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Case Series

Clinical manifestations of familial hypercholesterolemia: a case series

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ABSTRACT

Familial hypercholesterolemia is a rare, monogenic, co-dominant, life-threatening disorder resulting from loss of function mutations in the genes responsible for synthesis of low-density lipoprotein receptors or apo-B genes or gain of function mutations in PCSK9 genes in the liver which affects 0.2% of the population. It is characterized by severe lifelong elevation of LDL cholesterol and by development of xanthelasma, xanthomas, premature coronary artery disease and peripheral artery occlusive disease. Most patients develop PCAD and aortic stenosis before the age of 20 years and die before 30 years of age. The diagnosis of FH is usually based on clinical presentation and commonly used criteria are the Dutch lipid clinic network criteria, Simon Broome criteria or the WHO criteria. We encountered four cases of familial hypercholesterolemia over last 10 years. All the four patients presented with effort angina and all were found to have obstructive coronary artery disease oncoronary angiogram and two of them had severe supravalvular aortic stenosis. All four patients were on dietary modifications, high intensity statin and cholesterol absorption inhibitor. Two patients underwent coronary artery bypass grafting with aortoplasty, one patient underwent coronary artery bypass grafting and one patient underwent percutaneous transluminal coronary angioplasty. Familial hypercholesterolemia leads to development of life-threatening manifestations early in the second and third decades of life. Early diagnosis, aggressive treatment and control of risk factors and cascade screening are important in management and will help to reduce the morbidity and mortality associated with this disease.

Keywords: Familial hypercholesterolemia, Low density lipoprotein receptors, Xanthelasma palpebrarum tendon and tuberous xanthomas, Premature coronary artery disease, Supravalvular aortic stenosis

INTRODUCTION

FH (familial hypercholesterolemia) is a rare, monogenic, autosomal dominant disease caused by loss of function mutations in the LDL (low density lipoprotein) receptors or apo-B genes, or a gain-of-function mutation in the PCSK9 (proprotein convertase subtilisin/kexin type 9) gene; approximately 95% of FH cases are caused by mutations in LDLR.[1] Homozygous familial hypercholesterolemia (HoFH) is a rare and life-threatening disease with estimated frequency of 1 in 160,000 to 1 in 320,000.[2] HoFH clinically manifests as extensive tendon and tuberous xanthomas, xanthelasma, corneal arcus, markedly premature and progressive atherosclerosis, and TC (total cholesterol) >13 mmol/l (>500 mg/dl).[3] Most patients develop CAD (coronary artery disease) and aortic stenosis (AS) before the age of 20 years and die before 30 years of age.[4] Cholesterol lowering treatment should be initiated as soon as possible after diagnosis has been made and maximally tolerated pharmacological therapy must be maintained throughout life.[5] We encountered four cases of FH over last 15 years. Relevant clinical findings echo and angio findings are tabulated.

Lipid profiles on admission and on follow up at 6 months were documented.

CASE SERIES

Case 1

Mr. A, aged 24 years, a known case of Familial Hypercholesterolemia presented with exertional dyspnea of 6 months duration and exertional chest pain of 3 months duration, patient had noticed tendon xanthoma at the age of 10 years, patient's other siblings also had similar xanthomas. Other clinical and lab findings are documented in the table. ECG (electrocardiogram) showed sinus rhythm and LVH (left ventricular hypertrophy) by voltage criteria. 2D echocardiogram showed situs solitus, severe supra-valvular AS (AV. gradient 118/70 mmHg), mild AR (aortic regurgitation) concentric LVH, normal LV function. Patient was taken up for elective coronary angiography (CAG) which showed 95% ostial stenosis of RCA (right coronary artery) and left system was normal. LV (left ventricular) angiography showed supra-valvular aortic narrowing with post-stenotic dilatation of aorta, LV pressure-211/10 mmHg, aorta 131/78 mmHg, gradient of 80 mmHg. Patient was started on high dose statins (rosuvastatin 40 mg/day) and cholesterol absorption inhibitor (Ezetimibe 10 mg/day), in addition to dietary modifications and underwent CABG (coronary artery bypass grafting) with bypass graft to RCA and aortoplasty for supra-valvular AS.

