Case Report

An 11-Year-Old Boy with Familial Hypercholesterolemia Showing Multiple Xanthomas and Advanced Atherosclerosis, Who Responded to Lipid-Lowering Therapy Using Statin

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Familial hypercholesterolemia (FH) is characterized by a high level of LDL-cholesterol (LDL-C) and a high prevalence of atherosclerotic coronary heart disease; however, hypercholesterolemia is usually the only clinical finding in children with heterozygous FH in their first decade of life. We report a case of FH in an 11-year-old boy who presented with multiple xanthomas at both elbows, thickened Achilles tendons, and hyperplasia of the intima-media complex of the carotid artery. Echocardiogram revealed partial calcification of the aortic and mitral valves, but no stenosis of the coronary arteries was detected on 3D-computed tomography. The activity of LDL receptors was reduced to 32% by lymphocyte assay. The family history showed vertical transmission of hypercholesterolemia from father to son, thereby suggesting dominant inheritance. After 12 months of treatment with statin and resin, his LDL-C decreased from 446 to 220 mg/dL, thickening of the Achilles tendons decreased from 16–18 mm to 13 mm, and hyperplasia of the intima-media complex decreased from 1.3 mm to 0.7 mm. These findings suggest that our patient had heterozygous FH. However, based on his advanced atherosclerosis, we cannot exclude the possibility that our patient may be accompanying dyslipidemia due to causes in addition to heterozygous FH.

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Key words; Familial hypercholesterolemia, Drug therapy, Xanthoma, Atherosclerosis

Introduction

Familial hypercholesterolemia (FH) is one of the most common inherited metabolism errors, and is inherited as an autosomal dominant trait¹. Homozygote and heterozygote frequencies are estimated to be 1 in 1 million and 1 in 500 in the general population, respectively². The clinical diagnosis of homozygous FH (homo FH) is not difficult for a pediatrician because affected children have cutaneous xanthomas and juvenile atherosclerosis in addition to hypercholesterolemia. In contrast, hypercholesterolemia is usually the only clinical finding in children with heterozygous FH (hetero FH) in their first decade of life³. Pathologically, atherosclerotic changes in the coronary arteries

originate during childhood, and the extent of atherosclerotic lesions correlates positively with plasma LDL-cholesterol (LDL-C) levels and negatively with plasma HDL-cholesterol (HDL-C) levels, even in children and young adults⁴. These data suggest that the development of atherosclerosis might be accelerated in children with hetero FH, even if clinical symptoms are not observed. Here, we report a possible case of hetero FH in an 11-year-old boy with advanced atherosclerosis.

Case Presentation

An 11-year-old boy was referred to our hospital from a regional hospital and presented with thickened Achilles tendons, multiple xanthomas on both elbows, and high levels of total cholesterol (530 mg/dL). He had attended a regional hospital for removal of multiple xanthomas on both elbows. The father, who is hetero FH, recognized the xanthomas and thickening of Achilles tendons apparent in his son at the age of 8 years as being similar to his own case. The patient did

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Table 1. Lipid profiles of the patient's family

	Father	Mother	Patient	Sister
Age (ys)	39	39	11	9
Total cholesterol	486	206	524	154
Triglyceride	194	44	273	53
LDL-C	384	136	446	82
HDL-C	48	50	23	55

Values are expressed as mg/dL

not have his serum lipids tested before visiting the regional hospital. His father had been diagnosed with hetero FH at 20 years of age; a coronary arteriogram at 33 years of age revealed 50% stenosis of the coronary arteries. He was initially treated with statin and colestimide, but neglected to continue treatment with these drugs. At 39 years of age, his coronary artery stenosis increased to a maximum of 90% on three branches, and he underwent percutaneous transluminal coronary angioplasty (PTCA). No history of coronary artery disease or hypercholesterolemia was detected in the patient's paternal uncle and aunts. The patient's paternal grandfather had suffered acute myocardial infarction at 45 years of age (lipid data was not available) and died of coronary artery disease at 71 years. The patient's maternal grandfather had coronary artery stenosis detected at 72 years of age and underwent PTCA. In addition, the patient's maternal great-grandfather and great-grandmother had died of heart disease, but the details were unclear. **Table 1** shows the lipid profiles of patient's family. No lipid abnormalities were found in his mother or younger sister.

