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, Homozygous familial hypercholesterolemia, Dyslipidemia, coronary heart disease, Xanthoma.

ABBREVIATIONS

ACS: Acute coronary syndrome
CABG: coronary artery bypass graft
CHD: Coronary heart disease
CVD: cardiovascular disease
ESC: European Society of Cardiology
FH: Familial hypercholesterolemia
HDL: high-density lipoprotein
HoFH: Homozygous familial hypercholesterolemia
HF: heart failure
LDL: low-density lipoprotein
LDLc: low-density lipoprotein cholesterol
LDLR: low-density lipoprotein Receptor
LIMA: Left internal mammary artery
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 cholesterol (LDLc) levels (1). When untreated, men and women with heterozygous FH and total cholesterol levels of 8–15 mmol/L (310–580 mg/dL) typically develop CHD before the age of 55 – 60 years, respectively. While patients with homozygote FH and total cholesterol levels of 12–30 mmol/L (460–1160 mg/dL) typically develop CHD very early in life and die before the age of 30. However, once diagnosed, heterozygote FH can readily be treated with cholesterol lowering medication to attenuate development of atherosclerosis and to prevent CHD. In the contrary homozygote FH can be very difficult to treat and the prognosis is worse (2).

Diagnosis of FH relies on five criteria: family history, clinical history of premature CHD, physical examination for xanthomas and corneal arcus, very high LDLc on repeated measurements, and/ or a causative mutation (3). Secondary causes of hypercholesterolemia 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 and often undertreated. Even under high doses of lipid-lowering therapy, some patients will develop coronary atherosclerosis, MI and require revascularization that can be challenging because of diffuse atherosclerosis and the risk of recurrence. The management of revascularization in this population is extremely understudied. We present 2 cases of familial hypercholesterolemia among 2 brothers, who developed severe CHD at an early age that led to rapid death.

2. CASE PRESENTATION

Case 1: A male patient of 28 years old with a context of 1st degree consanguinity, a medical history of type I diabetes diagnosed at the age of 21 years treated by insulin; a history of FH type IIa (according to Frederickson Classification of dyslipidemias) diagnosed at the age of 10 years treated by Atorvastatine 80 mg, with poor adherence to this treatment. The patient had stopped the treatment 2 months before his presentation. History of FH was present in his brother as well. His parents didn't present any history of CAD and didn't show any symptoms or physical signs of dyslipidemias. There were two cases of unexplicated death in the family concerning 2 uncles before the age of 55 years.

In 2017 the patient presented to the emergency department with a symptomatology made of resting angina evolving since 18 hours prior to admission, preceded by multiples episodes of exercise-induced angina starting 4 months before. The patient did not have any other symptoms (no shortness of breath, no palpitations, no syncope). Upon examination the patient was clinically stable with a pulse rate of 105 ppm, normal blood pressure, without any signs of heart failure. There were no abnormal murmurs on auscultation of the vascular system. He had multiple xanthomas over both elbows, both knees, over the dorsal side of both feet, on Achilles tendons and his over both hand fingers (figure 1).

His ECG showed an ST-segment elevation with Q wave of necrosis in inferior territory. Echocardiography showed a hypokinesia of the inferior and infero-lateral walls with a left ventricular ejection fraction (LVEF) estimated at 58% by 2D-Simpson method. The blood test showed an abnormal lipid profile with a total cholesterol (TC) at 7,04 g/l, an LDLc at 5,84 g/l, a high-density lipoprotein (HDL) at 0,97 g/l and triglycerides (TG) at 1,13 g/l. His Troponin Ic level was at 36.57ng/dl. The haemogram and the rest of blood test 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 anti-aggregation therapy by aspirin and clopidogrel and a high dose of statins (Atorvastatin 80 mg).

