Atherosclerosis 239 (2015) 158–162

Contents lists available at ScienceDirect

Atherosclerosis

journal homepage: www.elsevier.com/locate/atherosclerosis

Impact of LDL apheresis on aortic root atheroma in children with homozygous familial hypercholesterolemia

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ARTICLE INFO

Article history:
Received 6 November 2014
Received in revised form
23 December 2014
Accepted 9 January 2015
Available online 14 January 2015

Keywords:
Hypercholesterolemia
Atherosclerosis
Aorta

ABSTRACT

Background: Homozygous familial hypercholesterolemia (HFH) is a rare genetic disease leading to early onset atherosclerosis, due to high concentrations of LDL-C in the blood. Aortic root atheromas may be complicated by obstruction to left ventricle outflow or coronary stenosis. The aim of this study was to describe the progression of aortic root atheroma in patients requiring lipoprotein apheresis before 16 years of age and to examine the requirement of these patients for aortic surgery.

Method: Clinical reports, lipid profiles and echocardiogram results were obtained retrospectively for patients with HFH from three French hemapheresis centers. Data are presented as group medians.

Results: Twenty patients were included, of which 53% had aortic root atheroma (as assessed by echocardiogram) before starting lipoprotein apheresis. These patients began lipoprotein apheresis later than children without aortic root atheroma (10.3 years old [range 5.6–15.9 years] vs. 5.0 years old [range 4.5–11.6 years], respectively, $p < 0.05$). After 16.4 years (range 2.2–22.8 years) of lipoprotein apheresis treatment, aortic root atheroma had progressed in 64% of patients. Five patients needed surgery for aortic stenosis, which was associated with a coronary artery by-pass for two of them. There were significantly more operations among patients with an aortic root atheroma at the beginning of lipoprotein apheresis than among patients without preexisting lesions ($p < 0.01$). One patient died after aorta replacement surgery during this period.

Conclusion: Our results suggest that the initiation of lipoprotein apheresis before the onset of aortic root atheroma should reduce the requirement for aortic surgery.

1. Introduction

Homozygous familial hypercholesterolemia (HFH) is an extremely rare disease with a prevalence of less than 1/1 000 000. Autosomal homozygous or double heterozygous co-dominant mutations of the LDL-receptor (LDL-R) gene result in the absence of the LDL-R or the synthesis of a partially functional protein [1]. Impaired clearance of LDL-cholesterol (LDL-C) leads to its substantial accumulation in blood at concentrations above 10 mmol/L, resulting in cutaneous and tendinous xanthomas. The oxidation of LDL-C in excess is the first step towards atheroma occurring in the supra aortic arteries, aortic root and coronary arteries. These atherosclerotic lesions can lead to premature death without effective treatment [2]. Hypocholesterolemic drugs and a low fat diet are not sufficient to prevent the accumulation of LDL-C. The most efficient treatment is lipoprotein apheresis, in which LDL-C is removed from the blood by extra corporeal circulation [3,4].

Here we report an observational, retrospective study focusing on HFH patients under 16 years of age at the time of the first lipoprotein apheresis treatment. The aim of this study was to describe both the onset of aortic root atheroma before starting lipoprotein apheresis and the progression of the atheroma after at least two years of lipoprotein apheresis treatment, and to look for

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http://dx.doi.org/10.1016/j.atherosclerosis.2015.01.007
0021-9150/

factors associated with cardiovascular outcome.

2. Methods

In the present article, the term HFH is used either for homozygous or double heterozygous co dominant mutation. Patients undergoing lipoprotein apheresis for HFH were recruited from three French University Hospitals (Poitiers, Lyon, and Paris). Inclusion criteria were: 1) documented gene code mutation for the LDL receptor (homozygous or double heterozygous co dominant mutation); 2) first lipoprotein apheresis before 16 years of age; and 3) echocardiogram before the initiation of lipoprotein apheresis.

This study examined the onset of aortic root atheroma (located on the valve or in the sinotubular region as assessed by echocardiography) before starting lipoprotein apheresis and its outcome during lipoprotein apheresis treatment. Echocardiograms were rated as negative or positive for aortic root atheroma, with or without stenosis. Aortic stenosis was defined by a maximal trans aortic Doppler pressure gradient of more than 20 mmHg. The progression of atheroma in the aortic root region was evaluated by comparing the last available echocardiogram with that performed before the initiation of lipoprotein apheresis. The need for aortic surgery was selected as the main outcome because of its robustness.

