotein receptor; PCSK-9, Proprotein convertase subtilisin/kexin type-9.

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2. Methods

All fasting serum lipid profiles consecutively performed over six months (from 3rd July 2016 to 29th December 2016) from a single tertiary hospital pathology laboratory (Monash Health, Melbourne, Australia) were reviewed. Monash Health is Victoria's largest public health service providing care to a population of over 3.6 million people. Lipid profiles with no reported LDL-cholesterol or reported non-calculated due to high triglyceride levels were excluded. Total cholesterol, triglyceride and high-density lipoprotein (HDL)-cholesterol were performed with enzymatic, colorimetric assays on a Beckman Coulter AU 5800 analyser (Beckman Coulter, Brea, CA, USA). The inter- and intra-assay percent coefficients of variation (%CVs) of these assays were <5%. LDL-cholesterol was calculated according to the Friedewald equation [13]. Patients with a serum LDL-cholesterol >4.9 mmol/L (correlating with a DLCNC score of at least 3) were further assessed.

Electronic hospital medical records were reviewed for clinical and medication history to evaluate further components of DLCNC and known secondary causes of hypercholesterolemia including untreated hypothyroidism, nephrotic syndrome, anorexia nervosa and cholestasis. The use of relevant medications at the time of performed lipid profile was recorded. In patients receiving LDL lowering therapies, the LDL-cholesterol plasma level was adjusted according to the intensity and the dose of administered statin or ezetimibe [14]. The specialty of the medical practitioner who referred the patient for lipid profiling was also collected and analysed. Microsoft Excel 2013 and MedCalc statistical software version 16.4.3 was used for statistical analysis [15]. This research was carried out according to the Code of Ethics of the World Medical Association (Declaration of Helsinki), and our institutional review board approved the study (RES-17-0000-433Q).

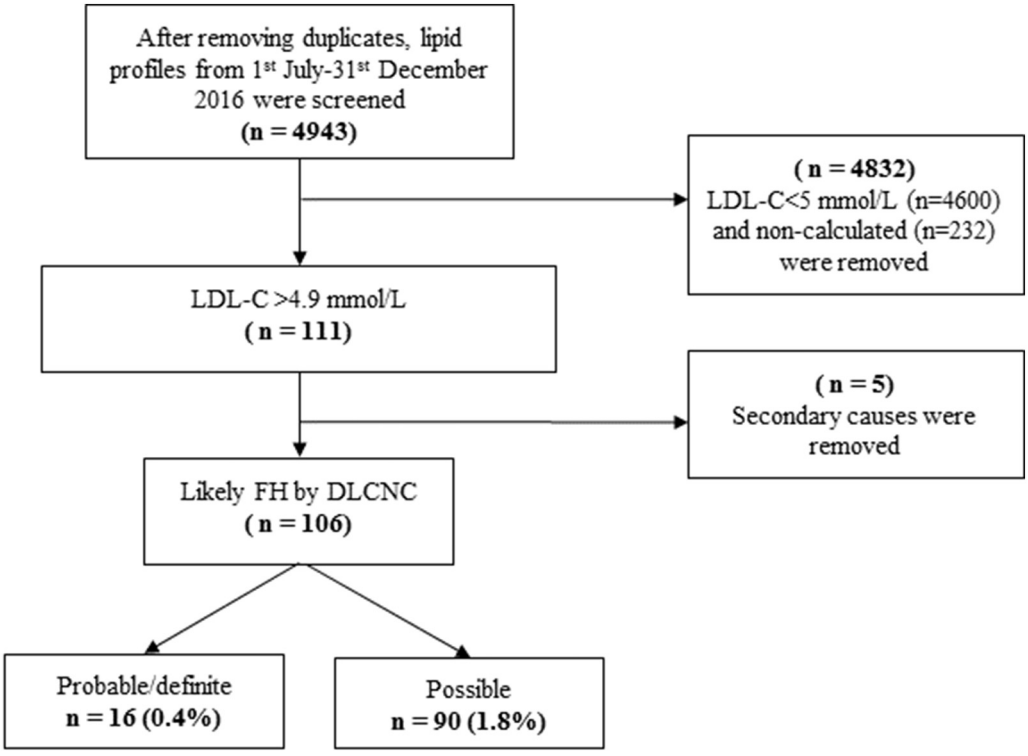
3. Results

Over the 6-month period, a total of 4943 serum lipid profiles were reviewed. There were 106 (2.2%) subjects with LDL-cholesterol >4.9 mmol/L after exclusion of five cases (0.1%) with identified secondary causes [untreated hypothyroidism (n = 1), severe renal failure (n = 2), cholestasis (n = 1), anti-HIV (human immunodeficiency virus) medication (n = 1)]. After review of 4943 electronic pathology result form, 1.8% of all patients who had LDL-cholesterol measured over the 6 months had a DLCNC score of 3–5, 0.3% scored 6–8 and 0.1% scored >8 indicating a possible, probable and definite diagnosis of FH respectively (Fig. 1). We adjusted the prevalence of possible FH to 0.03% accordingly. In total, the point prevalence of likely phenotypical FH based on DLCNC and a LDL-cholesterol >4.9 mmol/L was calculated as approximately 0.43% (1 in 232).