In 2018, the Evolution was marked by a worsening of his clinical case with recurrent angina, he had stopped all his treatment for 6 months. The ECG have shown Q waves of necrosis in

the inferior territory with electrical LV hypertrophy and negative T waves in lateral territory (figure 2). The control of his lipid profile showed a TC at 7,40 g/l; an LDLc at 6,52 g/l, a HDLc at 0,27 g/l and TG at 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. In the left coronary network, there was a long and tight stenosis (70-90%) of the circumflex artery at its middle segment extended to the first marginal artery. With another tight stenosis (70-90%) of the anterior interventricular artery at their middle segments. there was also a tight stenosis (70-90%) of the first diagonal artery which was of small caliber < 2mm. In the right coronary network, there was a sub-occlusive stenosis (90-99%) of the middle segment of the right coronary artery with a TIMI 1 flow and a tight stenosis (70-90%) 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 collateral flow from the left network. (figure 3 is a representation of his coronary artery lesions)

Over a period of 1 year, coronary artery lesions rapidly progressed from a mono-vessel status concerning only the right coronary artery to diffuse severe tri-vessel 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 rapid atheroma formation on the arterial graft. The patient was put on a combination of ezetimibe and high-doses of statins. Unfortunately, the patient died soon after by cardiac arrest at home.

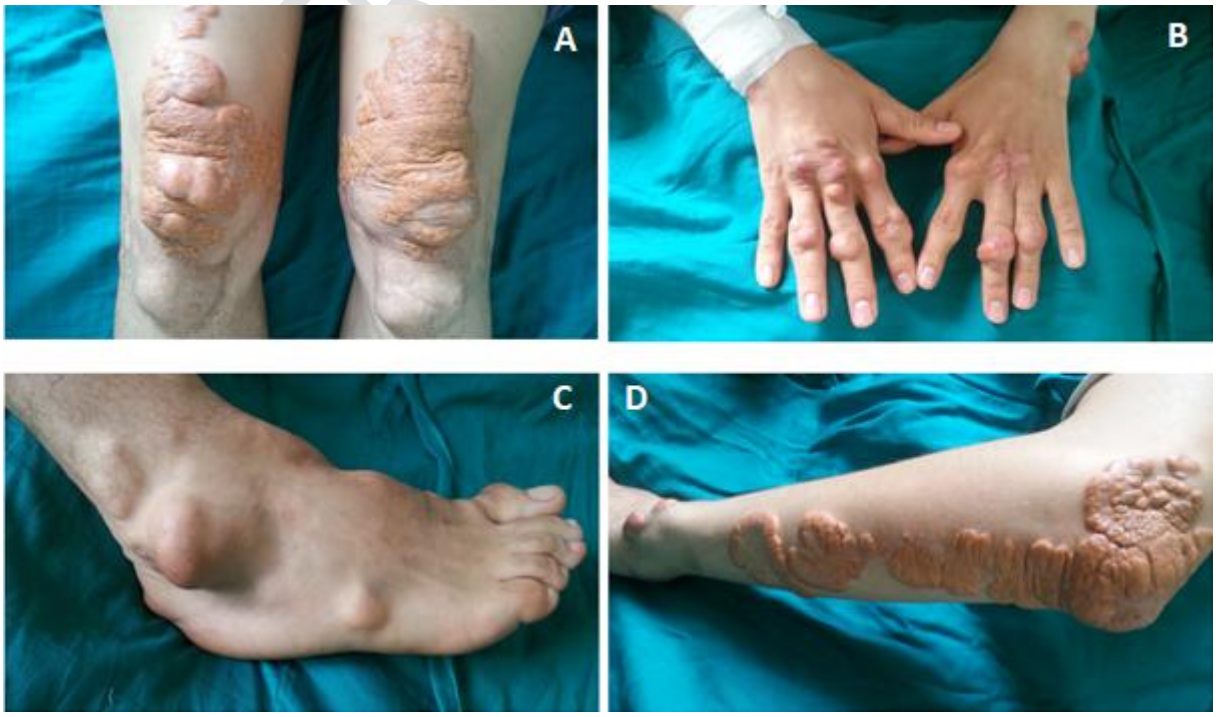

Figure 1: multiple xanthomas over knee (A), Hand fingers (B), Achilles tendon and foot (C) and elbow (D)

