Case report

Coronary heart disease secondary to familial hypercholesterolemia: A fast killer.

ABSTRACT

Familial hypercholesterolemia is an autosomal disorder characterized by increased levels of total cholesterol and low density lipoprotein cholesterol. The FH clinical phenotype has been shown to be associated with increased coronary heart disease and premature death. We report two cases of homozygote familial hypercholesterolemia (IIa) in brothers, presenting coronary artery disease at an early age, with a very disturbed lipid profile. Rapidly progressive and diffuse coronary lesions, with the occurrence of early death in both brothers before the age of 30.

KEYWORDS

Familial hypercholesterolemia, Dyslipidemia, coronary heart disease, Xanthoma,

ABBREVIATIONS

ACS: Acute coronary syndrome
CHD: Coronary heart disease
CVD: cardiovascular disease
FH: Familial hypercholesterolemia
HDL: high-density lipoprotein
HoFH: Homozygous familial hypercholesterolemia
HF: heart failure
LDL: low-density lipoprotein
LDLR: low-density lipoprotein Receptor
LVEF: Left ventricular ejection fraction
MI: myocardial infarction
PCSK9: proprotein convertase subtilisin/kexin type 9
TC: Total cholesterol
TG: Triglycerides

1. INTRODUCTION

Familial hypercholesterolemia (FH) is a common genetic cause of premature coronary heart disease (CHD), mainly myocardial infarction (MI) and angina pectoris, due to lifelong elevated plasma low-density lipoprotein (LDL) cholesterol levels. (1) If left untreated, men and women with heterozygous FH with total cholesterol levels of 8–15 mmol/L (310–580 mg/dL) typically develop CHD before the age of 55 – 60 years, respectively, while homozygote with total cholesterol levels of 12–30 mmol/L (460–1160 mg/dL) typically develop CHD very early in life and if untreated and die before the age of 20. However, once diagnosed, heterozygote can readily be treated with cholesterol lowering medication to attenuate development of atherosclerosis and to prevent CHD. (2)

Diagnosis of FH relies on five criteria: family history, clinical history of premature CHD, physical examination for xanthomas and corneal arcus, very high LDL cholesterol on repeated measurements, and/ or a causative mutation detected by molecular genetics (3) . Secondary causes of hyperlipidaemia must be excluded by determining that liver enzymes, renal function, and thyroid hormones are normal and that there is no hyperglycemia or albuminuria.(1) FH remains largely under diagnosed, often undertreated , even under optimal medical treatment, some will develop coronary atherosclerosis, MI and require revascularization. The management of revascularization in this population is extremely understudied. The authors propose 2 cases of familial hypercholesterolemia among 2 brothers.

2. CASE PRESENTATION

Case 1: A.M. is a 28-year gentleman with a context of 1st degree consanguinity, with a medical history of type I diabetes since the age of 21 years treated by insulin; a history of familial hypercholesterolemia type IIa (according to Frederickson Classification of dyslipidemias) since the age of 10 years under Atorvastatine 80 mg, the patient had stopped this treatment, 2 months before his presentation. History of familial hypercholesterolemia was present in fact his brother who was diagnosed as well with familial hypercholesterolemia type

IIa. The parents didn't present any history of CAD. There were two cases of unexplicated death in the family concerning 2 uncles before the age of 55 years.

In 2018 the patient presented with a symptomatology made of exercise-induced angina evolving for 4 months, complicated by resting angina occurring 18 hours prior to admission. The patient did not have shortness of breath, palpitations or syncope. Upon examination the patient was clinically stable with a pulse rate of 105 ppm, normal blood pressure, without any signs of heart failure. Bilateral carotid artery bruit was present. He had multiple xanthomas over elbows, knees , Achilles tendon, foot and his hand fingers (figure 1).

His ECG showed an ST elevation with Q wave of necrosis in inferior territory. Echocardiography showed a hypokinesia of the inferior wall and inferolateral. His left ventricular ejection fraction(LVEF) by Simpson method was at 58%. The lipid profile revealed a total cholesterol (TC) of 7,04 g/l; an LDL of 5,84 g/l, a high-density lipoprotein (HDL) of 0,97 g/l , and triglycerides (TG) of 1,13 g/l. His Troponin IC level was 36.57ng/dl. The haemogram and rest of biochemical investigations were normal.