The results of physical examination were as follows: height, 135.4 cm; weight, 31.9 kg; abdominal circumference, 56.8 cm; body mass index (BMI), 17.4 kg/m²; blood pressure, 116/78 mmHg. Xanthomas were present on both elbows (**Fig. 1**). Small xanthomas (about 1-mm diameter) were also found just beneath the eyes. Radiographs of the Achilles tendons revealed thickening of both tendons (right: 16 mm, left: 18 mm; **Fig. 2A**), which decreased following treatment. As shown in **Table 2**, serum concentrations of total cholesterol (TC), triglyceride (TG), LDL-C and apoB were very high, and that of HDL-C was very low (95th percentiles of TC, TG and LDL-C in Japanese schoolchildren were 220, 140, and 140 mg/dL, respectively). The 5th percentile of HDL-C in Japanese schoolchildren is 40 mg/dL⁵). The 90th percentile of apoB in schoolchildren at our hospital is 101 mg/dL (unpublished data). Serum concentration of Lp(a) was within the normal range. Serum concentrations of plant-derived sterols, such as sitosterol and cholestanol, were

Fig. 1. Xanthomas on both elbows (arrows).

all within normal ranges. ApoE phenotype was E3/E3. The activity of LDL receptor was reduced to 32% by lymphocyte assay⁶. Arterial intima-media thickness (IMT) was assessed by carotid echogram, which revealed plaque formation and hyperplasia of the intima-media complex (**Fig. 2B**: maximum thickness, 1.3 mm; IMT in control children in our department <0.5 mm). Atherosclerotic change of the coronary arteries was not detected on 3D-computed tomography. As the patient's father had been diagnosed with hetero FH, patient had followed a low-fat diet.

Effect of Lipid-Lowering Therapy

After the serum concentrations of plant-derived sterols and LDL-receptor activity were determined, the patient was tentatively diagnosed with severe hetero FH and began treatment with HMG-CoA reductase inhibitor (rosuvastatin). At first, he received colestimide (1–2 g/day), but there was no marked reduction of LDL-C. The rosuvastatin dose was increased every 4 weeks, based on the LDL-C levels, to a maximum of 15 mg/day. After 6 months of statin therapy, his LDL-C level had decreased by 22% but remained above 300 mg/dL; therefore, he received colestimide in addition to statin. His LDL-C level decreased to 220 mg/dL after 12 months of treatment (rosuvastatin 15 mg/day, colestimide 1.5 g/day), while HDL-C levels increased from 23 to 42 mg/dL. After 12 months of treatment, the thickness of the Achilles tendons had decreased from 16–18 mm to 13 mm, IMT from 1.3 mm to 0.7 mm, and the small xanthomas (about 1 mm in diameter) located beneath the eyes disappeared. LDL-C levels, however, did not fall below 220 mg/dL with rosuvastatin 15 mg/day and colestimide 1.5 g/day; colestimide was therefore changed to ezetimibe (10 mg/day). After 2 months of therapy with ezeti-

Fig. 2. Radiograph of the Achilles tendons (A) and carotid echogram images of arterial intima-media thickness before statin treatment (B).

Table 2. Results of laboratory tests on admission

Total Cholesterol	524 mg/dL (< 220 mg/dL)
LDL-Cholesterol	446 mg/dL (< 140 mg/dL)
Triglyceride	273 mg/dL (< 140 mg/dL)
HDL-Cholesterol	23 mg/dL (> 40 mg/dL)
ApoA-I	59 mg/dL (112–162 mg/dL)
ApoB	249 mg/dL (59–99 mg/dL)
ApoE	11.0 mg/dL (3.0–5.5 mg/dL)
Lp (a)	27 mg/dL (< 40 mg/dL)
AST	20 u/dL (14–33 IU/L)
ALT	8 u/dL (4–24 IU/L)
Glucose	75 mg/dL (68–105 mg/dL)
Insulin	9.4 μ u/mL (2.6–30.7 μ u/mL)
Cholestanol	3.4 μ g/mL (1–7.9 μ g/mL)
Sitosterol	5.1 μ g/mL (5.1–9.9 μ g/mL)
ApoE Phenotype	E3/E3
LDL-receptor activity	32% (101 $\pm$ 10.8%, mean $\pm$ SD)

Reference intervals are shown in parenthesis.

mibe, the LDL-C level was relatively unchanged (220–240 mg/dL); we are currently adjusting the dosage of rosuvastatin by measuring the IMT and the thickness of the Achilles tendons.