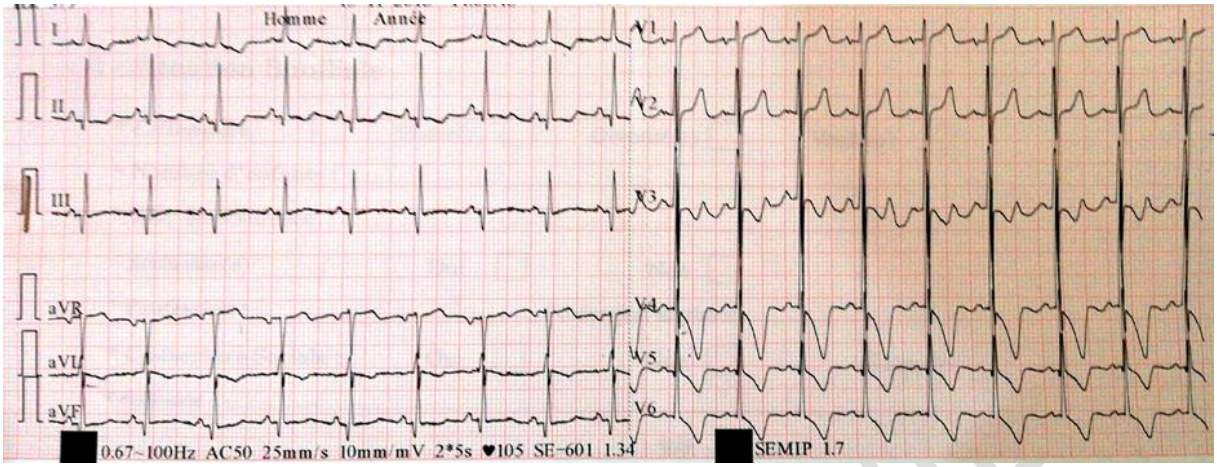

Figure 2: ECG of the patient showing Q wave of necrosis in the inferior territory with electrical LV hypertrophy and negative T waves in lateral territory.

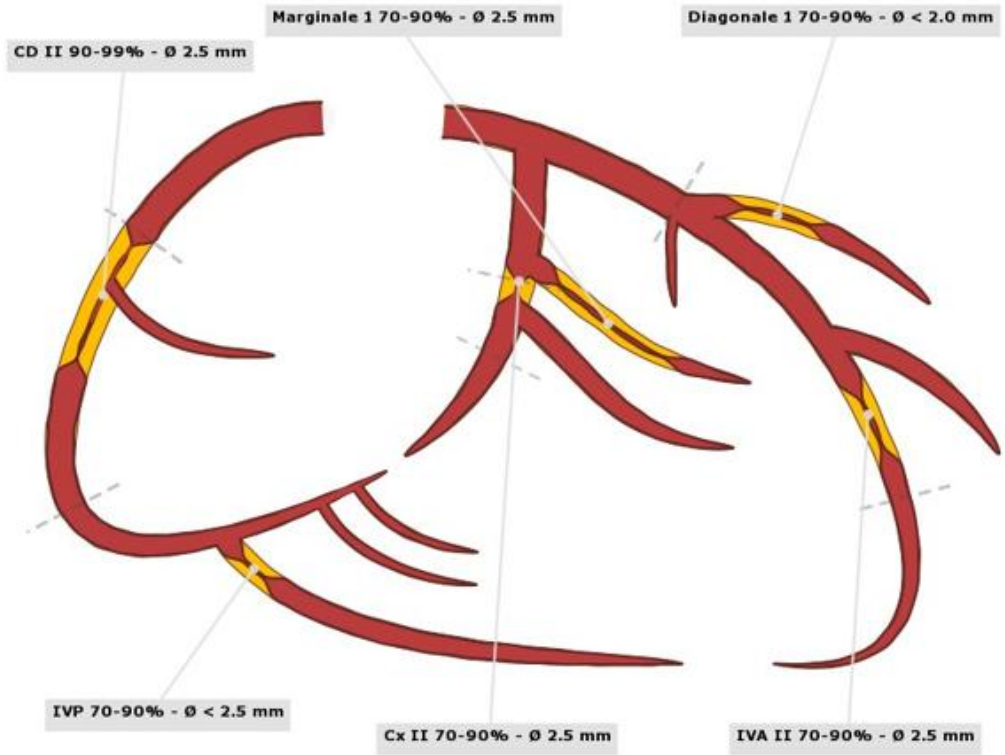

Figure 3: schematic representation of the patient's coronarography showing diffuse tri-vessel and severe coronary disease.