His coronary angiography revealed a very atheromatous left coronary network with multiple insignificant diffuse plaques. an intermediate stenosis of 50% at the level of the diagonal artery. The right coronary artery was difficult to intubate, with a very tight stenosis in its middle segment, with an indication for a stent angioplasty, which the patient refused (anxious, restless, did not tolerate the femoral puncture well, refused to continue and resume the procedure), he was discharged under medical treatment, including double platelet antiaggregation by aspirin and clopidogrel, a high dose of statins (Atorvastatin 80 mg).

In 2020, the Evolution was marked by the worsening of his clinical case with recurrent angina, he had stopped all his treatment for 6 months. The control of his lipid profile showed a TC of 7,40 g/l; an LDL of 6,52 g/l, a HDL of 0,27 g/l , and TG of 1,23 g/l. His Troponin IC level was 0.01 ng/dl at 2 measurements.

A second coronarography was performed after sedation, The coronary network was very atheromatous and calcified, At the level of left coronary network, there was a tight long stenosis of the circumflex artery With a tight stenosis of the anterior interventricular artery at its middle segment. there was also a tight stenosis of the diagonal artery which was of small caliber < 2mm. At the level of right coronary artery: there was a sub-occlusive stenosis of the middle segment of the right coronary artery with a TIMI 1 flow and a tight stenosis of the posterior interventricular artery which is of small diameter <2.5 mm, a reperfusion of the distal segment of the right coronary artery was ensured by a collateral of the left network.

Over a period of 2 years, the coronary lesions rapidly progressed from a monovessel status concerning the right coronary artery to diffuse trivessel lesions. After multidisciplinary consultation, it was decided to propose the patient for triple coronary artery bypass surgery after normalization of the lipid profile to avoid recurrences on the arterial graft. The patient was put on a combination of ezetimibe and high-dose statins. Unfortunately the patient died soon after by cardiac arrest at home in october 2020.

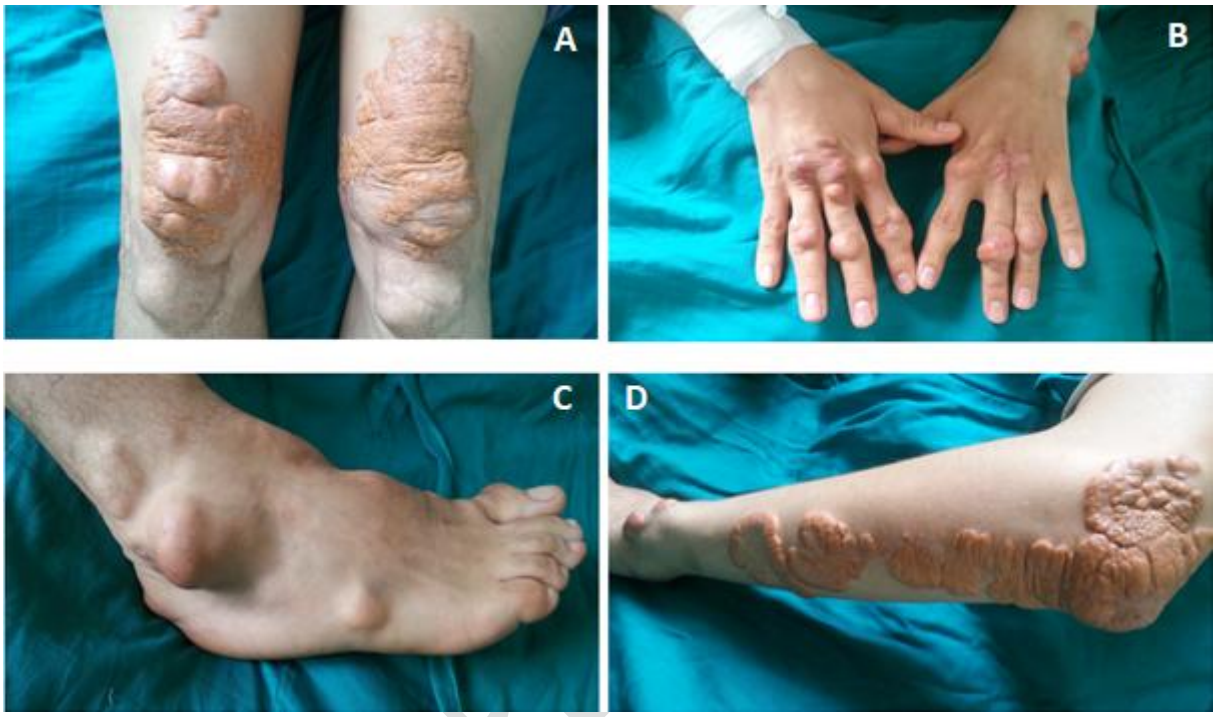

Figure 1: multiple xanthomas over knee (A), Hand fingers (B), Achilles tendon and foot (C) and elbow (D)

Case 2: The second brother O.M is a 26-year gentleman having as a medical history a familial hypercholesterolemia type IIa diagnosed at the age of 8 years, goiter under levothyroxine, coronary artery bypass surgery in 2012 after acute coronary syndrome (ACS) revealing a MI.

