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Homozygous familial hypercholesterolemia: Summarized case reports

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ABSTRACT

Background and aims: Homozygous familial hypercholesterolemia (hoFH) is a rare genetic disorder with potential severe atherosclerosis in the pediatric age.
Methods: We report on 9 patients with hoFH, who had been diagnosed within the last 30 years and who were consequently treated with apheresis and drugs.
Results: Two deaths occurred: one at age 36 years and the other at age four and a half years before effective treatment was commenced. All other patients are still in good clinical condition today, although four of them have proven aortic stenosis or arterial plaques.
Conclusions: Our case report highlights that adequate treatment should start as early as possible to delay the onset of clinical manifestations of atherosclerosis. It can be assumed that the introduction of new drugs can improve the outcome and possibly lengthen the life expectancy of patients affected by hoFH.

1. Introduction

Homozygous familial hypercholesterolemia (hoFH) is a rare genetic disorder, with a previously estimated prevalence of 1:1,000,000 [1]. More recent data from the Netherlands indicate that in Europe the prevalence could be about 1:300,000 or even higher [2]. HoFH is characterized by drastically increased levels of LDL-cholesterol from early childhood on.

The clinical signs of hoFH are characterized mostly by xanthomas, early onset of cardiovascular disease, and markedly elevated LDL-C concentrations in plasma.

More than 95% of the affected patients have mutations in both LDL receptor alleles. Approximately 5% of them are due to mutations in the apolipoprotein B, in the proprotein convertase subtilisin/kexin 9 (PCSK9) or, in even rarer cases, the LDL receptor adapter protein (so called autosomal recessive hypercholesterolemia) [3,4].

In children, the only clinical symptom is xanthoma tuberosum, which typically occurs predominantly on knees, elbows, and tendon achilles [5]. If left untreated, it is common that affected subjects die at an early age, due to cardiovascular diseases [6]. Before modern therapy regimens were established, affected subjects were treated with cholestyramine and/or nicotinic acid with poor results by modern standards. The average life expectancy was approximately 17.7 years. [7,8].The inadequacy of this type of treatment becomes evident when looking at a case series published in 1973 on patients suffering from hoFH, in which, out of 16 patients, only 7 reached their third decade without symptoms [9].

In a recent report, Thompson et al. described 44 patients with hoFH who had been detected and consequently treated in London from 1964 to 2014. Thirteen of them died and 30 are still alive. The average age of start of effective treatment was 11.9 years in the surviving patients *versus* 15.9 years in those who died [10].

In this paper, we describe 9 children with hoFH, who had been diagnosed at the Department of Pediatrics, Medical University of Vienna, from 1980 to 2010.

2. Patients

The 9 patients' characteristics are listed in Tables 1 and 2, including clinical data, LDL receptor gene-mutations and duration

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Table 1
Characteristics of 8 patients with hoFH at initial presentation.

Patient	Year of birth	Mutation	Age of diagonsis	Age at first apheresis	Year of apheresis	TC (untreated)	Lp(a) (untreated)
1	65	p.Asp221Gly [Padova 1]	17 years	17 years	16 years	650	?
2	74	p.Asp221Gly [Padova 1]	13 years	14 years	27 years	525	63
3	95	p.Trp577Arg [Marburg]	1 year	6 years (1st patient at that age)	14 years	813	18
4	99	p.Tyr828Cys [FH J.D- Bari/Potenza]	7,5 years	10 years	5 years	719	230
5	04	p.Trp577Arg [Marburg]	3,5 years	6 years	5 years	935	59
6	00	p.Trp577Arg [Marburg]	4 years	6 years	8 years	780	126
7	04	p.Trp577Arg [Marburg]	4 years	6,7 years	5 years	896	6
8	05	p.Gly478Arg [FH New York-2/Finn-9]	2 years	–	–	402	7

TC, total cholesterol (mg/dl).
Lp(a), lipoprotein(a) (mg/dl).

Table 2
Clinical features of 8 patients with hoFH.