*CD: Right coronary artery; Cx: Circumflex artery, IVA: anterior interventricular artery

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

In June 2020, the patient presented with a symptomatology made of exercise-induced dyspnea evolving for 2 months complicated by an aggravating dyspnea occurring 3 days prior to admission. The patient did not present any angina, palpitations or syncope. Upon examination the patient had a pulse rate of 110/min, a blood pressure at 90/50 mmHg. He had signs of heart failure represented by bilateral lower limb oedema and bilateral crepitant rales at the base of both lungs. He had multiple xanthomas over both elbows, over both hand fingers with surgery scars of xantoma removal on the dorsal surfaces of his left hand, as well as left xanthelasma palpebrarum (figure 4).

His ECG showed electrical LV hypertrophy with a sub-shift of the ST segment in the lateral and inferior territories and atypical elevation of the ST-segment in V2-V3 (Figure 5). Echocardiography showed a very dilated left ventricle with severe global hypo-contractility and a LVEF estimated at 23%. In addition, echocardiography showed a restrictive mitral flow with elevated left ventricular filling pressure, moderate mitral regurgitation, 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 at 2.28 g/l, an LDLc at 1.64 g/l, a HDLc at 0.19g/l, and triglycerides (TG) at 2.57g/l. His Troponin Hs was at 176 ug/l.

His coronary angiography revealed a significant stenosis (70-90%) of the common trunk, a sub-occlusive long stenosis (90-99%) of the anterior interventricular artery in its proximal and middle segments 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 (LIMA) bypass. A long and chronic occlusion of the middle segment of the circumflex artery protected by the LIMA bypass. Tight stenosis (70-90%) of the intermediate artery. Tight stenosis (70-90%) of both proximal and distal segments of the right coronary artery. Non-significant lesion of the proximal segment of the LIMA graft. (Figure 6 is a representation of his coronary artery lesions).

The patient was put under diuretics and potassium supplementation for the treatment of volume overload. He also received Aspirin, high dose of Atorvastatin. We introduced only low doses of Angiotensin converting enzyme inhibitors. Mineralocorticoid receptor antagonists haven't been introduced because of the low blood pressure. The evolution was marked by initial improvement of heart failure signs. The patient was discharged under oral treatment of HF. He presented a cardiac arrest 2 weeks after.

