IHJ Cardiovascular Case Reports (CVCR) 1 (2017) 111–115

Contents lists available at ScienceDirect

IHJ Cardiovascular Case Reports (CVCR)

journal homepage: www.elsevier.com/locate/ihjccr

Vascular profile of patient with familial hypercholesterolemia

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ARTICLE INFO

Article history:
Received 30 July 2017
Received in revised form 6 October 2017
Accepted 12 October 2017

Keywords:
Familial hypercholesterolaemia
Xanthomas
Premature atherosclerosis
Carotid artery stenosis

ABSTRACT

Familial Hypercholesterolaemia is a common genetic cause of premature Coronary heart Disease (CHD). It is an autosomal, dominant, inherited disorder of lipoprotein metabolism that results in a raised Low Density Lipoprotein Cholesterol (LDL-C) plasma concentration. The current study presented a 36 year old female having angina on exertion class 2 for past 1 year. She had large xanthomas over dorsal aspect of both the hands and feet and xanthelasma over eyelid. She was diagnosed as case of familial hypercholesterolemia. Her vascular profile revealed aortic root calcification, left main with triple vessel disease, right common carotid artery stenosis and atherosclerotic narrowing of aorta distal to left subclavian artery.

Case description

36 year old female with BMI of 20 kg/m^2 presented to us with complaints of angina on exertion class 2 for past 1 year. She had blood pressure of 132/70 mmHg and pulse rate of 76/min. She had xanthomas over dorsal aspect of both the hands (Fig. 1a), dorsal aspect of feet (Fig. 1b) and lateral aspect of right foot (Fig. 1c). She also had xanthelasma below left lower lid. On cardiovascular examination she had soft systolic murmur over aortic area and carotid bruit was heard over right side of neck.

Her father died at age of 47 years because of myocardial infarction. He had no xanthomas or xanthelasma. Her mother had no skin manifestations and her lipid profile was normal. She had one elder brother. Her elder brother had no skin manifestations and was on treatment for dyslipidemia with 20 mg rosuvastatin. His current lipid profile revealed total cholesterol 245 mg/dl, LDL cholesterol 168 mg/dl, triglycerides 191 and HDL 40 mg/dl.

Laboratory tests including CBC, LFT, and RFT were normal. Her lipid profile revealed total cholesterol 608 mg/dl, LDL cholesterol 429 mg/dl, triglycerides 126 mg/dl and HDL 54 mg/dl. The physical examination, lipid profile and family history of CAD in father and dyslipidemia in brother, were compatible with diagnosis of FH (familial hypercholesterolemia). The genetic analysis was not performed. She may be found to have homozygous FH on genetic testing if this could be performed.

Her electrocardiogram was normal. 2D echocardiography revealed thickened calcified aortic valves and aortic root (Fig. 2a), Mild aortic regurgitation (PHT 408 ms, aortic flow velocity 1.9 m/s) (Fig. 2b), right common carotid artery shows significant stenosis (Fig. 2c and d). There was evidence of atherosclerotic narrowing of aorta distal to left subclavian artery with peak gradient of 42 mmHg (Fig. 3). The left ventricular systolic and diastolic functions were normal.

On coronary angiography there was aortic root calcification, left main ostial stenosis, diseased proximal LAD, diseased proximal LCX and distal RCA (Fig. 4). On brachiocephalic trunk angiography, there was 50% stenosis of distal brachiocephalic trunk and around 70% stenosis of middle part of right common carotid artery, left common carotid showed only mild stenosis, and arch angio atherosclerotic narrowing of aorta distal to left subclavian artery with gradient of 40 mmHg (Fig. 5).

She was managed with 40 mg of rosuvastatin and 10 mg of ezetimibe. For secondary prevention of coronary artery disease she was started on ecosprin 75 mg and metoprolol 50 mg. She was taken for angioplasty but it was abandoned because we were not able to cross the wire into right coronary artery as lesion was calcified and on hooking left main coronary artery there was dampening of pressures along with ST-segment elevation on electrocardiogram. So she was referred for CABG with carotid endartrectomy.

Discussion

Familial hypercholesterolemia (FH) is an inherited condition resulting in high levels of low-density lipoprotein cholesterol (LDL-C) and increased risk of premature cardiovascular disease in men

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https://doi.org/10.1016/j.ihjccr.2017.10.003

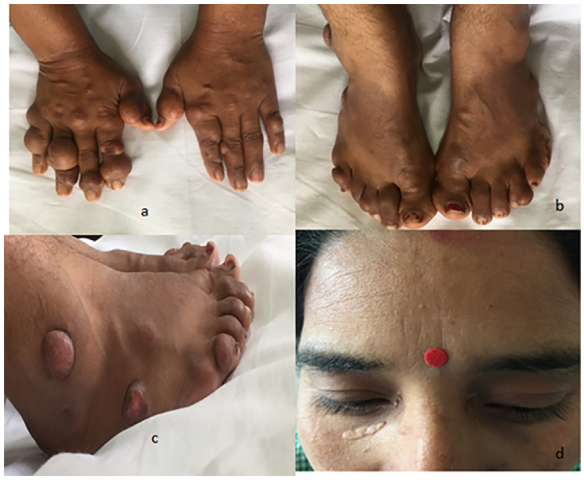

Fig. 1. Multiple skin xanthomas over hands (a) and feet (b,c). Note xanthelasma below the lower eyelid (d).

and women. Heterozygous FH (HeFH) is the most common monogenic disorder, affecting 1 in 200–250, twice as high as previously thought,[1] with a penetrance of greater than 90%.[2] If HeFH is left untreated, there is a significant likelihood of CHD onset prior to age 55 (men) and 60 (women). Half of all untreated HeFH men and 15% of women will die of CHD-induced myocardial infarction (MI) before these ages.[3,4] Homozygous FH (HoFH) is rare with an estimated global prevalence of 1/160,000–300,000.[5] In communities with founder effects, higher disease prevalence is observed.

