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Homozygous familial hypercholesterolemia in childhood: Genotype-phenotype description, established therapies and perspectives

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ABSTRACT

Familial hypercholesterolemia (FH) is a co-dominantly inherited disorder of plasma lipoprotein metabolism. The prevalence of heterozygous FH (HeFH) is between 1/500 and 1/200 whereas that of homozygous form (HoFH) is about 1/1,000,000. Diagnosis is based on cutaneous xanthomas and untreated levels of LDL-cholesterol over 500 mg/dl before 10 years of age. Life expectancy, without treatment, does not exceed 20 years of age.

The aim of this study is to characterise in details a cohort of 8 HoFH paediatric patients in order to illustrate all the current therapeutic options and to add some clinical and genetic information about this rare disease. We collected demographic, clinical, biological, imaging and genotype details. Furthermore, clinical and biochemical response to different treatment methods was retrospectively evaluated.

All patients had genetically proven HoFH. All patients were subject to a lipid-lowering diet and medical treatment (except one), three patients underwent a liver transplant and one an hepatocytes infusion. Medical treatment was well tolerated with a median reduction of 44% and 47% in LDL-Cholesterol and Total Cholesterol respectively. The hepatocytes transplant produced a further, though slight, decrease in cholesterol levels as opposed to medical therapy alone. Transplanted patients normalized their cholesterol levels.

Since the very high cardiovascular risk, HoFH requires immediate diagnosis, treatment and monitoring. Nowadays, the use of statins remains the cornerstone of medical therapy and liver transplantation is the possibly curative therapy. Besides, high hopes are pinned in new drugs (antibody targeting PCSK9, Mipomersen and Lomitapide) and stem cells.

1. Introduction

Familial hypercholesterolemia (FH) is a co-dominantly inherited disorder of plasma lipoprotein metabolism. It is caused by defects in the low-density lipoprotein (LDL) receptor gene (LDLR) [1,2]. The prevalence of heterozygous form is between 1/500 and 1/200, whereas that of homozygous FH (HoFH) is around 1/1,000,000. However, the latter is probably underestimated [1,3]. HoFH diagnosis is based on the presence of planar or tuberous cutaneous xanthomas and untreated LDL-cholesterol (LDL-C) above 500 mg/dl (13 mmol/L) before 10 years of age [3–5]. The atherogenic risk is extremely high and cardiovascular complications may occur even before 10 years of age [4]. Several factors such as age, gender, diet, type of *LDLR* mutations, or other genes play a role in this disease [3,5]. Three different proteins regulating sterol and lipoprotein pathways may lead to similar phenotype with varying severity:

Abbreviations: FH, familial hypercholesterolemia; HoFH, homozygous familial hypercholesterolemia; LDLR, low-density lipoprotein receptor; TC, total cholesterol; LDL-C, low-density lipoprotein-cholesterol; HDL-C, high density lipoprotein-cholesterol; Tg, triglycerides; PCSK9, proprotein convertase subtilisin-like kexin type 9; ARH, autosomal recessive hypercholesterolemia; SREBP-2, sterol regulatory element-binding protein-2; LT, liver transplant.

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these are the apolipoprotein B-100 (Apo B-100), the proprotein convertase subtilisin-like kexin type 9 (PCSK9) and the autosomal recessive hypercholesterolemia (ARH) adaptor protein [3,5].

Since life expectancy without treatment is less than 20 years, HoFH screening is strongly recommended for the offspring of heterozygous parents [1,4]. And accordingly, treatment must be started as soon as the diagnosis is made. The first line therapy is represented by statins in combination with ezetimibe or bile acid chelators. Nevertheless, this approach is generally unable to achieve target levels of TC and LDL-C. Second line therapy includes LDL-apheresis [6], hepatocyte transplantation [7], liver transplantation [8], antisense therapy [9] or gene therapy [10,11]. Pharmacological inhibition of PCSK9, the serine protease responsible of the LDLR degradation [12], is being evaluated in adult and adolescent clinical trials [13,14].

The aim of this study is to report a cohort of 8 HoFH paediatric patients, their genotype and phenotype description and their evolution in response to different treatments in order to illustrate all the current therapeutic options and to add some clinical and genetic information about this rare disease.

2. Materials and methods

Over the last 25 years, 8 HoFH children were evaluated at Cliniques Universitaires Saint-Luc in Brussels, Hôpital de Jolimont and Hôpital Femme-Mère-Enfants in Lyon. We collected demographic, clinical, biological, imaging and genotype details. Furthermore, clinical and biochemical response to different treatment methods was retrospectively evaluated.

The retrospective use of patients data for scientific purpose is approved by the Institutional Ethical Committee.

2.1. Genetic analysis

Most patients were analysed for point mutations and small deletions/insertions in the LDLR gene using exon-by-exon screening with DGGE [15–17] followed by Sanger sequencing of the abnormal PCR-amplified fragment, whereas for large rearrangements by multiplex ligation-dependent probe amplification (MLPA® from MRC Holland) [18,19] or by Expand Long Template PCR System (Roche®) [20], followed by sequencing.

Table 1
Patients demographic, clinical and biological characteristics.* Case 6 and 7 are brothers.# Growth retard is linked to the Leri-Weill Syndrome. There is no interference between this syndrome and the HoFH.

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6*	Case 7*	Case 8
Date of birth	1987	1992	2004	2007	2006	1998	1994	1989
Sex	M	F	F	M	F	M	M	F
Origin	Portugal	Belgium	Belgium	Belgium	Algeria	Algeria	Algeria	Italy
Years of diagnosis	1988	2000	2006	2009	2010	2001	1999	1993
Age of presentation	At birth	5 years	9 month	8 years	2 years	4 month	7 month	3 years
Circumstances of discovery	Xanthomas	Blood test for growth retard#	Xanthomas	Xanthomas	Xanthomas	Xanthomas	Xanthomas	Xanthomas
Follow-up (month)	310	149	96	69	60	20	10	232
Xanthomas	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Xanthelasmas	Yes	No	No	No	No	Yes	Yes	No
Corneal arcus	No	Yes	No	No	No	Yes	Yes	No
Cardiac involvement		insufficiency 1/4	No	Mild to moderate aortic valve insufficiency 2/4	Mild tricuspid valve insufficiency 1/4		Small not significant atheromatous plaque of the right coronary ostium. Mild aortic valve insufficiency 1/4	No
Mild pulmonary valve			Aorto-coronary by-pass at 17 years old for coronary stenosis	No				
Vascular involvement			No	Mild thickening of carotid arteries without significant stenosis	Right internal carotid plaque (0.2 mm) and left internal carotid palque (0.3 mm)	No	No	Mild thickening of carotid arteries without significant stenosis
70–80% left common carotid stenosis	Small cacification at the ostium of left internal carodit							
Blood levels (mg/dl) at the diagnosis								
•TC	767	973	692	806	1036	887	788	844
•LDL-C	698	893	626	603	991	796	701	777
•HDL-C	27	38	20	44	28	76	62	46
•Tg	210	210	228	82	84	74	124	104
Other	No	Leri-Weill Syndrome#	No	No	No	No	No	No