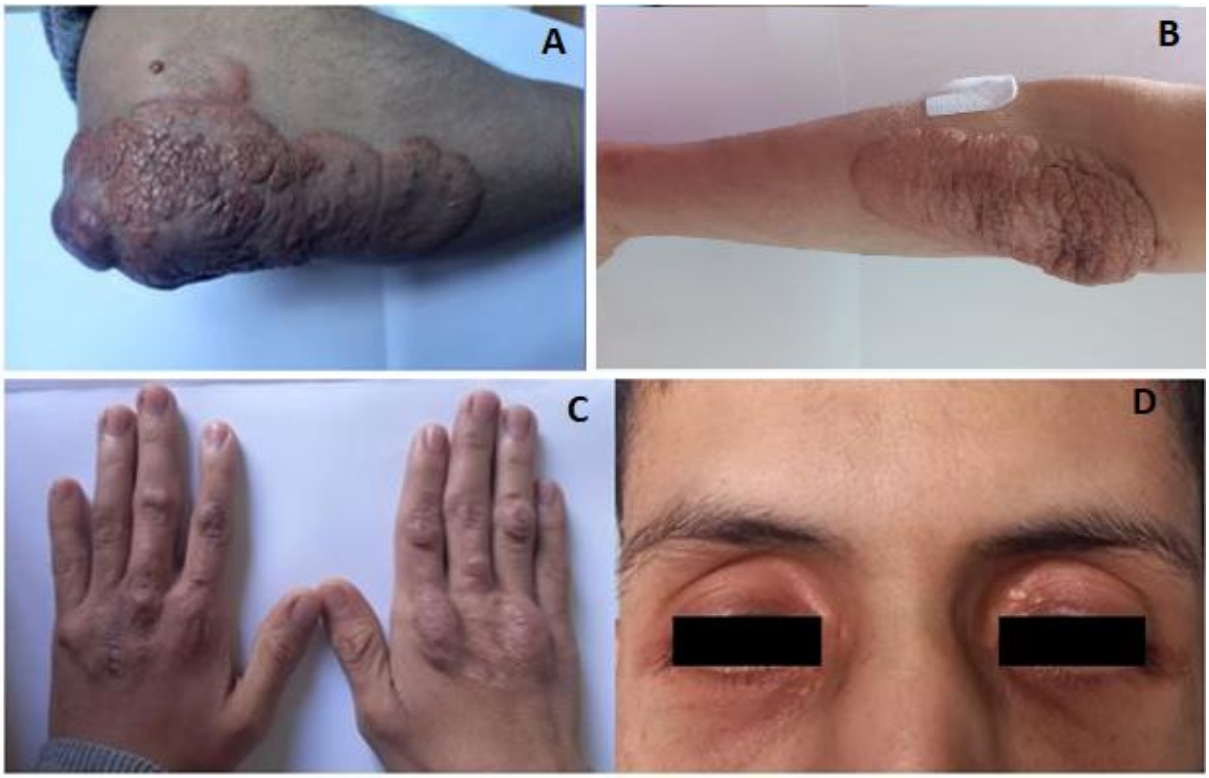

Figure 4: Multiples xanthomas over Rright elbow (A), Left elbow (B), Hand fingers with surgery scars of xantoma removal on the dorsal surfaces of the left hand and left xanthelasma palpebrarum (D)

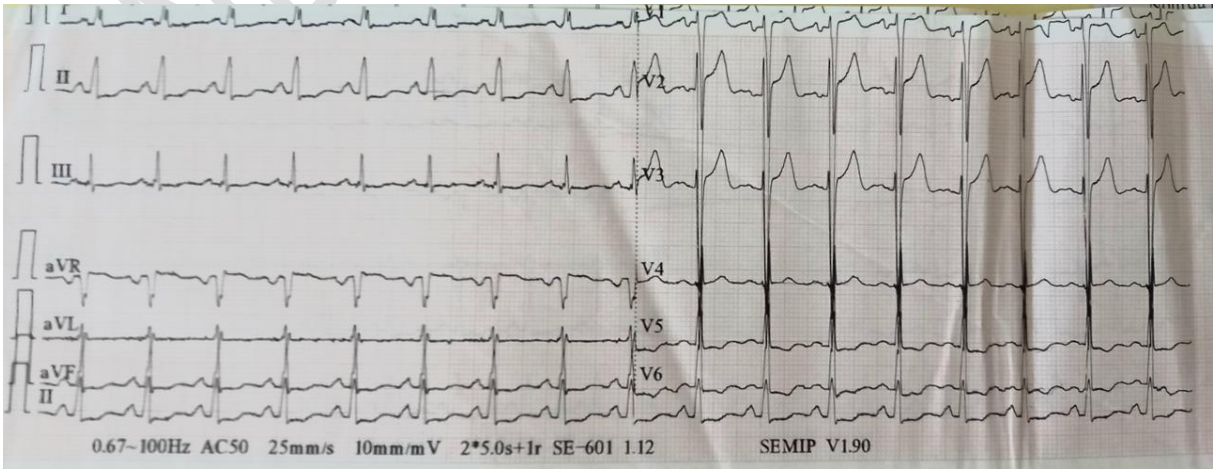

Figure 5: ECG of the patient showing electrical LV hypertrophy with a sub-shift of the ST segment in the lateral and inferior territories. Atypical elevation of the ST-segment in V2-V3. *LV: Left ventricle

