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Drug-eluting Stents in Premature Coronary Disease in Young People with Homozygous Familial Hypercholesterolemia and Prior Liver Transplant. A Report of Two Cases

Case Report

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Keywords: Atherosclerosis; Hypercholesterolemia; Stents; Liver; Transplantation.

Abbreviations: FH: Familialhypercholesterolemia; CD: Coronary disease; LDL-c: Low density lipoproteins

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Introduction

Lipoprotein metabolism disorders, as well as high fat diets, obesity and physical inactivity have given rise to an atherosclerotic disease epidemic worldwide. The interaction of these adverse environmental factors with genetic and acquired lipoprotein disorders predispose to an increasingly earlier development of atherosclerosis. In the United States, mortality due to coronary artery disease (CD) in middle aged people has decreased by 31% during the last decade. However, atherosclerotic cardiovascular disease continues to be the most frequent cause of death, both in men and women. The general mortality rate due to cardiovascular diseases is 235.5 per 100,000 population and CD only caused 1 out of 6 deaths in the United States in 2010 [1].

Familial hypercholesterolemia (FH) is an autosomal dominant disease characterized by very high serum cholesterol and low density lipoprotein levels, being clinically expressed intendinous xanthomas and premature atherosclerosis [2]. More than 85% of FH cases are attributable to inherited mutations of the LDL receptor gene (LDLR), of which more than 1,600 mutations have been identified [3]. The LDLR gene mutation leads to defects in LDL-c capture in the blood. Less frequently, FH may also be caused by mutations in the proprotein convertase subtilisin/kexintype 9 (PCSK9) gene, or other rare mutations in related genes [4, 5].

Heterzygous FH is the most common form of the disease (prevalence of approximately 1 in 300 to 500 individuals worldwide, and which can be as high as 1 in 100 individuals in some special populations) [3-6]. Homozygous autosomal dominant FH is a very rare form of the disease (prevalence of 1 in 1 million individuals). Some populations, such as French Canadians, Ashkenazi Jews, Lebanese and Dutch of African origin, are at a higher risk for FH due to the increased prevalence of mutations associated with heterozygous FH [7-10].

FH is characterized by severe hypercholesterolemia which results in premature cardiovascular disease. Individuals with FH have a greater risk of cardiac events such as myocardial infarction and death due to premature CD, especially in patients with severe forms of the disease, if they are not treated [11, 12]. Homozygous FH is a serious and aggressive form of the disease which frequently does not respond to traditional hypercholesterolemia treatment due to the lack of functional LDL-c receptors [12, 13]. In general, the average age at diagnosis of cardiovascular manifestations is 20 years [12]. The elevation of LDL-c levels reflects the severity of the genetic mutation. Patients with heterozygous FH typically present levels double or triple those of healthy individuals (approximately 200-400mg/dL); while patients with homozygous FH have LDL-c levels that may be more than 6-10 times normal values (> 600 mg/dL) [13].

Homozygous FH is associated with coronary artery disease and premature death, with several reports of individuals under 17 years of age who developed severe coronary artery stenosis [2, 14] and supravalvular aortic stenosis [15], an increase in intima-media thickness of the carotid and femoral arteries [16], and tendinous xanthomas caused by cholesterol deposits on tendons and skin, observed mainly on the elbows, knees, Achilles heel, and dorsum of hands and feet. Tendinous xanthomas are highly suggestive of

homozygous FH and are a basic criterion in the clinical diagnosis of this disease. Xanthomas are seen in up to 50% of patients with FH [17]. Excess cholesterol may also be deposited on the cornea, causing pigmentation manifested as a corneal arc.

Patients and Methods

We describe our experience with two young patients who presented to our Interventional Cardiology department in September and October, 2013, with clinical characteristics of homozygous FH and severe CD, and underwent percutaneous myocardial revascularization with drug-eluting stent (DES) implantation.

Case 1

Fifteen year old male (Tables 1 and 2). Presents with a two week history of chest pain and decreased functional class. Clinical presentation on admission was recorded as myocardial infarction without ST elevation, based on positive troponin and electrical changes in the anterior wall. He has a history of homozygous FH (Figure 1) with cutaneous xanthomas (Figure 2), severe hyperlipidemias (LDL-c up to 850 mg/dL), grade 1 arterial hypertension, Ebstein´s Anomaly and WPW syndrome which was ablated in September, 2011. Due to FH and poor control of LDL-c levels he underwent liver transplant in June, 2013. Submaximal stress test was positive for ischemia. Currently being treated pharmacologically with ezetimibe 10mg/day, simvastatin 20mg/day, amlodipine 5mg/day, prednisolone 2.5mg/day and tacrolimus 3mg/day. Coronary angiography shows severe CD in the proximal anterior descending artery and the ostial right coronary. He underwent coronary angioplasty with implantation of 2.25x15mm and 3.0x12mm Resolute Integrity™ (Medtronic Vascular, Santa Rosa, CA) drug-eluting stents, respectively, post-dilation with high pressure non-compliant balloon at 18 atms. (Figures 3 and 4). He was asymptomatic at six month clinical follow-up.

