

A boy with autosomal recessive hypercholesterolaemia

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ABSTRACT

We describe a 9-year-old Iranian boy with tuberous xanthomas, elevated LDL-cholesterol levels of 15.5 mmol/l, and vague complaints of chest pain while playing soccer. The consanguineous parents of the boy had normal cholesterol concentrations, which indicated an autosomal recessive disorder rather than autosomal dominant familial hypercholesterolaemia. The diagnosis of autosomal recessive hypercholesterolaemia (ARH) was confirmed by the presence of a mutation in the phosphotyrosine binding domain of a putative adaptor protein, which prevents normal internalisation of the LDL receptor (LDLR) in the liver. The clinical phenotype of ARH is similar to that of classical homozygous familial hypercholesterolaemia caused by defects in the LDLR gene, but it is more variable, generally less severe, and more responsive to lipid-lowering therapy. The patient's complaints of chest pain were not caused by ischaemia as was tested by an exercise and 24-hour electrocardiogram and by a myocardial perfusion scan. His LDL-C dropped by about 60% after being treated with a combination of 40 mg atorvastatin and 10 mg ezetimibe.

INTRODUCTION

Familial hypercholesterolaemia (FH) is an inherited autosomal dominant disorder of lipoprotein metabolism caused by a plethora of mutations in the low-density lipoprotein receptor (LDLR) gene.¹ Clinically, FH is associated with elevated levels of low-density lipoprotein cholesterol (LDL-C) that are two- to four-fold higher than in healthy

individuals (*table 1*) and premature atherosclerosis.

Patients develop symptoms of atherosclerotic cardiovascular disease (CVD) in the third or fourth decade of their life and xanthomas on the extensor tendons of the hands and on the Achilles tendons.¹

In patients with two defective alleles, homozygous or compound heterozygous FH, there is little or no LDLR activity, leading to plasma LDL-C levels about six-fold higher than in healthy individuals. They develop tendon and cutaneous xanthomas early in childhood and have manifestations of premature atherosclerosis within the first two decades of life.¹

In addition to the classical autosomal dominant form of FH, some patients have been described with the clinical expression of homozygous familial hypercholesterolaemia, but with an autosomal recessive genetic trait: autosomal recessive hypercholesterolaemia (ARH). Recently, the disorder was shown to be caused by mutations in the phosphotyrosine binding domain protein (PTB).²⁻⁴ PTB domains are responsible for intracellular signalling and transport. The PTB domain binds the consensus sequence NPXY, a motive that is present in the cytoplasmic domains of several cell-surface receptors, such as the LDLR.⁵ The intact NPXY sequence is required for internalisation of the LDLR. Dysfunction of the binding between the PTB and the NPXY prevents internalisation of the LDLR, which results in an impaired LDLR activity. Patients with ARH have impaired hepatic LDLR function, but in contrast with homozygous FH patients, LDLR function in cultured fibroblasts *in vitro* is normal or only slightly decreased.⁶ Therefore, the fibroblasts are still able to bind and

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Table 1
Lipid disorders characterised with xanthomas

	INHERITANCE	FREQUENCY	LDL- CHOLESTEROL	XANTHOMAS	CVD	TREATMENT	MOLECULAR DEFECT
Heterozygous familial hypercholesterolaemia	Autosomal dominant	1:400-500	2-4 fold elevated	++	3 rd -4 th decade	HMG CoA reductase inhibitors, cholesterol absorption inhibitors	Mutation in low-density lipoprotein receptor
Homozygous familial hypercholesterolaemia	Autosomal dominant	1:1,000,000	6-fold elevated	++++	1 st -2 nd decade	HMG CoA reductase inhibitors, cholesterol absorption inhibitors	Mutation in low-density lipoprotein receptor
Autosomal recessive hypercholesterolaemia	Autosomal recessive		4-fold elevated	++++	4 th decade	HMG CoA reductase inhibitors, cholesterol absorption inhibitors	Mutation in phosphotyrosine binding domain protein
Sitosterolaemia	Autosomal recessive	1:1,000,000	Normal or slightly elevated	+++++	2 nd -3 rd decade	Low plant sterols diet, bile acid resins	Mutation in adenosine triphosphate binding cassette
Cerebrotendinous xanthomas	Autosomal recessive		Normal or low	+++		Chenodeoxycholic acid	Mutation in sterol 27 hydroxylase

LDL = low-density lipoprotein, CVD = cardiovascular disease, HMG-CoA = hydroxy methyl glutaryl Co enzyme A.