In Juin 2020 the patient presented with a symptomatology made of exercise-induced dyspnea for 2 months and resting dyspnea occurring 3 days prior to admission. However, he did not have angina, palpitations or syncope. Upon examination the patient had a pulse rate of 110/min, a blood pressure at 90/50mmHg, signs of heart failure represented by bilateral lower limb oedema, and bilateral crepitant rales. He had multiple xanthomas over both elbows, hand fingers with surgery scars of xantoma removal on the dorsal surfaces of his left hand, as well as left xanthelasma palpebrarum (figure 2).

His ECG showed a sub-shift of the ST segment with negative T waves in the lateral and inferior territories. Echocardiography showed a very dilated left ventricle with severe hypo contractility and an LVEF of 23%. A restrictive mitral flow with elevated left ventricular filling pressure. A moderate mitral regurgitation, A calcified aortic valve with a low flow- low gradient aortic stenosis associated to a mild to moderate aortic regurgitation. The right ventricle was dilated with systolic dysfunction, as the tricuspid annular plane systolic excursion (TAPSE) was at 12 mm and pic systolic annular tricuspid S' Wave at 6cm/s. Pulmonary arterial pressure was estimated by Doppler tricuspid regurgitation flow at 64mmHg. The inferior vena cava was dilated at 23 mm.

The lipid profile revealed a total cholesterol of 2.28 g/l, an LDL of 1.64 g/l, a high-density lipoprotein (HDL) of 0.19g/l, and triglycerides (TG) of 2.57g/l.

His coronary angiography revealed a significant stenosis of the common trunk, a significant long stenosis of the anterior interventricular artery in its proximal segment including the origin of the 1st diagonal with a pathological downstream bed, a chronic occlusion of the distal segment of the anterior interventricular artery protected by the Left internal mammary artery bypass. A long and chronic occlusion of the middle segment of the circumflex artery protected by the bypass. Tight stenosis of both proximal and distal segments of the right coronary artery.

The patient was put under diuretics and potassium supplementation for the treatment of volume overload. He also received Aspirin, high dose of Atorvastatine. We introduced only low doses of Angiotensin converting enzyme inhibitors, nor Mineralocorticoid receptor antagonists because of low blood pressure. The evolution was marked by initial improvement of heart failure signs. The patient was discharged under oral diuretics. The patient presented a cardiac arrest 2 weeks after.