Case 2

Fourteen year old female (Tables 1 and 2). Recent onset of chest pain and dyspnea. History of homozygous FH (Figure 5). A review of the family history shows an extensive history of heterozygous FH and cardiovascular events in both maternal and paternal families. Genetic analysis through LDLR and ApoB gene sequencing showed a homozygous or hemizygous mutation onan

Table 1. Demographic and clinical manifestations of the two cases with homozygous FH.

		Case 1	Case 2
Demographic Factors	Age (years)	15	14
	Sex	M	F
	Race	Hispanic	Hispanic
Clinical criteria	Angina (CCS)	II/IV	III / IV
	Dyspnea (NYHA)	II/IV	IIIIV
	NSTEMI	Yes	No
History	Arterial hypertension (Stage)	1	No
	Total Cholesterol (mg/dL)	575	850
	LDL-c (mg/dL)	573	644
	Ebstein's Anomaly	Yes	No
	WPW Syndrome	Yes - Ablation Sept -2011	No
	Liver transplant	Yes (Jun, 2013)	Yes (Sept, 2013)
	Supravalvular aortic stenosis	Yes	No
Physical exam	Weight (kg)	52	47
	Height (cm)	163	150
	BMI	19.6	20.8
	Blood pressure (mmHg)- average	121/69	100/60
	Heart rate (beats/min) - average	72	88
	Carotid murmur	Yes	No
	Aortic murmur	Yes	No
	Xanthomas	Yes	Yes
	Corneal arc	No	Yes
Blood tests	Hemoglobin (gr/dL)	14.7	11.5
	Hematocrit (%)	45	36.7
	Glycemia (mg/dL)	88	90
	Creatinine (mg/dL)	0.7	0.6
	ALT (U/Lt)	19	33
	AST (U/Lt)	22	25
	GGT /U/Lt)	16	75
	Total cholesterol (mg/dL)	90	170
	Triglycerides (mg/dL)	33	114
	HDL-c (mg/dL)	31	24
	LDL-c (mg/dL)	39	97

Table 2. Paraclinical manifestations of the two cases with homozygous FH.

		Case 1	Case 2
Exam-Images	Ejection fraction (%)	65	70
	Stress test	Positive - Submaximal	No
	Coronary angiography	Yes	Yes
	ECG	Sinus, right bundle branch block pattern ST-T changes	Sinus. ST-T changes
Medications	Ezetimibe	Yes	Yes
	Simvastatin	Yes	Yes
	Amlodipine	Yes	No
	Prednisolone	Yes	No
	Tacrolimus	Yes	Yes
	Aspirin	Yes	Yes
	Clopidogrel	Yes	Yes
	Valgaciclovir	No	Yes
	Metoprolol	No	Yes
Coronary angiography	Ostial lesion	Yes	Yes
	Calcium	Moderate	Moderate
	Proximal LAD	Yes	No
	Right coronary	Yes	Yes
	Circumflex	No	No
	PCI/DES	Yes-2 vessels	Yes - 1 vessel
Non-coronary vascular disease	Carotids	30%	No
	Aorta	Supravalvular stenosis, calcified plaques descending aorta	No
	Renal		No
	Lower limbs	No	No

Figure 1. Family history of the patient (case 1) with homozygous FH.

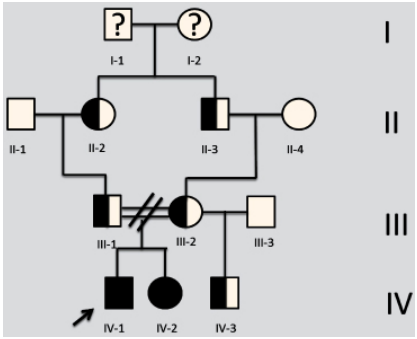


Figure 2. Cutaneous manifestations of FH. Absence of corneal arc (A), tuberous xanthomas on the elbows (B and C), hands (D), knees (E) and Achilles tendon (F).