degrade LDL. ARH has been mapped at the short arm of chromosome 1 (1p36.1-p35).² Today, eight mutations have been identified in patients from Lebanon, Sardinia, Iran, Italy and the United States.^{7,8}

There are several other rare conditions that are accompanied by the development of xanthomas, but they are not always accompanied by severe disturbance in plasma lipid levels per se. A similar but milder phenotype than FH is familial defective apolipoprotein B-100 (FDB). FDB is an autosomal dominant disorder associated with hypercholesterolaemia in which an amino acid substitution in apoprotein B-100 leads to low-density lipoprotein (LDL) particles which have defective binding to the LDL receptor.⁹

Sitosterolaemia, caused by accumulation of plant sterol in tissues and plasma,¹⁰ is clinically characterised by extensive tuberous and tendon xanthomas, accelerated atherosclerosis, arthralgias and arthritis.^{11,12} In contrast to patients with FH or ARH, sitosterolaemia patients usually have normal to moderately elevated total cholesterol levels but very high levels of plant sterols in their plasma, due to mutations in gene encoding for the ABCG5 and ABCG8 transporters in the gut.¹³ CTX is a rare inborn disorder of bile acid synthesis in which hepatic conversion of cholesterol to cholic and chenodeoxycholic acids is impaired due to a mutation in the 27-hydroxylase gene. This disorder is clinically characterised by strongly elevated levels of cholestanol, diarrhoea in childhood, cataracts, several neurological dysfunctions, Achilles tendon xanthomas

and premature atherosclerosis.¹⁴ Another hypercholesterolaemic phenotype similar to that in heterozygous FH has also been reported in a family with homozygous mutations in the gene for 7 α -hydroxylase, another enzyme in the pathway of bile acid synthesis in the liver,¹⁵ but further families with this disorder remain to be identified.

In this report we describe a case of ARH.

CASE REPORT

A 9-year-old boy of Iranian descent was referred to our hospital. He had vague complaints of chest pain while playing soccer. Beside this problem, he had noticed strange lumps on both knees since the age of 7 years. Physical examination revealed tuberous xanthomas on both elbows, both knees and buttocks (*figure 1*). There were clear arcus cornealis lipoides. Further physical examination revealed no abnormalities, particularly no bruits or other signs of atherosclerotic disease. Laboratory investigations revealed severely elevated levels of total serum cholesterol (TC), and low-density lipoprotein cholesterol (LDL-C), and decreased levels of high-density lipoprotein (HDL-C) (*table 2*). Triglyceride levels were normal. The concentration of apolipoprotein B-100 was at 4.0 g/l also higher than the normal values of 0.6 to 1.4 g/l, and that of apolipoprotein A1 was with 0.69 g/l lower than the normal range of 1.1 to 1.8 g/l.



Figure 1
Tuberosus xanthomas on knees and buttocks in autosomal recessive hypercholesterolaemia

Table 2
Serum cholesterol concentrations of the patient and the 5th, 50th and 95th percentiles of 5 to 9-year-old boys

	PATIENT	5 TH PER-CENTILE	50 TH PER-CENTILE	95 TH PER-CENTILE
TC (mmol/l)	16.5	3.13	4.15	5.26
LDL-C (mmol/l)	15.5	1.74	2.41	4.91
HDL-C (mmol/l)	0.66	1.01	1.45	1.89
Triglycerides (mmol/l)	0.71	0.34	0.63	1.14

His lipoprotein (a) was 270 mg/l, which is within the normal range (<300 mg/l). No other laboratory abnormalities were found.

An exercise electrocardiogram and a 24-hour electrocardiogram were normal, in particular no ST-T segment abnormalities. A myocardial perfusion scan did not show ischaemia. Echography of the carotid arteries demonstrated thickening of the intima medial layer.

The patient's family history appeared to be positive for premature atherosclerosis. His father's mother probably died of a myocardial infarction at the age of 20 and her father died at a young age too. His mother's brother suffered from a myocardial infarction at the age of 37. The father of the boy's mother died at the age of 56 of a myocardial infarction (figure 2). Based on the thickening of the intima medial layer and on this family history and the diagnosis homozygous familial hypercholesterolaemia was considered. However, the boy's parents have normal cholesterol levels

(mother 26 years, TC 4.5 mmol/l; father 33 years, TC 5.7 mmol/l). His 7-year-old brother also has normal cholesterol levels (TC 3.3 mmol/l). In addition, the patient's parents are blood relatives. The cholesterol levels of his parents indicate a lipid disorder of recessive origin rather than homozygous FH. This was confirmed by DNA analysis.