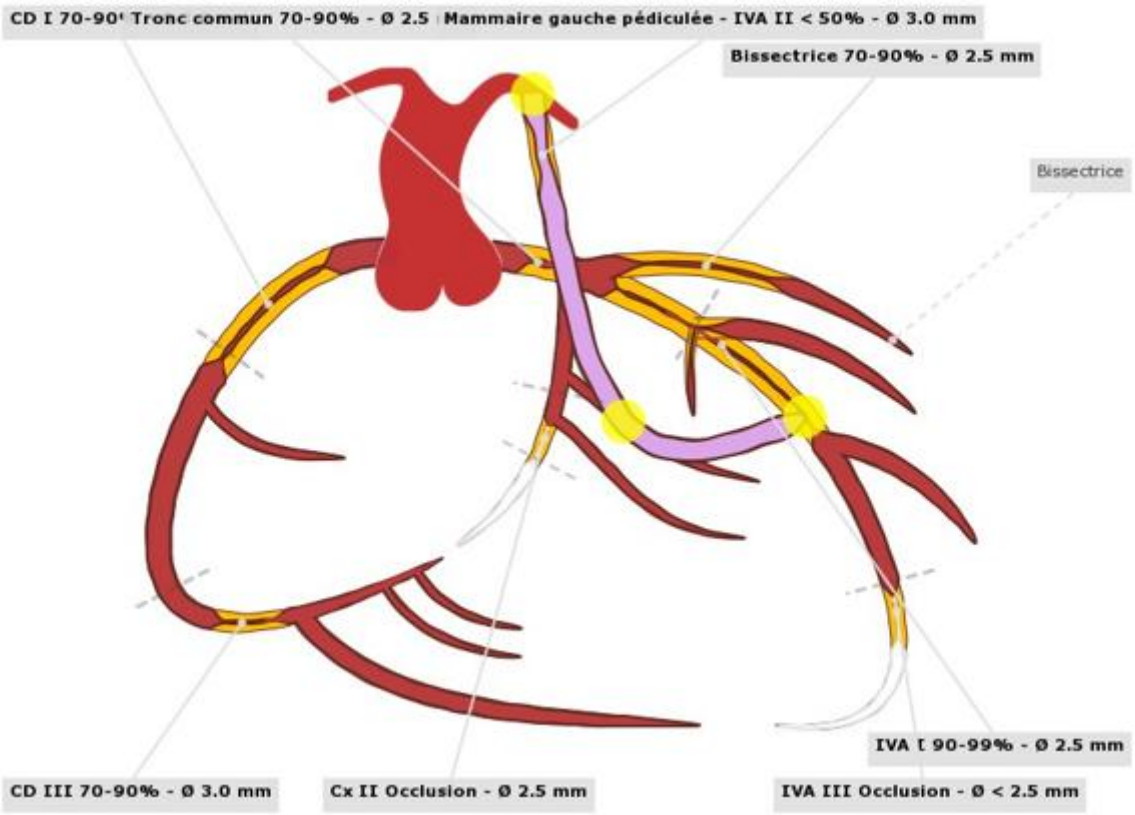

Figure 6: schematic representation of the patient's coronarography showing diffuse tri-vessel and severe coronary disease of the native coronary network with non-significant atheroma of the proximal segment of the left internal mammary artery graft.
*CD: Right coronary artery; Cx: Circumflex artery, IVA: anterior interventricular artery; Bissectrice: intermediate artery)

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. When left untreated, Patients develop CAD at an early age. (7)

FH is a genetic disorder caused by a mutation of the LDL Receptor (LDLR) in 95 % of cases. In this setting, numerous mutations affecting the LDLR have been identified and are responsible for a

reduce or a complete loss the LDLR function. The severity of FH is correlated to the degree of LDLR function impairment. In the other cases, mutations affect the apoB genes in 4–5% causing reduced binding to LDLR or affect the proprotein convertase subtilisin/kexin type 9 gene (PCSK9) gene in 1% 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 diagnostic criteria are those from the Dutch Lipid Clinic Network (DLCN) (4,5). According to those criteria, the 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 the presence of personal or family history of premature coronary artery disease, cutaneous xanthomas, high level of TC>3,1 g/l or family history of sudden death. (4,5).

Homozygous FH (HoFH) is the most serious and rare form of FH. It causes lipid accumulation in vessels and tissues secondary to very high total cholesterol and LDLc levels and causing extensive xanthomas, premature and progressive CVD. CAD and aortic stenosis occur very early in life and are responsible for early death (before 30 years). An early detection of this disease, an adequate and early treatment using high doses of cholesterol lowering drugs and, when available, lipoprotein apheresis may improve the prognosis in this population of patients (6).

As familial hypercholesterolemia is already considered at high-risk of cardiovascular events occurrence, the SCORE system is not applicable in this population of patients. Intensive risk factor advice and management must be carried out in all patients with FH (7).