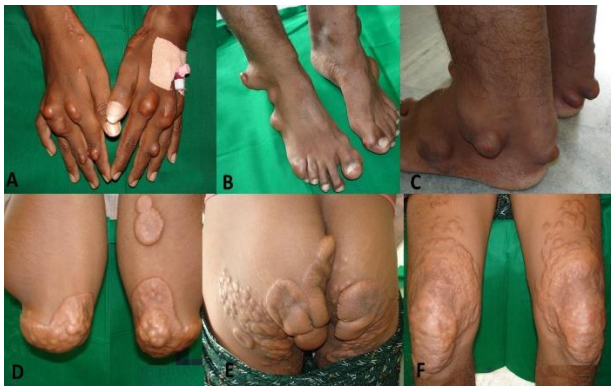

Figure 1: A, B, C) patient 1 with tendon xanthomas on dorsum of hand, foot and Achilles tendon, tuberous xanthomas on D) elbow, E) Hip and F) Knees.

Case 2

Mr. B aged 24 years, non-smoker, non-diabetic, non-hypertensive presented with history of angina on exertion of 4 months duration, functional class III. Patient was a known case of familial hypercholesterolemia with tendon xanthomas which started at the age of 7 years. Clinical and lab findings are documented in the table. ECG showed sinus rhythm and LVH by voltage criteria. 2D Echo was normal. Patient underwent elective CAG which showed normal LMCA (left main coronary artery), 90% stenosis of proximal LAD (left anterior descending artery), 80-90% stenosis of distal LCX (left circumflex artery), 95% ostial stenosis of RCA. Patient was started on high dose statins (atorvastatin 80 mg/day initially, switched to rosuvastatin 40 mg/day later) and cholesterol absorption inhibitor (ezetimibe 10 mg/day), in addition to dietary modifications. Patient chose to undergo PTCA (percutaneous transluminal angioplasty) over CABG after discussing risks and benefits of both the procedures and underwent successful PTCA with stenting to LAD with deployment of 3.0 x 18 mm sirolimus eluting stent at proximal LAD at 12 atm and a 3.0 x15 mm bare metal stent was deployed at distal LCX at 10 atm. He presented 4 years later with history of exertional angina and repeat angio showed patent stents but new lesion in LMCA extending in to ostial LAD and underwent PTCA with stenting from ostial LMCA to LAD.

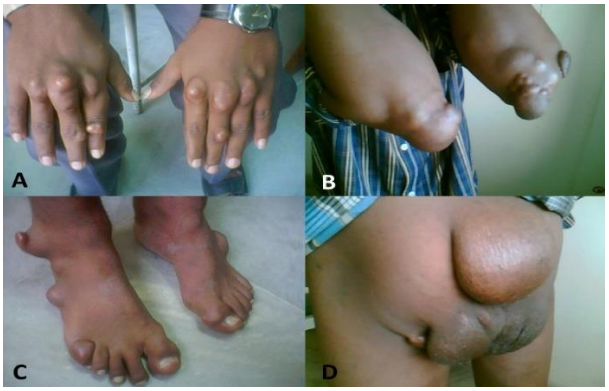

Figure 2: Tendon xanthomas was present on A) fingers, B) elbow, C) achilles tendon and D) buttocks.

Case 3

Mr. C aged 18 years, non-smoker, non-diabetic, non-hypertensive presented with history of angina on exertion of 2 months duration and intermittent rest pain in the past 1 week. Clinical findings were documented. ECG showed sinus rhythm and ST segment depression in multiple leads with ST segment elevation in lead AVR. Patient underwent elective CAG which showed mildly diseased LMCA, 90% stenosis of proximal LAD, 80-90% stenosis of distal LCX, 95% stenosis of proximal RCA. Patient was started on high dose statins (rosuvastatin 40 mg/day) and cholesterol absorption inhibitor (ezetimibe 10 mg/day), in addition to dietary modifications and underwent CABG.