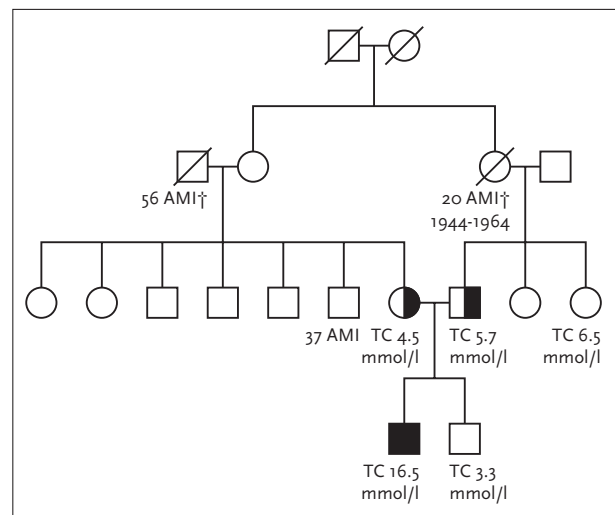


Figure 2
Family tree of the patient with ARH

Circles present females and squares present males. Open symbols indicate that no genetic defect is present or that the genetic profile is unknown, half-open symbols indicate heterozygous persons and closed symbols indicate homozygous persons. AMI = acute myocardial infarction, TC = total cholesterol. †Died.

Our patient was tested for the mutation by Professor H.H Hobbs and colleagues from the Department of Molecular Genetics, University of Texas Southwestern Medical Center, Dallas, Texas, USA, and appeared to be homozygous for the ARH5 frame shift mutation² that results in a premature stop codon in amino acid 33.

Treatment with an HMG-CoA reductase inhibitor was initiated. Pravastatin was started at a dosage of 40 mg upon which the LDL-C level decreased to 11.4 mmol/l. Later, the patient was treated with 40 mg of atorvastatin and his LDL-C decreased to 8.3 mmol/l. The xanthomas on his knees and buttocks became smaller, but are still present. The patient is now 14 years old; we recently added a new cholesterol absorption inhibitor, ezetimibe 10 mg, to his medication. His LDL-C decreased further to 6.6 mmol/l and his HDL-C slightly increased to 0.9 mmol/l. When asked about his condition, he still complains of shortness of breath during exercise, but a yearly exercise electrocardiogram was still negative for ischaemia.

DISCUSSION

In 1973, Khachadurian *et al.* described the first case of a patient with the clinical expression of homozygous familial hypercholesterolaemia but with an autosomal recessive genetic trait.¹⁶ The clinical characteristics of patients with ARH resemble those of homozygous hypercholesterolaemia, but ARH patients have cholesterol levels intermediate between those of heterozygous FH and homozygous FH⁶ and the onset of symptomatic CVD is somewhat later (*table 1*). In spite of the lower plasma cholesterol levels compared with homozygous FH, patients with ARH often have large and bulky xanthomas,^{3,17} as was seen in the patient described here.

Patients with ARH are sensitive to a cholesterol-lowering diet and HMG-CoA reductase inhibitors. The presence of residual LDLR activity in skin fibroblasts might explain the plasma cholesterol concentrations and the response to cholesterol-lowering medication in patients with ARH.⁷ The family history suggested autosomal dominant FH initially, because some relatives probably died of a myocardial infarction at a young age. However, the boy's parents turned out to have normal cholesterol concentrations, and therefore, autosomal dominant FH could not be the disorder that caused the high cholesterol concentration in the boy. Besides, we could not establish whether the relatives died from coronary artery disease as the data were only obtained by history, and autopsy or tests for the mutation were not performed. This indicates that other (inherited) disorders might have been involved. Furthermore, if ARH was the cause of premature death of the relatives, then those individuals had to be homozygous for the disease. Thus, the only fact we were certain of is that both parents

of the boy were heterozygous for ARH and that they were consanguineous. Therefore, they are the only ones who are marked as being heterozygous for ARH in *figure 2*. The patient's complaints of chest pain were not caused by ischaemia as was tested by the exercise or 24-hour electrocardiogram and by the myocardial perfusion scan. We considered the results from these tests adequate to rule out coronary artery disease. Therefore, a coronary angiography was not indicated. Furthermore, a coronary angiography is invasive and not without risk for children at this young age.

CONCLUSION

We present a young patient with xanthomas in skin and tendons and severely elevated plasma LDL-C levels, who is homozygous for the ARH5 mutation, which confirms the clinical diagnosis of ARH.

Treatment with HMG-CoA reductase inhibitors coadministered with ezetimibe resulted in a nearly 60% reduction of LDL-C. To obtain optimal plasma cholesterol levels LDL apheresis may be indicated in these cases.

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