The serum LDL-C distribution is shown in Fig. 2, and the basic characteristics of individuals with likely FH are summarised in Table 1. The 95th, 99th and 99.75th percentiles for serum LDL-cholesterol were 4.4, 5.5 and 6.4 mmol/L, respectively. None of these patients had a previously documented diagnosis of FH according to the medical record. The vast majority of these patients with likely FH and elevated LDL-cholesterol were statin naïve (85.9%). Patients were referred for lipid profiling by specialists in 63% (cardiologists were 21% of specialist's referrals) of cases and by general practitioners in 37% with the majority of these initiated after recent hospital admission.

4. Discussion

The current study demonstrated an LDL-cholesterol >4.9 mmol/L with DLCNC score consistent with probable/definite or possible FH



DLCNC: Dutch Lipid Clinic Network Criteria; FH: familial hypercholesterolemia; LDL-C: Low Density Lipoprotein Cholesterol

Fig. 1.. Patient selection and study design. Diagram demonstrating study inclusion and exclusion criteria.

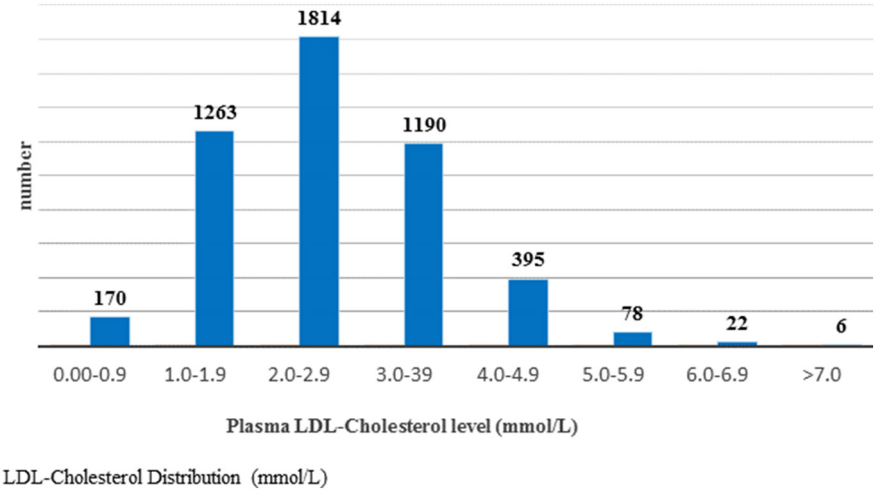


Fig. 2.. Plasma LDL-cholesterol distribution in a tertiary laboratory.

was seen with a prevalence of 1:50 in our screened population. Our results on the basis of DLCNC screening are significantly higher than the approximately 1:200–250 proposed in the general population. A recent large case-control study suggested that about 2% of individuals with elevated LDL-C > 4.9 mmol/L have an FH genetic mutation [16], if this result is applicable to our population of possible FH identified by DLCNC criteria (i.e. 2% of 1.8%), a final adjusted prevalence of approximately 0.43% (1 in 232) results. This is comparable to the proposed prevalence in the general population (1 in 200–250).

We anticipate that by applying genetic mutation adjustment, the actual prevalence of diagnosed FH in the tertiary hospital might be underestimated. Firstly, overall patients referred to a tertiary laboratory have more serious co-morbidities than the general population, so there is a higher likelihood of FH patients requiring hospitalisation. Secondly, the specificity of LDL-cholesterol cut-off point of 4.9 mmol/L may have been reduced by unknown confounders in this population. Finally, due to poor correlation (only ~40%) between mutation and a clinical diagnosis of FH [2], by using adjusted prevalence rate for possible FH, some cases with FH may have been excluded.