Case 4

Mr. A, aged 12 years, presented with exertional chest pain of 2 months duration, patient had noticed tendon xanthoma at the age of 10 years, patient's other siblings also had similar xanthomas. Clinical and lab findings were documented. ECG showed sinus rhythm and LVH by voltage criteria. 2D Echocardiogram showed situs

solitus, severe supra-valvular AS (AV gradient 86/54 mmHg), mild AR, concentric LVH, normal LV function. Patient was taken up for elective coronary angiography which showed 95% ostial stenosis of RCA and 90% stenosis of proximal LAD. LV angiography showed supra-valvular aortic narrowing with post-stenotic dilatation of aorta, LV pressure of 184/10 mmHg and aortic pressure of 110/78 mmHg with gradient of 74 mmHg. Patient was started on high dose statins (rosuvastatin 40 mg/day) and cholesterol absorption inhibitor (ezetimibe 10 mg/day), in addition to dietary modifications and underwent CABG with bypass graft to RCA and LAD and aortoplasty for supra-valvular AS. All patients were started on high dose statins (rosuvastatin 40 mg/day) and cholesterol absorption inhibitor (ezetimibe 10 mg/day), in addition to dietary modifications. Patients were followed up after 6 months with clinical and lipid profile.

Table 1: Clinical data.

Parameters	Patient 1	Patient 2	Patient 3	Patient 4
Age (years)	24	24	18	12
Gender	Male	Male	Male	Male
Presentation	Effort angina	Effort angina	Effort angina	Effort angina
Duration of symptoms (months)	6	4	2	2
Clinical signs	Tendon xanthoma/ unequal carotid pulse (Figure 1).	Tendon xanthoma/ B/L carotid bruit (Figure 2).	Tendon xanthoma/B/L carotid bruit.	Tendon xanthoma. Unequal carotid pulsation/ unequal U/L BP
BMI	25.5	26	23.4	21.5
Blood pressure	120/80 mmHg	130/80 mmHg	136/86 mmHg	106/72 mmHg in RUL and 96/80 mmHg in LUL
Routine investigations*	NAD	NAD	NAD	NAD
ECG changes	LVH	LVH	ST depression	LVH
Echo	Supravalvular AS	Normal	Normal	Supravalvular AS
CAG	Single vessel disease	Triple vessel disease	Triple vessel disease	Two vessel disease
LMCA	Normal	Normal	Mild disease	Normal
LAD	Normal	Proximal LAD 90% stenosis	Proximal LAD 90% stenosis	Proximal LAD has 90% stenosis
LCX	Normal	90% stenosis of distal LCX	95% stenosis of distal LCX	Normal
RCA	Ostial RCA 90% stenosis	Ostial RCA 95% stenosis	95% stenosis of proximal RCA	95% stenosis of ostial RCA
Treatment	CABG+aortoplasty	Mutivessel PTCA	CABG	CABG+aortoplasty

*CBC (complete blood count), RFT (renal function test) and RBS (random blood sugar).

Table 2: Lipid Profile at first visit.

Lipid profile	Patient 1	Patient 2	Patient 3	Patient 4
Total cholesterol (mg/dl)	486	447	350	551
LDL (mg/dl)	415	430.9	297	521
VLDL(mg/dl)	39.9	13.8	22	19.0
TG (mg/dl)	195	69	110	93
HDL (mg/dl)	31.1	27.6	30.8	11.1

*VLDL (very low density lipoprotein), TG (triglycerides) and HDL (high density lipoprotein).

Table 3: Lipid profile after 6 months.

Lipid profile	Patient 1	Patient 2	Patient 3	Patient 4
Total cholesterol (mg/dl)	454	409	331	402
LDL (mg/dl)	391	364.7	273	327
VLDL(mg/dl)	41.1	12.6	27	26

Continued.

Lipid profile	Patient 1	Patient 2	Patient 3	Patient 4
TG (mg/dl)	174	70.1	107	132
HDL (mg/dl)	27.8	30.3	36.4	49
Symptoms	Asymptomatic	Effort Angina	Asymptomatic	Asymptomatic

Table 4: Dutch lipid clinic network diagnostic criteria for familial hypercholesterolaemia criteria.

