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Homozygous familial hypercholesterolaemia in Vietnam: Case series, genetics and cascade testing of families

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ABSTRACT

Background and aims: Familial hypercholesterolaemia has not been previously described in the Vietnamese population. We aimed to describe the features of patients with homozygous familial hypercholesterolaemia (hoFH) in Vietnam and the outcomes of screening family members using genetic and cholesterol testing.

Methods: Mutation testing by massively parallel sequencing for genes causative of FH was undertaken in five index cases presenting to a single cardiac center with a presumptive diagnosis of hoFH. Cascade testing of all available family members was subsequently undertaken. The number of new cases of FH detected and commenced on lipid-lowering treatment was evaluated.

Results: All five index cases had true homozygous mutations in the LDL receptor gene (*LDLR*). Cascade screening was undertaken in four families. 107 relatives were screened and FH was identified in 56 relatives (52%), including 3 new cases of hoFH. Only 5 FH relatives (9%) were subsequently treated owing to the adverse perceptions and comparative high cost of drug treatment, and lack of awareness of FH among patients and local doctors.

Conclusions: HoFH due to *LDLR* mutations is a severe disorder in Vietnam that needs early detection and treatment with LDL-cholesterol lowering drugs. Cascade testing of families allows effective detection of new cases of FH that may also benefit from early treatment. However, convincing patients to commence statin treatment is a challenge. Extended education and awareness programs and treatment subsidies are imperative to improve the care of patients and families suffering from FH in Vietnam.

1. Introduction

Familial hypercholesterolaemia (FH) is an autosomal co-dominantly inherited disorder of lipoprotein metabolism due to mutations in the low-density lipoprotein (LDL) receptor (*LDLR*), apolipoprotein B (*APOB*) or proprotein convertase subtilisin-kexin type 9 (*PCSK9*) genes [1]. Homozygous FH (hoFH) is a rare disorder with severely elevated LDL-cholesterol since birth and high cardiovascular morbidity and mortality from premature atherosclerosis [2]. Heterozygous FH (heFH) is relatively less severe but still confers a high risk of premature coronary artery disease (CAD) [1].

Guidelines recommend early diagnosis and early treatment to reduce the risk of CAD in FH patients [1]. However, many patients are undiagnosed and those that are diagnosed, are undertreated [3]. Cascade screening is one strategy to increase diagnosis of FH once an index case with FH is identified [4]. The effectiveness of family screening in Vietnam has not been reported previously. We describe the features of five patients with hoFH in Vietnam and the outcome of screening their family members using genetic and cholesterol testing.

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2. Patients and methods

Between November 2014 and October 2016, five index cases with severe phenotypic FH presented at Bach Mai Hospital. They were referred to our hospital by general physicians or cardiologists at the local medical centers. With consent, family members of index case were screened for FH. Supplementary Fig. 1 is a schematic of the protocol that was followed. All patients gave written informed consent to their de-identified information for analysis and reporting. For children, parental/guardian written informed consent was obtained. Written informed consent for use of each of the images in Fig. 1 was obtained, and parental/guardian consent was obtained for children. The study was approved by the Council for Science of Vietnam National Heart Institute, Bach Mai Hospital (No.: 183/VTM-BVBM).

Adult index cases were diagnosed based on extreme hypercholesterolaemia and/or physical signs (arcus cornealis, xanthelasma, tendinous xanthoma) [3]. Pre-treatment LDL-cholesterol concentrations were derived from medical records or by adjusting concentrations for treatment [5]. For children, we adopted the phenotypic diagnosis based on LDL-cholesterol ≥5 mmol/L, or LDL-cholesterol ≥4 mmol/L with family history of premature cardiovascular disease and/or high baseline cholesterol in one parent [6]. Demographic and clinical data were collected on the index cases.

Coronary artery disease (CAD) was defined by coronary computed tomography angiography or invasive coronary angiography. Symptomatic CAD as defined as acute coronary syndromes (myocardial infarction, unstable angina). Peripheral artery disease (PAD), including carotid arteries (CA) and supra-aortic stenosis were defined by ultra-sonography. Smoking was defined as cigarette smoking at the time of screening. Hypertension was defined in adults as a systolic blood pressure (BP) ≥140 mmHg or diastolic BP ≥90 mmHg, and in children as either systolic and/or diastolic BP ≥95th percentile measured on three or more separate occasions. Diabetes mellitus was defined as fasting plasma glucose concentration ≥7.0 mmol/L or 2-h plasma glucose concentration ≥11.1 mmol/L during an oral glucose tolerance test. Hypothyroidism was defined asthyroid-stimulating hormone (TSH) >0.5 mU/L and free thyroxine (FT4) <12 pmol/L. Nephrotic syndrome was defined as proteinuria greater than 3.5 g/24 h and serum albumin <25 g/L. Hypercholesterolemia caused by liver disease was defined as plasma ALT/AST levels >40 UI/L and clinic signs of cirrhosis.