Both of our patients suffered from acute coronary syndrome (ACS) in a context of a familial hypercholesterolemia responsible for rapid evolving and diffuse coronary artery disease. Data from specific trials and meta-analysis (8 – 10) support routine early use of prompt, intensive and prolonged statin therapy. Thus Early, intensive and prolonged statin use is recommended during the 4-6 weeks after ACS hospitalization; therapeutic goal is LDL-C of 0.55 g/L or a 50% reduction in LDLc. Lipids should be reassessed 4 to 6 weeks after ACS to verify therapeutic goals and adjust therapy. If LDLc goals are not achieved on maximum tolerated dose of statins, Ezetimibe must be recommended in combination with statins. And when LDLc goals are not achieved on Ezetimibe alone or in

combination with the maximum tolerated dose of statins, PCSK9 inhibitors must be recommended in combination with statins or alone or in combination with Ezetimibe in case of statin intolerance or contraindications.

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 occurrence of HF is considered a poor prognostic factor. (7)

In our second patient, echocardiography revealed a severe aortic stenosis. Suggestions for an association between LDLc, Lp(a) and aortic stenosis were described. As well as an association between high cholesterol levels and an increased risk for calcification of bio-prosthetic valves. In addition, aortic stenosis increases the risk of CV events and mortality. (11,12)

Clinical trials haven't showed benefits of lipid-lowering drugs (High dose of statin or Statin plus Ezetimibe) on apparition or progression of mild and moderate aortic stenosis. However ischemic events were reduced by lipid-lowering therapy (13).

In 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 more likely to have multi-vessels coronary lesions and a higher risk of cardiogenic shock and congestive HF. Alarmingly, they also were less likely to achieve LDLc targets at 1 year. (14)

In the onset of CAD management when it is associated to FH, the first question to ask is the interest of conducting a primary coronary intervention (PCI) or not. PCI in patients with FH in STEMI or NSTEMI is not controversial. However, in case of chronic coronary syndrome, most studies; including the COURAGE study and the FAME study; were conducted in the general population. Therefore, the benefit of PCI in FH population with stable angina remains unclear. The second question is surely which revascularization technique should be preferred. PCI or coronary artery bypass graft (CABG)? If we apply the same reasoning to FH patients as for diabetic and multi-vessels patients with high syntax score as reported in the 2018 European Society of Cardiology (ESC) recommendations for myocardial revascularisation, aorto-coronary bypass surgery appears to be more beneficial. Arterial

bypass graft is largely preferred over venous graft, given the young age and the inevitable and continuous deterioration of venous bypass surgery (15). There are insufficient data on the duration of double platelet anti-aggregation therapy after ACS in HoFH patients. However, given rapid evolving and extensive coronary artery lesions, it seems wise to propose a prolongation of double platelet anti-aggregation therapy when the bleeding risk is low.

In our cases presentation, 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 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 undertreated. Certainly it's a rare affection but it remains a life threatening disease, very difficult to treat. Current management aims to achieve primary and secondary prevention of CV events using intensive lipid lowering therapy (statins, ezetimibe and PCSK9 inhibitors). Revascularization in FH is extremely understudied and the optimal interventional approach is not clear in this population of patients. The man remaining questions concern the indications and techniques of revascularization (PCI or CABG), as well as related outcomes in comparison to medical therapy. Further studies focused on FH patients are needed, to better management of these patients.

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.

5. BIBLIOGRAPHY

1. Nordestgaard, B. G., Chapman, M. J., Humphries, S. E., Ginsberg, H. N., Masana, L., … Descamps, O. S. (2013). Familial hypercholesterolaemia is underdiagnosed and undertreated in the general population: guidance for clinicians to prevent coronary heart disease: Consensus Statement of the

European Atherosclerosis Society. European Heart Journal, 34(45), 3478–
3490. doi:10.1093/eurheartj/eht273

2. Versmissen J, Oosterveer DM, Yazdanpanah M, Defesche JC, Basart DC, Liem AH, Heeringa J, Witteman JC, Lansberg PJ, Kastelein JJ, Sijbrands EJ. Efficacy of statins in familial hypercholesterolaemia: a long term cohort study. BMJ 2008;337:a2423.

3. Civeira F. Guidelines for the diagnosis and management of heterozygous familial hypercholesterolemia. Atherosclerosis 2004;173:55–68.

4. Risk of fatal coronary heart disease in familial hypercholesterolaemia. Scientific Steering Committee on behalf of the Simon Broome Register Group. BMJ 1991;303:893 –896.

5. World Health Organization. Human Genetics Programme. Familial hypercholesterolemia: report of a second WHO consultation. WHO/HGN/FH/Cons/992. Geneva: World Health Organization, 1999.