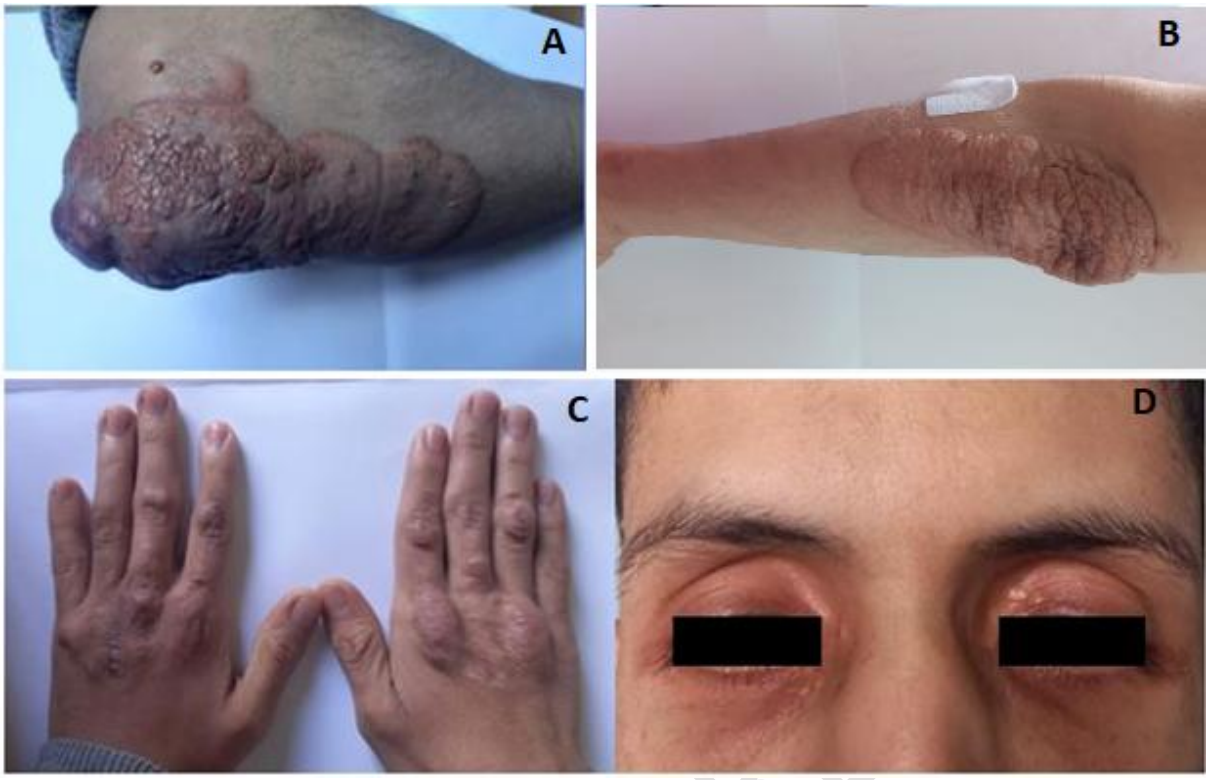

Figure 2 : Multiples xanthomas over Rright elbow (A), Left elbow (B), Hand fingers with surgery scars of xantoma removal on the dorsal surfaces of the left hand and left xanthelasma palpebrarum (D)

3. DISCUSSION

FH in its heterogenic form is a common monogenic dyslipidaemia causing premature cardiovascular disease (CVD) due to lifelong elevation of plasma levels of LDL-C. If left untreated, Patients develop CAD at an early age. (7)

FH is a monogenic disease caused by loss of function mutations in the LDL Receptor (LDLR) or apoB genes or a gain of function mutation in the PCSK9 gene; 95% of FH is caused by mutations in LDLR. More than a thousand different mutations have been identified in LDLR causing FH. The different mutations cause reduced function or complete loss of function. Complete loss of receptor function is associated with more severe disease. A total of 4–5% of FH is caused by mutations in apoB causing reduced binding to LDLR and 1% is caused by mutations in PCSK9 causing increased catabolism of LDLR. (7)

The diagnosis of FH is in most cases based on the clinical picture. Different criteria for the diagnosis have been developed. The commonly used criteria from the Dutch Lipid Clinic Network (DLCN) (4,5) Clinical diagnosis is based on :

- Family history of hypercholesterolemia, premature coronary artery disease or other CVD, xanthomas or corneal arches
- Personal history of coronary artery disease, CVD
- Clinical examination: skin xanthomas or corneal arches
- LDL-C level
- Genetic mutations: 60 to 70% of cases (polygenic or unidentified genes).

Family screening is recommended in case of presence of indexes: (personal or family history of premature coronary artery disease, cutaneous xanthomas, high level of TC>3,1 g/l, family history of sudden death). (4,5) .

Homozygous FH (HoFH) is a rare and life-threatening disease. The clinical picture is characterized by extensive xanthomas, marked premature and progressive CVD and total cholesterol 13 mmol/L (500 mg/dL). Most patients develop CAD and aortic stenosis before the age of 20 years and die before 30 years of age. The frequency of HoFH is estimated to be 1/160 000–1/300 000. The early identification of these children and prompt referral to a specialized clinic is crucial. The patients should be treated with available cholesterol lowering drugs and, when available, with lipoprotein apheresis.(6)

As familial hypercholesterolemia is already considered at high-risk, the SCORE system is not applicable in this population of patient and need intensive risk factor advice and management.(7)

Both cases that we presented in our article suffered from acute coronary syndrome (ACS) in a context of a familial hypercholesterolemia. Data from specific trials (8 – 10) and meta-analysis support routine early use of prompt, intensive and prolonged statin therapy. Thus we recommend Early, intensive and prolonged statin use is recommended during the first 1-4 days of ACS hospitalization; therapeutic goal is LDL-C of 0.55 g/L or a 50% reduction in LDL-C. If LDLc goals are not achieved on maximum tolerated dose of statins, eczemetide may be considered in combination with statins. If goals are not achieved on eczemetide alone or in combination with the maximum tolerated dose of statins, PCSK9 inhibitors may be considered in combination with statins and alone or in combination with ezetimibe in case of statin intolerance or contraindications. Lipids should be reassessed 4 to 6 weeks after ACS to verify therapeutic goals and adjust therapy.