Data were recorded in a custom made clinical research file and filed by the same pediatrician. The mean inter-apheresis LDL level (LDL-Cm) was calculated as described previously [5]: LDL-Cm = LDL-C_{post} + 0.73 x (LDL-C_{pre} − LDL-C_{post}), averaged over the last three sessions. The reduction in LDL level was calculated for each LDLa session with the following equation: acute reduction of LDL-C (%) = 100 x (LDL-C_{pre} − LDL-C_{post})/LDL-C_{pre}, averaged over the three last sessions. HDL-Cm and the acute reduction of HDL-C level were calculated with the same formulas.

Factors potentially associated with aortic atheroma at the echocardiogram before starting lipoprotein apheresis were tested with the non-parametric Mann–Whitney test for non-categorical data and the Fisher exact test or chi^2 test for categorical data. Factors potentially associated with aortic surgery were tested with univariate analysis and the non-parametric Mann–Whitney test for non-categorical data and Fisher exact test or the chi^2 test for categorical data. Selected factors were also tested by multivariate logistic regression analysis. Factors included in the analysis were: sex, autosomal homozygous mutation, autosomal double heterozygous co dominant mutation of the LDL receptor gene, current age, age at diagnosis and at the initiation of LDLa, LDL-C levels at the initiation of LDLa, presence of xanthomas at the initiation of lipoprotein apheresis, presence of atheroma in the aortic root region at the initiation of lipoprotein apheresis, years of lipoprotein apheresis treatment, LDL-Cm and HDL-Cm levels (three last sessions) and reduction in LDL-C and HDL-C levels (three last sessions). Results are presented as group medians because the data showed a nonparametric distribution. Statistical significance was defined as a p value <0.05.

The Ethics Committee in Human Research of Tours Hospital approved the study (approval no. 2014 009).

Table 1
Characteristics of patients treated with lipoprotein apheresis.

	Mutation	Sex	Age (years)	Age at first apheresis (years)	Years on apheresis	Baseline LDL-C (mmol/L)	LDL-C on apheresis (mmo/L)	Baseline echocardiogram: aortic atheroma	Last echocardiogram: aortic atheroma	Status
1	HFH (del TC, cysteine 83)	F	31.1	15.9	15.2	13.3	3.4	++	Aortic surgery before LDLa	
2	DHFH(del exon4, exon9 G387A)	M	21.7	8.0	13.7		3.7	++	Aortic surgery	Progressed
3	DHFH(del exon4, exon9 G387A)	F	17.6	11.3	6.3	14.6	3.9	++	Aortic surgery	Progressed
4	HFH (Q12X)	F	22.6	5.6	17	23.6	5.4	+	Aortic surgery	Progressed
5	HFH (Q12X)	M	25.1	4.9	20.2	18.1	6.5	–	+	Progressed
6	HFH (G618A)	F	17.6	13.9	3.7	8.4	3.1	+	Not available	
7	D HFH	F	32.7	9.6	23.1		4.6	–	–	Stable
8	HFH (ApoB 3500)	M	28.3	10.5	17.8	15.1	3.3	–	–	Stable
9	DHFH (C2043A, C660X)	F	29.3	10.0	19.3	15.6	4.3	++	++	Progressed
10	DHFH (I402T, D206E)	M	28.1	11.4	16.7	17.2	3.3	+	–	Improved
11	DHFH (exon4 + del exon 15)	F	15.3	5.0	10.3	19.3	6.8	–	+	Progressed
12	DHFH (S156L, E336K)	F	30.4	11.6	18.8	14.4	4.7	–	+	Progressed
13	DHFH	M	7.1	4.7	2.4	17.9	6.2	–	+	Progressed
14	DHFH (C2043A, C660X)	M	23.0	10.3	12.7	21.1	10.0	+	Aortic surgery	Progressed
15	HFH (D283Y)	M	25.1	4.9	20.2	15.9	9.4	–	+	Progressed
16	HFH (D283Y)	F	22.5	5.8	16.7	15.4	3.7	–	–	Stable
17	DHFH (C2043A, C660X)	F	†	10.0	16.0	15.6	4.7	++	Aortic surgery	Progressed
18	DHFH(G571E, del Prom-exon 1)	F	14.3	13.7	0.6	5.7	3.4	+	Not available	
19	DHFH (E207X, G682T)	M	7.9	4.5	3.4	24.9	8.9	–	–	Stable
20	DHFH (del exon3, exon 14)	M	16.3	8.8	7.5	18.7	4.8	+	+	Stable

HFH: homozygous familial hypercholesterolemia, DHFH: double heterozygous familial hypercholesterolemia, LDLa: low-density lipoprotein apheresis, –: no atheroma, +: aortic root atheroma without aortic stenosis, ++: aortic root atheroma with significant aortic stenosis; aortic stenosis: maximal trans aortic Doppler pressure gradient of more than 20 mmHg, †: death.