Although there is no other data regarding the prevalence of FH identified in tertiary laboratory screening, our results support previous studies that demonstrated a beneficial role of LDL-cholesterol cut-offs in screening for FH, in the absence of genetic testing [17]. Also, a serum LDL-cholesterol of >4.9 mmol/L in adults over 16 years of age is the cornerstone of laboratory diagnosis of possible FH by the Simon Broome criteria [18] as an alternative method for FH diagnosis. MED-PED criteria is another assessment tool to identify patients with FH; however, this would be more challenging to use for screening as it requires age adjustment in conjunction with plasma LDL-cholesterol cut-off levels [19]. The suitability of each diagnostic criterion versus genetic testing in a specific target population has been studied in one of the countries located in the Persian Gulf region [20].

Due to several limitations such as suboptimal documentation of medical records, ethnicity variation and underdiagnosed secondary hypercholesterolemia, determination of the exact prevalence of FH in a tertiary laboratory or even in the clinical setting remains challenging. Using an LDL-cholesterol cut off level criteria at least raises the possible presence of this preventable high-risk condition and prompts clinicians to explore for other diagnostic criteria. Furthermore, the fact that there is a weak correlation between positive FH genetic testing and clinical diagnostic criteria, the role of LDL-cholesterol cut-off level in screening for patients with FH will be more prominent [21,22]. Considering the described caveats and also the absence of consensus about the best diagnostic criteria to identify patients with phenotypical FH, the feasibility of screening FH via a tertiary laboratory using solely LDL-cholesterol cut-offs appears reasonable.

The majority of referrers for tertiary hospital lipid profile testing in our study were specialists particularly cardiologists; thus this study also highlights the importance of awareness and knowledge about FH among cardiologists in promoting management in this high-risk group. However, numerous referrals from high risk hospitalised patients might limit the validity of our findings when applied to a less homogenous and lower risk population. The fact that these index cases identified with probable or possible FH had not been diagnosed and therefore a vast majority of them were statin naïve illustrates that much education is still required of specialists and general practitioners in detecting FH. It also supports that laboratories performing lipid profiles should create a routine “alert system” for all LDL-cholesterol >4.9 mmol/L to the requesting doctor to ensure further screening for FH or referral to a lipid specialist is considered.

Table 1
Characteristics of patients with likely FH (n = 106).

Characteristics	Probable/definite (n = 16)	Possible (n = 90)
Age, y ± SD	53.3 ± 12.4 (38–66)	53.2 ± 13.0 (14–82)
Male	7 (43%)	36 (40%)
Total cholesterol (mmol/L)	7.9 ± 0.8	7.9 ± 0.8
LDL-C (mmol/L)	5.7 ± 0.6	5.6 ± 0.6
Diabetes %	5 (31%)	7 (8%)
Hypertension %	3 (27%)	10 (11%)
Smoking %	5 (31%)	4 (5%)
Family history of early ASCVD %	7 (63%)	4 (5%)
Peripheral arterial disease	1 (%6)	1 (1%)
DLCNC mean ± SD	7.7 ± 0.5	3.1 ± 0.5
Ischemic heart disease %	11 (69%)	8 (9%)
STEMI	3 (19%)	1 (1%)
Non-STEMI	5 (31%)	4 (5%)
Unstable angina	3 (19%)	3 (3%)
Stroke/TIA %	1 (6%)	2 (2%)
Use of statins	14 (13.2%)	1 (1%)

ASCVD: Atherosclerotic Cardiovascular Disease; DLCNC: Dutch Lipid Clinic Network Criteria; FH: familial hypercholesterolemia; LDL-C: Low Density Lipoprotein Cholesterol; SD: Standard deviation; STEMI: ST Elevation Myocardial Infarction; TIA: Transient Ischemic Attack.

5. Limitations

This was a retrospective study screening patients mainly by existing LDL-cholesterol levels in the biochemistry laboratory. In cases associated with high triglycerides (above 4.5 mmol/L) and also some patients with combined hyperlipidemia, calculated LDL-cholesterol level was

diluted due to erroneously applied Freidewald's formula [23]. Conversely, patients with lower LDL-cholesterol level may have other clinical manifestation of FH which would be underdiagnosed by the use of solely biochemical criteria. There was no genetic testing information in this FH detected patients, which may provide an additional diagnostic and prognostic value to this high-risk subgroup. We cannot describe whether the higher rate of FH in a tertiary hospital laboratory is related to lower specificity of screening or if this is a selection bias due to a high frequency of referral of severe cases such as acute coronary syndromes, stroke or peripheral arterial disease to a tertiary centre.

6. Conclusions

This study demonstrates a high yield from opportunistic screening for FH in a tertiary hospital laboratory with a prevalence of at least analogous to the general population. The detection of previously undiagnosed and undertreated cases of likely FH supports the benefit of establishing an efficient “alert system” in tertiary laboratories to facilitate screening and referral to a lipid specialist in this high-risk population.

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Conflict of interest statement

SM received an honorarium from Amgen.

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