In patients undergoing PCI (7), High-dose statin pre-medication (2 weeks) in statin-naïve patients or loading dose in patients on background statin therapy should be considered in patients undergoing PCI for unstable angina or NSTEMI, it reduces the risk of MI and adverse events over 30 days. While High-dose statin pretreatment or loading before primary or delayed PCI for ST elevation MI (STEMI) requires further study (7). Statin pretreatment is also effective in reducing the risk of contrast-induced acute kidney injury after coronary angiography.

The onset of heart failure (HF), FH increases the risk of mortality and morbidity three to four times compared with patients without FH, among patients with coronary artery disease caused by a FH the installation of a heart failure is considered as a poor prognostic factor. (7)

The second case noted that our patient had a severe aortic stenosis associated; in fact, aortic stenosis increases the risk of CV events and mortality. Suggestions for an association between aortic stenosis, LDL-C and Lp(a), as well as between cholesterol and increased risk for calcification of bioprosthetic valves, were reported. (11,12)

The Scottish Aortic Stenosis and Lipid Lowering Trial, Impact on Regression (SALTIRE; 155 patients, 80 mg atorvastatin or placebo), the SEAS (1873 patients, simvastatin 40 mg plus ezetimibe 10 mg or placebo) and the Aortic Stenosis Progression Observation: Measuring Effects of Rosuvastatin (ASTRONOMER; 269 patients, rosuvastatin 40 mg or placebo) trials failed to show a reduction in the progression of aortic stenosis or related events in patients with mild to moderate aortic stenosis. Notably, ischaemic events were reduced by 21% in the SEAS trial. Furthermore, in a post hoc analysis of the RCTs Incremental Decrease In Endpoints Through Aggressive Lipid-lowering Trial (IDEAL) and Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL), high-dose versus usual-dose statin therapy or placebo did not impact the incidence of aortic valve stenosis among patients without known aortic valve stenosis. (13)

A Chinese study that investigated the prevalence and treatment of FH in young patients admitted for STEMI, the patients classified as possible FH were younger, were multi-truncular with a higher risk of cardiogenic shock and congestive HF, and alarmingly, at 1 year they were less likely to achieve LDL targets. (14)

In the pnset of CAD associated to FH: The first question to ask is the interest of conducting a primary coronary intervention(PCI). PCI in patients with FH in STEMI or NSTEMI is not controversial. But in case of chronic coronary syndrome the studies carried out, including the COURAGE study and the FAME study, were conducted in the general population. The benefit of PCI in this population with stable angina remains unclear. The second question is surely how to intervene, PCI or CABG? If we apply the same reasoning to FH patients as to diabetic and multi-vessels patients with high syntax score as reported in the 2018 ESC recommendations for myocardial revascularisation, aorto-coronary bypass surgery appears to be more beneficial, particularly arterial bypass surgery, given the young age and the inevitable and continuous deterioration of venous bypass surgery associated to a patency rate of less than 60% at 10 years. (15)

As we saw in our cases presentations, the two brothers died at a young age (late twenties) due to severe coronary artery disease and related complications including heart failure. This can give us an idea on the prognosis of these patients who suffer from FH. Some studies discussed the prognosis after revascularization, an Australian study concluded to that patients with probable or definite FH faced an approximate 2-fold increased risk for long-term MACE compared with patients without FH despite the widespread use of high-intensity statins. The new option of proprotein convertase subtilisin/kexin type 9 gene (PCSK9) inhibitors in addition to other current optimal lipid-lowering strategies might help to further improve clinical outcome in patients with probable/definite FH. (16)

4. CONCLUSION

FH is a serious genetic disease, under-diagnosed and under-treated ; certainly it's a rare affection but it remains difficult to treat and a life threathning disease ; current management is aimed at primary and secondary prevention of CV events (statins, ezetimibe and PCSK9 inhibitors). Revascularization in FH is extremely understudied and the optimal interventional approach for these patients is poorly understood. The main remaining questions concern the indications and techniques of revascularization, PCI or bypass ; as well as corresponding outcomes in comparison to medical therapy. For a better treatment of these patients, longitudinal interventional studies should be done among the FH population.

COMPETING INTERESTS DISCLAIMER:

Authors have declared that no competing interests exist. The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

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