6. Cuchel M, Bruckert E, Ginsberg HN, Raal FJ, Santos RD, Hegele RA, Kuivenhoven JA, Nordestgaard BG, Descamps OS, Steinhagen-Thiessen E, Tybjærg-Hansen A, Watts GF, Averna M, Boileau C, Bore´n J, Catapano AL, Defesche JC, Hovingh GK, Humphries SE, Kovanen PT, Masana L, Pajukanta P, Parhofer KG, Ray KK, Stalenhoef AF, Stroes E, Taskinen MR, Wiegman A, Wiklund O, Chapman MJ. Homozygous familial hypercholesterolaemia: new insights and guidance for clinicians to improve detection and clinical management. A position paper from the Consensus Panel on Familial Hypercholesterolaemia of the European Atherosclerosis Society. Eur Heart J 2014:35:2146 –2157.

7. Mach F, Baigent C, Catapano AL, Koskinas KC, Casula M, Badimon L, et al. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. Eur Heart J. 2020 Jan 1;41(1):111–88.

8. Schwartz GG, Olsson AG, Ezekowitz MD, Ganz P, Oliver MF, Waters D, Zeiher A, Chaitman BR, Leslie S, Stern T. Effects of atorvastatin on early recurrent ischemic events in acute coronary syndromes: the MIRACL study: a randomized controlled trial. JAMA 2001;285:1711 –1718.

9. de Lemos JA, Blazing MA, Wiviott SD, Lewis EF, Fox KA, White HD, Rouleau JL, Pedersen TR, Gardner LH, Mukherjee R, Ramsey KE, Palmisano J, Bilheimer DW, Pfeffer MA, Califf RM, Braunwald E. Early intensive vs a delayed conservative simvastatin strategy in patients with acute coronary syndromes: phase Z of the A to Z trial. JAMA 2004;292:1307 –1316.

10. Ray KK, Cannon CP, McCabe CH, Cairns R, Tonkin AM, Sacks FM, Jackson G, Braunwald E. Early and late benefits of high-dose atorvastatin in patients with acute coronary syndromes: results from the PROVE IT-TIMI 22 trial. J Am Coll Cardiol 2005;46:1405 –1410.

11. Cowell SJ, Newby DE, Prescott RJ, Bloomfield P, Reid J, Northridge DB, Boon NA. A randomized trial of intensive lipid-lowering therapy in calcific aortic stenosis. N Engl J Med 2005;352:2389 –2397.

12. Chan KL, Teo K, Dumesnil JG, Ni A, Tam J. Effect of lipid lowering with rosuvastatin on progression of aortic stenosis: results of the aortic stenosis progression observation: measuring effects of rosuvastatin (ASTRONOMER) trial. Circulation 2010;121:306 – 314

13. Arsenault BJ, Boekholdt SM, Mora S, DeMicco DA, Bao W, Tardif JC, Amarenco P, Pedersen T, Barter P, Waters DD. Impact of high-dose atorvastatin therapy and clinical risk factors on incident aortic valve stenosis in patients with cardiovascular disease (from TNT, IDEAL, and SPARCL). Am J Cardiol 2014;113:1378 –1382

14. Auckle, R., Su, B., Li, H., Xu, S., Xie, M., Song, Y., … Che, W. (2017). Familial hypercholesterolemia in Chinese patients with premature ST-segment-elevation myocardial infarction: Prevalence, lipid

management and 1-year follow-up. PLOS ONE, 12(10), e0186815. doi:10.1371/journal.pone.0186815 10.1371/journal.pone.0186815

15. Neumann, F.-J., Sousa-Uva, M., Ahlsson, A., Alfonso, F., Banning, A. P., Benedetto, U., … Head, S. J. (2018). 2018 ESC/EACTS Guidelines on myocardial revascularization. European Heart Journal. doi:10.1093/eurheartj/ehy394 10.1093/eurheartj/ehy394

16. Tscharre, M., Herman, R., Rohla, M., Piackova, E., Vargas, K. G., Farhan, S., … Huber, K. (2018). Prognostic impact of familial hypercholesterolemia on long-term outcomes in patients undergoing percutaneous coronary intervention. Journal of Clinical Lipidology. doi:10.1016/j.jacl.2018.09.012 10.1016/j.jacl.2018.09.012