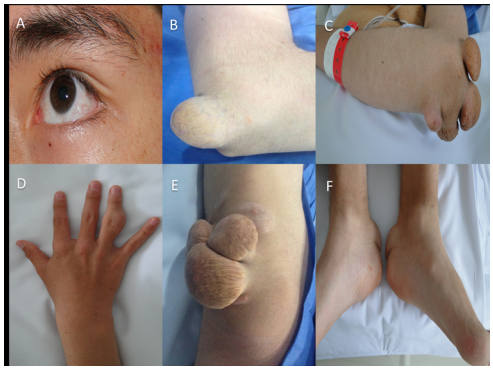


Figure 3. Severe coronary disease in the anterior descending (A), drug-eluting stent implantation (B) and final result (C).

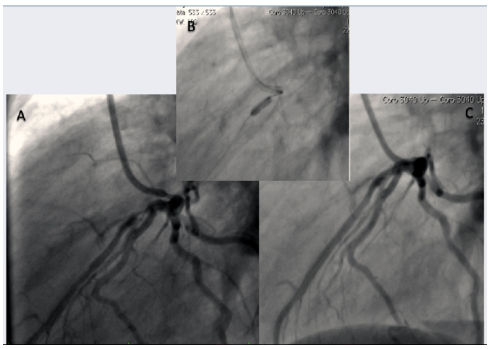


Figure 4. Severe coronary disease in ostial right coronary (A), drug-eluting stent implantation (B) and final result (C).

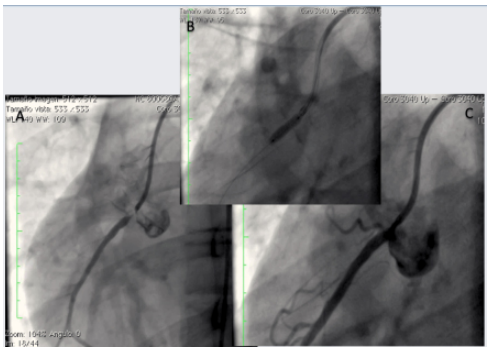


Figure 5. Family history of the patient (case 2) with homozygous FH.

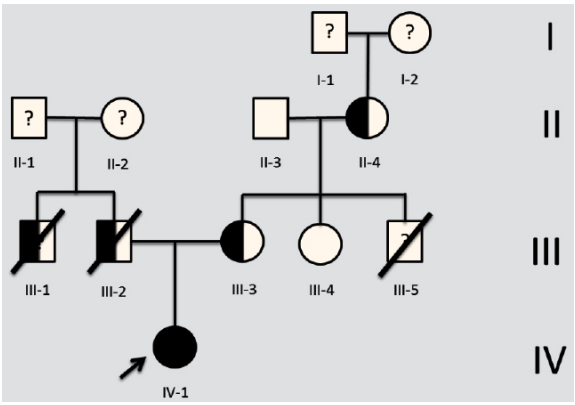


Figure 6. Cutaneous manifestations of FH.Inferior corneal arc (A), planar xanthomas on elbows (A), hands (C), knees (D) and Achilles tendon (E).

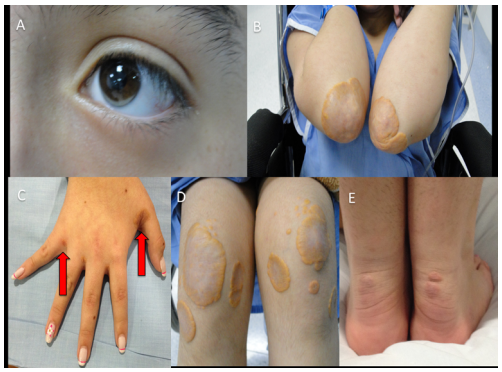
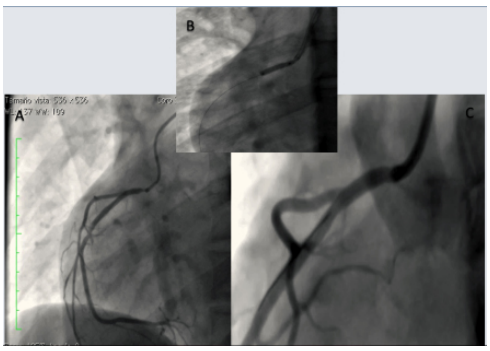


Figure 7. Severe coronary disease in ostial right coronary (A), drug-eluting stent implantation (B) and final result (C).



LDLR intron and a homozygous or hemizygous mutation on an LDLR exon. She presents with cutaneous xanthomas and corneal arc (Figure 6), severe hyperlipidemia (LDL-c up to 610mg/dL) and liver transplant in September, 2013. Currently being treated with ezetimibe 10mg/day, simvastatin 20mg/day, valganciclovir, tacrolimus 3mg/day and ursacol. Coronary angiography showed severe CD in ostial right coronary. Coronary angioplasty was carried out, implanting a 2.5x15 mm Resolute Integrity™ (Medtronic Vascular, Santa Rosa, CA) drug-eluting stent following dilation with a high pressure non-compliant balloon at 16 atms. (Figure 7). She was asymptomatic at six month clinical follow-up.