The majority of FH cases are caused by mutations in the *LDLR* gene, resulting in defective synthesis, assembly, transport, recycling or vesicle formation. Mutations in the *LDLR* gene cause FH in 79% of cases. Apolipoprotein B (*ApoB*) helps the LDL-receptor to bind LDL and mutations in *ApoB* accounts for ~5% of FH cases. Proprotein convertase subtilisin/kexin type 9 (*PCSK9*) degrades the LDL-receptor and gain of function mutations in PCSK9 account for <1% of FH cases.[6] A very rare recessive form of FH is caused by mutations in low-density lipoprotein receptor adaptor protein 1 (*LDLRAP1*). The remaining 15% of FH cases are either polygenic or are driven by monogenic mutations whose prevalence is not yet determined.[6]

Diagnosis of FH is based on lipid levels, family history, physical findings (if present), and if available, genetic analysis (Tables 1 and 2). Physical examination findings of tendon xanthomas, arcus corneae (under the age of 45), and tuberous xanthomas or xanthelasma (under the age of 25) when present at an early age should also prompt suspicion for FH. However, physical findings are not present in all patients with FH. There are different clinical criteria to diagnose FH like Simon Broome diagnostic criteria, Dutch Criteria, MEDPED criteria. These criteria are based on family history, LDL levels, physical screening and genetic analysis.[7]

According to Nice guidelines 2008, cascade screening should be done in first and second degree relatives of index case by either genetic testing or lipid screening. Genetic testing should be done in 1st degree relatives only if genetic mutations were found in index

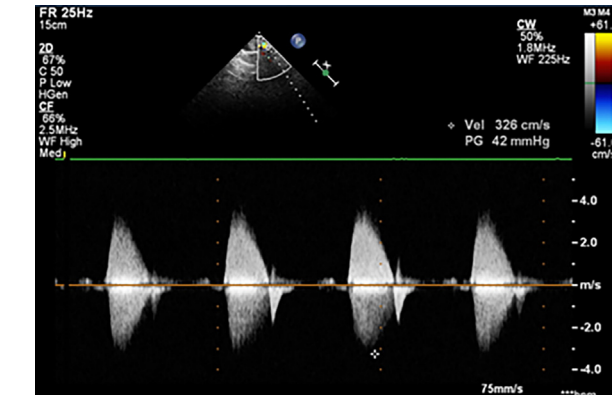

Fig. 3. Echocardiogram showing coarctation of aorta distal to left subclavian with peak gradient of 42 mm Hg.

Table 1
Clinical approach to diagnosis of familial hypercholesterolemia.

Consider FH in the following
1. Presence of premature atherosclerotic cardiovascular disease
2. Fasting LDL-C levels greater than 190 mg/dL in adults after exclusion of secondary causes of elevated LDL-C (hypothyroidism, nephritic syndrome)
3. Fasting untrea ted LDL-C levels that have an 80% probability of FH in the general population: >250 mg/dL in adults >30 years, >220 mg/dL in adults aged 20 to 29, 190 mg/dL in patients under the age of 20
4. Presence of full corneal arcus under the age of 40
5. Presence of tendon xanthomas
6. Family history of premature atherosclerotic cardiovascular disease
7. Family history of high cholesterol levels

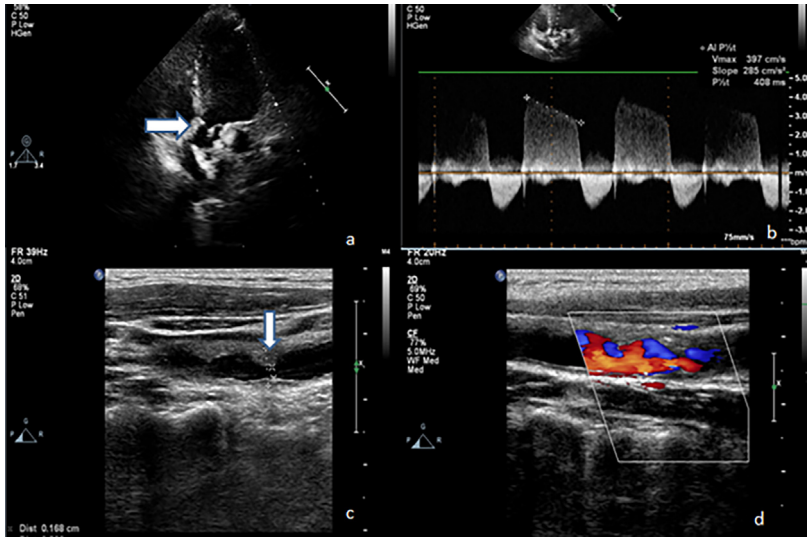

Fig. 2. Echocardiogram showing thickened and calcified aortic valve and aortic root (a), mild aortic regurgitation (b), plaque (arrow) causing significant obstruction (c, d).