Discussion

In children, xanthomas with hypercholesterolemia are usually found in patients with homo FH or sitosterolemia or cerebrotendinous xanthomatosis (CTX)^{7,8}. Similar to sitosterolemia, serum concentrations of cholestanol increase in patients with CTX⁸. Thus, after determining serum concentrations of cholestanol and sitosterol (Table 2, all within normal ranges), sitosterolemia and CTX were excluded from the differential diagnosis in our patient. The leading cause of homo FH is a loss of function of the LDL receptor that is inherited in an autosomal-dominant manner.

In addition, homo FH is recessively inherited when mutations disrupt the function of an adaptor protein for endocytosis of the LDL receptor, known as autosomal recessive hypercholesterolemia (ARH)⁹. The pedigree of our patient shows vertical transmission of hypercholesterolemia from father to son, thereby suggesting an autosomal-dominant manner. In addition, a low level of LDL-receptor activity and good response to lipid-lowering therapy using statin suggested that our patient was very likely to have hetero FH.

Pathologically, atherosclerotic changes in the coronary arteries originate during childhood, with the extent of atherosclerotic lesions correlating positively with plasma LDL-C levels and negatively with plasma HDL-C levels, even in children and young adults⁴. In our preliminary studies (unpublished data), serum levels of LDL-C, Triglyceride (TG) and HDL-C in schoolboys with untreated FH were 220 $\pm$ 42 mg/dL, 86 $\pm$ 56 mg/dL and 62 $\pm$ 12 mg/dL, respectively (n = 24, mean $\pm$ SD). Serum levels of LDL-C, TG and HDL-C in our patient were more than twice (LDL-C and TG) and less than half (HDL-C) when compared with average levels, respectively. The phenotype of dyslipidemia in our patient and his father was type IIb. As reported previously, children with IIb usually showed lower HDL-C levels than those with normolipidemia and IIa^{10,11}. In Japanese adults patients with hetero FH, IIb showed increased coronary artery disease compared to cases of IIa¹². Furthermore, cases of low HDL-C had increased coronary artery disease in hetero FH¹². Thus, in our patient, early development of xanthomas and advanced atherosclerosis (increased carotid IMT and thickened Achilles tendons) may have been caused by the interactions of high LDL-C, high TG and low HDL-C levels. In this patient, however, coronary artery disease was common in his maternal family, although their detailed medical histories are not available at present. Because his mother's serum levels of LDL-C and HDL-C were within normal ranges, fac-

tors other than dyslipidemia may have contributed to the early development of atherosclerosis in our patient. Although the possibility may be very low, interactions of FH and ARH should also be considered. Recently, as a cause of severe phenotype in hetero FH, dominant gain-of-function mutations in the gene encoding a member of the proprotein convertase family, PCSK9, have been reported⁹⁾. To clarify the mechanism behind the early development of atherosclerosis in our patient, further studies, including genetic analysis, are needed.

In Japan, there are currently no guidelines for the pharmacological treatment of children with hetero FH; however, recent studies of children and adolescents with hetero FH have established the effectiveness and safety of statin therapy^{13, 14)}. Based on these data, the American Academy of Pediatrics (AAP) released revised recommendations for the management of hypercholesterolemia¹⁵⁾. According to this report, statins are recommended as first-line pharmacologic agents, and drug therapy may be instituted from 8 years of age. Although AAP recommendations for drug therapy have elicited controversy¹⁶⁾, the urgency for statin treatment in our patient may override any possible adverse effects of statins. Thus far, we have not observed any adverse effects of statin therapy.

In our patient, drug therapy enabled a 50% reduction in LDL-C levels and 100% increase in HDL-C levels, but these values remained greater than 220 mg/dL and less than 50 mg/dL, respectively. This 50% reduction in LDL-C and 100% increase in HDL-C delivered a greater than expected improvement in the thickness of the Achilles tendons and carotid IMT. As reported¹⁷⁾, initiation of statin treatment in children may be more effective than in adults to achieve regression and/or delay the progression of atherosclerosis. In the present patient, we will control the statin dosage by measuring carotid IMT and the thickness of the Achilles tendons in addition to serum levels of LDL-C and HDL-C.

In conclusion, careful evaluation of atherosclerosis should be considered, even in children with hypercholesterolemia. If advanced atherosclerosis is detected, pharmacological therapy should be considered in addition to dietary treatment.

