Atherosclerosis Supplements 18 (2015) 16–20

ATHEROSCLEROSIS SUPPLEMENTS

www.elsevier.com/locate/atherosclerosis

Managing homozygous familial hypercholesterolaemia from cradle to grave

Gilbert R. Thompson*

Metabolic Medicine, Imperial College, Hammersmith Hospital, London, W12 0NN, UK

Abstract

Objective: To describe the phenotypic and genotypic features and management of clinically homozygous familial hypercholesterolaemia (FH).
Methods: An analysis of current knowledge based on personal experience and published evidence.
Results: Atherosclerotic involvement of the aortic root is common in homozygous FH and can cause death before age 5. Receptor negative patients are at greatest risk, irrespective of whether they have identical mutations (homozygous) or dissimilar mutations (compound heterozygous).
Conclusions: Lipoprotein apheresis combined with high dose statin and ezetimibe slows but does not arrest progression of atherosclerosis. Adjunctive use of novel compounds such as lomitapide and evolocumab should facilitate achieving the latter objective by enhancing the reduction in LDL cholesterol.

Keywords: Hypercholesterolaemia; Homozygote; Compound heterozygote; Lipoprotein apheresis

1. Introduction

Homozygous familial hypercholesterolaemia (FH) is a rare and potentially fatal disorder of lipoprotein metabolism caused by mutations affecting both alleles of the genes that determine LDL receptor function. FH has a dominant mode of inheritance with a frequency of homozygotes in Europe that is estimated to be between 1:640,000 and 1:1,000,000 [1]. Based on the higher estimate a country like Germany, with a population of 80 million, will contain approximately 125 homozygotes. Thus although this disorder is a major problem for an affected individual it is a relatively minor one for a nation.

This brief review describes the phenotypic features and management of homozygous FH from infancy to motherhood, exemplified by the history of a homozygote who has been treated for more than 25 years at Hammersmith Hospital and who recently gave birth to a homozygous infant. This is followed by an analysis of the influence of LDL receptor status and genotype on the phenotypic expression of the disorder, and of the therapeutic options currently available and those that are in the pipeline.

2. Case study

This case history is an abbreviated version of a previously published account [2]. The index patient (IP) is a 27 year old South East Asian who has undergone lipoprotein apheresis since the age of 6. She presented at age 3 with cutaneous xanthomas on her arms, knees, back, buttocks and Achilles tendons and a serum total cholesterol of 29 mmol/l. Her parents were first cousins and a paternal uncle had died suddenly at age 9. Subsequent studies

* Tel./fax: +44 20 8994 6143.
E-mail address: g.thompson@imperial.ac.uk.

http://dx.doi.org/10.1016/j.atherosclerosissup.2015.02.002
1567-5688/

revealed that IP had inherited a paternal point mutation in the EGF-precursor region of the LDL receptor, which retained 15% of normal LDL receptor activity, and a maternal 1 base pair deletion in the ligand binding domain, resulting in a non-functioning receptor. Thus genetically she is a compound heterozygote but has a clinical phenotype indistinguishable from a true FH homozygote.

At age 6, IP had an arteriovenous (A/V) fistula created in her arm to provide vascular access for lipoprotein apheresis, which she underwent bi-weekly plus oral simvastatin 40 mg and then atorvastatin 40 mg daily. This treatment reduced her serum cholesterol by approximately 60% between the ages of 6 and 15 [2] and she continued to undergo lipoprotein apheresis in adulthood, for a total of 23 years to date. Against medical advice she became pregnant and had a heterozygous son and, nine years later, a homozygous daughter. It was only then that her unrelated husband consented to undergoing genetic testing, which showed he was a heterozygote with the same point mutation as that inherited by IP from her father. Both men originated from the same village in India.