Patient	LDL-C (untreated)	Symptoms	Family history	Consanguity	Totel apheresis (Dec. 15)
1	600	12 years: MI, LAD-Stop	2001 MI	Not known	>250
2	470	Minor xanthomas	Brother (Pat 1) died at 36 years (HoFH)	Not known	1.109
3	765	Xanthomas AS, AI, MI Plaque car. Int. with 6 years	Father MI, ACBO 42 y	Parents: Cousins	587
4	628	Xanthomas, Acrus lipoides IMT ↑, Plaque	Grandfather 45 y. MI Father: LDL-C 320 mg/dl Mother: LDL-C 340 mg/dl Uncle 42 y. MI	Parents: Cousins	366
5	870	Xanthomas	Grandmother p. MI 64 y. Related to Pat. 3	Parents: Cousins	126
6	632	Xanthomas, Plaque aortic insufficieny	Father MI 20 y, ACBP Uncle v. ACBP 45 y. Mother xanthomas Brother died at age of 5 years	Parents: related	?
7	838	Xanthomas, Plaque acrus lipodies, Slight aortic stenosis	13 y hormonal treatment of the mother	Parents, Cousins	?
8	297	None	Father LDL-C: 400 mg/dl Grandgrandfather 67 y. MI Grandgranduncle 65 y. MI	?	0

ACBP, aortocoronary bypass; AS, aortic stenosis; AI, aortic valve insufficiency; car. int., arteria carotis interna; IMT, intima media thickness; LDL-C, low density lipoprotein cholesterol (mg/dl); MI, myocardial infarction; total apheresis, number of total apheresis procedures.

of treatment. All patients were true homozygotes generally from consanguineous marriages.

The first patient has been referred to our center in 1982 due to massive xanthomas on the knees, elbows, tendon achilles and corneal arcus; he had a history of several episodes of syncope without obvious cause at the age of 9 years.

Total cholesterol and LDL-cholesterol were extremely high (650 and 550 mg/dl).

At the age of 12 years, by means of a myocardial scan, a retrospective diagnosis of myocardial infarction (probably at the age of 9 years) was established.

At the age of 17 years, coronary angiography was performed, showing a complete occlusion of the left coronary artery (LAD).

Immediately after the final diagnosis (*LDLR* mutation p.Asp221Gly (FH Padova1)), plasmapheresis was started [11]. Since 1987, a total of over 250 LDL-apheresis procedures were carried out (Table 1). The patient suffered from sudden cardiac arrest at the age of 36 years, during physical activity, and subsequently died.

As it can be seen from Table 1, the 2nd patient (brother of patient 1) had been diagnosed in 1986 (*LDLR* mutation p.Asp221Gly (FH Padova 1)) and plasmapheresis was started the same year. From 1987 onwards, regular LDL-apheresis has been performed. The last coronary angiography (2014) did not show any marked atherosclerotic changes. So far, 1109 apheretic procedures have been carried out. The patient remains clinically well.

The 3rd patient was diagnosed at the age of 1 year due to multiple xanthomas. He is the child of Turkish cousins and shows the typically aggressive *LDLR* mutation p.Trp577Arg (FH Marburg) [12].

Due to the initially poor venous conditions, starting age of treatment was delayed. Apheresis was started at the age of 6 years, as venous access permitted. At that age, he showed a marked atherosclerotic plaque in the carotid artery and an aortic stenosis. He is still on a weekly apheresis regimen today and otherwise healthy.

Patient 4 carries the *LDLR* mutation p.Tyr828Cys (FH J.D-Bari/Potenza) and has much lower cholesterol concentrations compared to the other patients, however, they present with markedly increased Lp(a) levels. At the time of first presentation, sonography revealed the existence of plaques in the carotid artery. Coronary angiography at the age of 13 revealed no pathological findings. Echosonography showed that the patient did not suffer from aortic stenosis. Lp(a) levels dropped from 230 mg/dl to 84 mg/dl after LDL-apheresis. Regular treatment started at the age of 10 years.

Patient 5 has the *LDLR* p.Trp577Arg mutation (FH Marburg) with no signs of atherosclerosis but xanthomas. Apheresis has been started at 6 years.

Patient 6 was also diagnosed with the *LDLR* p.Trp577Arg mutation (FH Marburg) and showed a single plaque in the carotid artery, a slight aortic stenosis, but is still in good condition. Weekly LDL-apheresis was initiated at the age of 6 years. Due to poor venous access, a Cimino shunt had to be placed.

Patient 7 had the *LDLR* p.Trp577Arg mutation (FH Marburg) as