References

- Goldstein JL, Brown MS: The LDL receptor locus and the genetics of familial hypercholesterolemia. *Annu Rev Genet*, 1979; 13: 259-289
- Mabuchi H, Tatami R, Haba T, Ueda K, Ueda R, Kametani T, Itoh S, Koizumi J, Oota M, Miyamoto S, Takeda R, Takeshita H: Homozygous familial hypercholesterolemia in Japan. *Am J Med*, 1978; 65: 290-297
- Kwiterovich PO Jr, Fredrickson DS, Levy RI: Familial hypercholesterolemia (one form of familial type II hyperlipoproteinemia). A study of its biochemical, genetic, and clinical presentation in childhood. *J Clin Invest*, 1974; 53: 1237-1249
- Pathobiological Determination of Atherosclerosis in Youth Research Group: Relationship of atherosclerosis in young men to serum lipoprotein cholesterol concentrations and smoking. *JAMA*, 1990; 264: 3018-3024
- Okada T, Murata M, Yamauchi K, Harada K: New criteria of normal serum lipid levels in Japanese children: the nationwide study. *Pediatr Int*, 2002; 44: 596-601
- Hattori H, Hirayama T, Nobe Y, Nagano M, Kujiraoka T, Egashira T, Ishii J, Tsuji M, Emi M: Eight novel mutations and functional impairments of the LDL receptor in familial hypercholesterolemia in the north of Japan. *J Hum Genet*, 2002; 47: 80-87
- Salen G, Shefer S, Nguyen L, Ness GC, Tint GS, Shore V: Sistosterolemia. *J Lipid Res*, 1992; 33: 945-955
- Berginer VM, Gross B, Morad K, Kfir N, Morkos S, Asref S, Falik-Zaccai TC: Chronic diarrhea and juvenile cataracts: think cerebrotendinous xanthomatosis and treat. *Pediatrics*, 2009; 123: 143-147
- Soutar AK, Naoumova RP: Mechanisms of disease: genetic causes of familial hypercholesterolemia. *Nat Clin Pract Cardiovasc Med*, 2007; 4: 214-225
- Ohta T, Kiwaki K, Endo F, Umehashi H, Matsuda I: Dyslipidemia in young Japanese children: its relation to familial hypercholesterolemia and familial combined hyperlipidemia. *Pediatr Int*, 2002; 44: 602-607
- Asato Y, Katsuren K, Ohshiro T, Kikawa K, Shimabukuro T, Ohta T: Relationship between lipid abnormalities and insulin resistance in Japanese school children. *Arterioscler Thromb Vasc Biol*, 2006; 26: 2781-2786
- Bujo H, Takahashi K, Saito Y, Maruyama T, Yamashita S, Matsuzawa Y, Ishibashi S, Shionoiri F, Yamada N, Kita T; Research Committee Primary Hyperlipidemia of the Ministry of Health, Labour, and Welfare of Japan: Clinical features of familial hypercholesterolemia in Japan in a database from 1996-1998 by the research committee of the Ministry of Health, Labour and Welfare of Japan. *J Atheroscler Tromb*, 2004; 11: 146-151
- de Jongh S, Lilien MR, op't Roodt J, Stoes ES, Bakker HD, Kastelein JJ: Early statin therapy restores endothelial function in children with familial hypercholesterolemia. *J Am Coll Cardiol*, 2002; 40: 2117-2121
- Wiegman A, Hutten BA, de Groot E, Rosenberg J, Bakker HD, Buller HR, Sijbrands EJ, Kastelein JJ: Efficacy and safety of statin therapy in children with familial hypercholesterolemia. *JAMA*, 2004; 292: 331-337
- Daniels SR, Greer FR; Committee on Nutrition: Lipid screening and cardiovascular health in childhood. *Pediatrics*, 2008; 122: 198-208
- de Ferranti S, Ludwig DS: Storm over statins - The controversy surrounding pharmacologic treatment of children. *N Engl J Med*, 2008; 359: 1309-1312
- Rodenburg J, Vissers MN, Wiegman A, van Trotsenburg AS, van der Graaf A, de Groot E, Wijburg FA, Kastelein JJ, Hutten BA: Statin treatment in children with familial hypercholesterolemia: The younger, the better. *Circulation*, 2007; 116: 664-668