Biochemical testing included fasting plasma lipid and glucose profiles. Total cholesterol (TC), triglyceride (TG), high-density lipoprotein (HDL)-cholesterol and glucose was measured by an automatic biochemistry analyzer (AU5800 Clinical Chemistry System, Beckman Coulter) at the Department of Biochemistry, Bach Mai Hospital according to ISO 15189:2007 standards. LDL-cholesterol was calculated using the Friedewald equation [7]. Massively parallel sequencing of cardio-metabolic genes with targeted analysis of hypercholesterolaemia genes (*LDLR*, *APOB*, *PCSK9*) and multiplex ligation-dependent probe amplification (MLPA) of *LDLR* was used to detect pathogenic variants in index cases, as previously described [8].

Pedigree diagrams were drawn for each family, starting with the index case. Cascade screening was undertaken in close relatives at the home of the index case or at a local medical center on a fixed date. Relatives were interviewed for personal medical history, family health history and risk factors for cardiovascular disease (body-mass-index, smoking, hypertension, diabetes) and examined by echocardiography. Fasting blood lipid profiles were analysed in the relatives. Genetic testing was performed by Sanger sequencing of the relevant region of the *LDLR* gene, or by MLPA of the *LDLR* gene. Some relatives who could not attend at the fixed date were tested based on a fasting plasma lipid profile alone. The Starr et al. [9] age- and gender-specific LDL-cholesterol cut-offs were applied

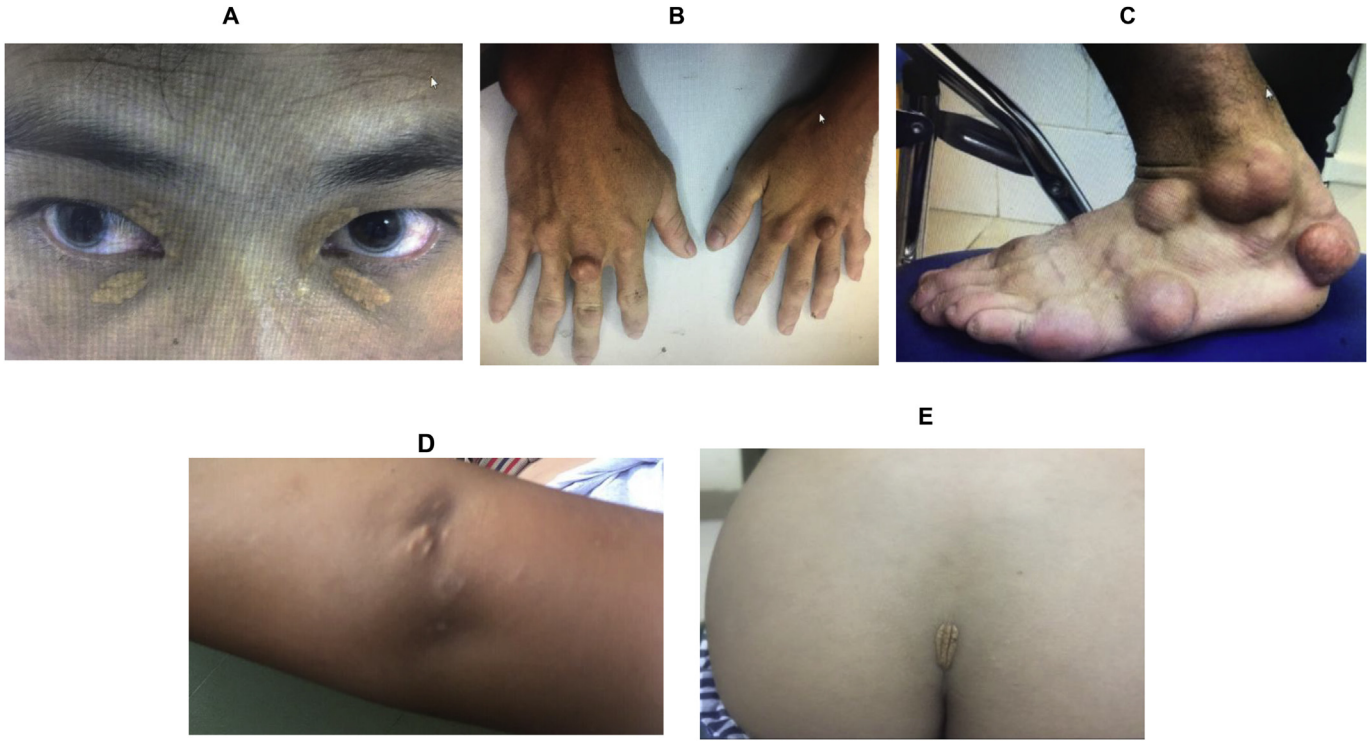

Fig. 1. Physical signs in index cases with hoFH.
(A) Arcus cornealis and xanthelasma palpebrarum (index case 1), (B) extensor tendon xanthomata of the hands (index case 1), (C) extensor and achilles tendon xanthomata (index case 1), (D) small planar xanthomata on the elbow (index case 2), and (E) planar xanthoma in natal cleft (index case 5).