Discussion

FH is a monogenic, autosomal dominant disorder caused by mutations in the LDL receptor gene. We present two cases of homozygous FH in young people 14 and 15 years of age and severe CD of main vessels (anterior descending and right coronary) who underwent successful DES implantation. They have the particular characteristic of cardiovascular manifestations (chest pain) at their age, and being post-liver transplant (3 months and 2 months, respectively) with no evidence of rejection and a normal lipid profile.

The literature describes a mean age for cardiovascular disease diagnosis in patients with homozygous FH of 20 years [11, 18]. Several publications have been issued with homozygous patients under 17 years of age who developed severe CD and supravalvular aortic stenosis in the ´80s when percutaneous coronary revascularization with stents was just beginning [2, 15, 19, 20].

Tellez A et al. [28] described in 2010 the vascular response which occurs following implantation of a bare metal stent (BMS) in a porcine model with FH, showing a more agressive neointimal formation than that which occurs in domestic animals, which suggests the need to consider the use of DES in FH conditions. Recently, Shankarappa RK et al. [14] reported 5 patients treated at the Sri Jayadeva Cardiology Institute in Bangalore, India. Four men and one woman. They all presented with coronary symptoms, tendinous xanthomas and severe CD. All had total cholesterol levels >435mg/dL and LDL-c >392mg/dL. Arterial revascularization surgery was necessary in 3 patients, and the other two required angioplasty with successful stent implantation. In one 24 year old man, a drug-eluting stent in the anterior descending and a bare metal stent in the circumflex, and in a 17 year old woman a drug-eluting stent in the left main trunk.

Percutaneous coronary intervention (PCI) is commonly used in adult patients with severe CD. In patients with unstable angina or NSTEMI, an early invasive strategy (that is, angiogiographic diagnosis with the intention of performing a revascularization) is indicated with Class I and B level of evidence [27]. But PCI information in children and adolescents is very limited. Most cases described in those under 18 years of age have had a non-atherosclerotic indication such as transplant coronary vasculopathy [21, 23, 25, 26], coronary dissection [21], and coronary compression or occlusion as a sequela of prior heart surgery [21, 22, 24].

The Guidelines published by the US National Lipid Association (NLA) and NICE in the United Kingdom recommend a reduction in LDL-c concentration of >50% with respect to pre-treatment levels in patients with FH [34, 35, 36, 37]. The Canadian and European guidelines recommend a reduction of LDL-c levels to <116mg/dL in patients at moderate risk for cardiovascular disease; <97mg/dL in patients at high risk, and <70mg/dL in patients at very high risk. There are different treatment options already available for patients with FH. Diet, pharmacologic therapy, lipid apheresis, and some surgical techniques, such as portacaval shunt surgery which limits the absorption of cholesterol and promotes the loss of bile acids, and liver transplant are among the different treatments. Liver transplant to make functional LDLRs available is an alternative for the most serious cases [29].

A few years after Brown and Goldstein won the Nobel Prize in Medicine in 1985 when they described that FH was due to an intrinsic defect of the hepatocyte in the deficiency of LDL-c receptors as an explanation for the extremely high serum cholesterol levels [20], Starzl et al. [33] reported the first orthotopic liver transplant performed for reasons beyond the usual indication of liver failure, as treatment for hyperlipidemia in the context of homozygous FH. It was the first time an anatomically normal liver was surgically removed from a six year old patient, for presumptive treatment of a hypercholesterolemic condition.

As it is known that most LDL receptors are found in the liver, liver transplant has become the treatment of choice for affected patients who do not respond to routine pharmacologic treatments [30, 31]. The transplanted liver retains the specific qualities of the donor and therefore the transplant can be a source of abundant functional LDL receptors, and may lead to a cure of the hypercholesterolemia [29]. Progress in experience of the transplant groups, long-term immunosuppression, improvements in surgical techniques and immunologic methods have yielded favorable results following transplant both in the adult and the pediatric populations [32, 33].

Conclusions and Recommendations

FH is an autosomal dominant genetic disorder associated with

elevated LDL-c levels, which may lead to premature cardiovascular disease. The early diagnosis of FH is important in order to prevent morbidity and mortality. FH is generally diagnosed based on clinical characteristics, family history, and serum cholesterol levels. The current Guidelines highlight the importance of lowering LDL-c levels in patients with FH. We report two patients with homozygous FH, in young people 14 and 15 years old, with clinical manifestations and severe hypercholesterolemia treated pharmacologically and with liver transplant. They presented acute coronary syndrome without ST elevation and severe CD treated successfully with implantation of drug-eluting stents.

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