Parameters	Score
Family history	
First-degree relative with known premature (men aged <55 years; women <60 years) coronary or vascular disease or first-degree relative with known LDL-C above the 95th percentile	1
First-degree relative with tendinous xanthomata and/or arcus cornealis, or children aged <18 years with LDL-C above the 95th percentile	2
Clinical history	
Patient with premature (men aged <55 years; women <60 years) CAD	2
Patient with premature (men aged <55 years; women <60 years) cerebral or peripheral vascular disease	1
Physical examination	
Tendinous xanthomata	6
Arcus cornealis before age 45 years	4
LDL-C levels (without treatment)	
LDL-C ≥8.5 mmol/l (≥325 mg/dl)	8
LDL-C 6.5-8.4 mmol/l (251-325 mg/dl)	5
LDL-C 5.0-6.4 mmol/l (191-250 mg/dl)	3
LDL-C 4.0-4.9 mmol/l (155-190 mg/dl)	1
DNA analysis	
Functional mutation in the LDLR, apo-B, or PCSK9 genes	8
Choose only one score per group, the highest applicable; diagnosis is based on the total number of points obtained	
A 'definite' FH diagnosis requires >8 points	
A 'probable' FH diagnosis requires 6-8 points	
A 'possible' FH diagnosis requires 3-5 points	

DISCUSSION

Homozygous familial hypercholesterolemia (HoFH) is a rare and life-threatening disease which clinically manifests as extensive tendon and tuberous xanthomas, xanthelasma, corneal arcus, markedly premature and progressive atherosclerotic CVD.[6] Most patients develop CAD and aortic stenosis before the age of 20 years and die before 30 years of age.[4] Diagnosis of Familial Hypercholesterolemia was done using Dutch lipid clinic network diagnostic criteria for familial hyper-cholesterolemia criteria as shown in (Table 4).[7]

Cholesterol lowering treatment should be initiated as soon as possible after a diagnosis has been made and maximally tolerated pharmacological therapy must be maintained throughout the life.[5] In FH patients at very high risk of ASCVD due to a prior history of ASCVD (atherosclerotic cardiovascular disease) or another major risk factor, LDL-C goals are a ≥50% reduction of LDL-C from baseline and an LDL-C <1.4 mmol/l (<55 mg/dl).[5] In the absence of ASCVD or another major risk factor, patients with FH are categorized as high-risk, and LDL-C goals are a ≥50% reduction of LDL-C from baseline and an LDL-C <1.8 mmol/l (<70mg/dl).[5,8] PCSK9 inhibitors lower LDL-C levels by up to 60% on top of statins. Treatment should be initiated with high-intensity statin therapy, in most cases in combination with ezetimibe.[5] PCSK9 inhibitors are recommended in very-high-risk patients with FH if the treatment goal is not achieved on maximal tolerated statin plus ezetimibe.[5,9] PCSK9 inhibitors are also recommended in FH patients who cannot tolerate statins.[5,10] In current case series three patients were started on rosuvastatin 40 mg, one patient received atorvastatin 80 mg which was later switched over to rosuvastatin 40 mg and all patients received ezetimibe 10 mg and underwent cardiovascular interventions as discussed above. Due to non-availability of PCSK-9 inhibitors and also due to financial constraints, lipid apheresis could not be done. Patients are on follow up, three of them are free of angina. Case 2 patient underwent repeat angiogram for new onset angina and underwent repeat angiogram which showed patent stents but significant lesion in LMCA extending to LAD and underwent which PTCA with stenting to LMCA to LAD. Serum LDL-C levels of all the patients remained high.

CONCLUSION

Familial hypercholesterolemia leads to development of life-threatening manifestations early in the second and third decades of life. Early diagnosis, aggressive treatment of hypercholesterolemia and control of risk factors and cascade screening are important in management of these patients and will help to reduce the morbidity and mortality associated with this disease.

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