During her second pregnancy, lipoprotein apheresis was maintained but all lipid-lowering drugs except colesevelam were stopped. Despite increasing the frequency of apheresis, IP's mean total cholesterol rose from its previous level of 7.0–7.6 mmol/l during the preceding 15 months to 10.5 mmol/l during the first 6 months of pregnancy. Echocardiography revealed supravalvular aortic root narrowing with a mean gradient of 18 mm Hg across the aortic valve, indicative of mild stenosis. During the 3rd trimester metoprolol was prescribed for her increasing angina. She was induced at 37 weeks and a healthy but hypercholesterolaemic female baby was delivered by forceps. IP was discharged on anti-anginal medication and aspirin and resumed treatment with lipoprotein apheresis, atorvastatin and ezetimibe 1 month post-partum.

The cholesterol level in the infant's cord blood was 10 mmol/l and this had risen to 25 mmol/l by 12 months. Genetic analysis showed that she had the same mutations as her mother. Tiny cutaneous xanthomas appeared when she was 7 months old and have since enlarged. She was started on atorvastatin 10 mg daily at 27 months, which was increased to 20 and then 40 mg daily but without much effect and her cholesterol level had reached 27 mmol/l by age 3. Recently she had an A/V fistula created with a view to commencing lipoprotein apheresis as soon as feasible.

3. Influence of LDL receptor status and genotype on the clinical phenotype

In an analysis of 57 clinical homozygotes, Goldstein and Brown [3] divided them into receptor negative and receptor defective categories according to whether their cultured fibroblasts exhibited no high affinity binding of LDL (<2%) or whether they bound a subnormal amount (2–25%). The frequency of coronary disease was similar in the 2 groups (45% and 42% respectively) but mortality was higher in the 31 receptor negative subjects than in the 26 who were receptor defective (26% versus 4%). This presumably reflected more severe atherosclerosis among the former consequent on their having higher serum cholesterol levels, but no data on the latter were provided.

As in cholesterol-fed rabbits, so too in homozygous FH, the aortic root is the site of the greatest atherosclerotic involvement, resulting in valvular and supravalvular aortic stenosis and coronary ostial stenosis. In a series of 15 homozygotes studied at Hammersmith Hospital, 11 had aortic stenosis including all 4 fatal cases [4]. As shown in Table 1, 5 patients were genotypic homozygotes and 10 were compound heterozygotes. Pre-treatment total cholesterol levels were slightly higher among the former (24.8 versus 22.2 mmol/l) but the frequency of aortic stenosis was similar in both genotypes. LDL receptor status was determined in 13 patients, of whom 3 were receptor negative (2 homozygous and 1 compound heterozygous) and 10 were receptor defective (2 homozygous and 8 compound heterozygous). All the receptor negative patients had aortic stenosis, with mean serum cholesterol of 21.8 mmol/l, compared with 8 of 10 receptor defective patients, with mean serum cholesterol of 20.1 mmol/l.

In addition to the 7 cases recorded by Guatschi et al. [5] there has been at least one other instance of FH homozygotes dying before the age of 5 (Coote, personal communication). Four of the 8 were male, 4 female and the mean age of death was 3.3 years. Pre-treatment serum cholesterol averaged 25.1 mmol/l and in the 4 instances where the genotype was known, all were homozygous.

At the other end of the spectrum there are 5 reported cases [6–8] and one unpublished instance (Thompson, personal communication) of clinical homozygotes surviving past the age of 50, 3 of whom are still alive. Their mean age now or at death is 59.5 years and 4 of the 6 are females. The mean pre-treatment serum cholesterol was 16.0 mmol/l, considerably lower than the homozygotes who

Table 1
Relation of genotype to phenotypic expression of clinically homozygous familial hypercholesterolaemia (based on data from Ref. 4).

Genotype	*n*	M/F	Age[b]	Phenotype			
				Receptor negative	Cholesterol[a] mmol/l	Aortic stenosis	Dead
Homozygous	5	3/2	25	2 of 4	24.8 ± 3.8	4	1
Compound heterozygous	10	4/6	24	1 of 9	22.2 ± 4.5	8	3

[a] Mean ± SD.
[b] Current or at death, years.