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Long-Term Follow-up by Coronary Angiography in a Patient With Heterozygous Familial Hypercholesterolemia : A Case Report

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Abstract

A 47-year-old man with heterozygous familial hypercholesterolemia was followed up by coronary angiography for 9 years. During these 9 years, he experienced inferior myocardial infarction twice, at segment 1 of the right coronary artery. A coronary atherosclerotic lesion (50% stenosis) was also present at segment 6 of the left anterior descending coronary artery. This lesion remained unchanged for the first 7 years, but then rapidly progressed to 90% stenosis in the 8th year. While the rate of the progression of coronary atherosclerosis is generally unpredictable, it may progress rapidly in this case of heterozygous familial hypercholesterolemia.

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Key Words
Cholesterol (familial hypercholesterolemia), Lipoproteins, Heterozygote, Coronary artery disease, Cholesterol-lowering drugs

INTRODUCTION

Familial hypercholesterolemia is an autosomal dominant disorder caused by mutations in the low-density lipoprotein (LDL) receptor gene[1–3]. Molecular analysis of naturally occurring mutations in the LDL receptor gene in patients with familial hypercholesterolemia has revealed many aspects of the structure-function relationship in LDL receptor[4], and such mutations eventually cause a marked impairment of LDL catabolism. Clinically, increased levels of total cholesterol and LDL cholesterol in the blood, premature coronary heart disease, and tendon xanthomas are generally observed in such patients[1–5].

Homozygous familial hypercholesterolemia patients are usually unresponsive to diet and cholesterol-lowering drugs, while the more common heterozygous familial hypercholesterolemia usually responds well to LDL-lowering drugs[6,7], especially 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors. Several prospective trials that have included angiographic endpoints in patients with familial hypercholesterolemia using hypolipidemic drugs and LDL-apheresis have been reported[8,9]. Generally, lowering cholesterol levels can reduce heart attack mortality and prevent the recurrence of myocardial infarction[10–12].

We report here a heterozygous familial hypercholesterolemia patient whose clinical data and coronary angiography findings were closely monitored. The rate of lesional progression with refer-

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Selected abbreviations and acronyms

CABG=coronary artery bypass grafting
HDL=high-density lipoprotein
LAD=left anterior descending coronary artery
LCX=left circumflex coronary artery
LDL=low-density lipoprotein
RCA=right coronary artery

ence to the clinical background of this patient will be discussed.

CASE REPORT

The patient was a 47-year-old Japanese man who had initially come to our hospital at the age of 38 years for examination by coronary angiography, since an electrocardiography had revealed Q wave in II, III and aVF and he had experienced chest oppression for 10 days. Since blood examination was not performed, changes in serum enzyme levels were not monitored. One min after the injection of isosorbide dinitrate through the Judkins catheter over 20 sec, coronary angiography was performed from several projections over 7 min, as described previously[13,14]. Severe stenosis (99% with delay) was observed at segment 1 of the right coronary artery (RCA), while 50% stenosis was observed at segment 6 of the left anterior descending coronary artery (LAD). Collateral arteries from the LAD and left circumflex coronary artery (LCX) to the RCA were well developed (**Figs. 1–A, B**). Percutaneous transluminal coronary angioplasty (PTCA) was conducted at segment 1, and 50% stenosis of the coronary artery was achieved. Left ventriculography showed partial ventricular dysfunction, with moderate reduction at segments 5 and 7. These findings suggested that the patient had experienced an acute myocardial infarction. When serum total cholesterol and triglyceride were measured by enzymatic methods[15,16], HDL-cholesterol was determined by the heparin Ca^{2+} precipitation method[17], serum total cholesterol levels were over 350 mg/d*l*, and Achilles tendon xanthomas (rt : 15 mm, lt : 14 mm) were present. Thus, the diagnosis was heterozygous familial hypercholesterolemia. The patient's niece showed whole body skin xanthomatosis with serum total cholesterol >500 mg/d*l*, and was diagnosed as having homozygous familial hypercholesterolemia by consanguinity matching in another university hospital.

The patient was treated with nitrates, Ca^{2+} channel blocker, aspirin, and the hypolipidemic agents; simvastatin, probucol, probucol with niceritrol/pravastatin/bezafibrate and pravastatin, in our outpatient clinic (**Fig. 2**).

When acute myocardial infarction occurred again at the age of 45 years (more than 7 years after the first attack), a second angiography showed 100% stenosis of the RCA (segment 1) (**Figs. 1–C, D**). Direct PTCA resulted in revascularization (50% stenosis) whereas the 50% stenosis observed at segment 6 of the LAD remained unchanged (**Figs. 1–E, F**). Thereafter, he was seen in the outpatient clinic and received antianginal drugs and hypolipidemic agents every month.

A third angiography 3 months after the second showed 75% stenosis (restenosis after PTCA) at segment 1 and 50% stenosis at segment 6 (**Figs. 1–G, H**). No intervention was conducted at segment 1, since he did not show any anginal symptoms.

A fourth angiography at the age of 46 years, when he felt left lateral chest pain on an exercise stress electrocardiography, showed 75% stenosis at segment 1 and 90% stenosis at segment 6 (**Figs. 1–I, J**). PTCA was applied to stenotic segment 6, and 50% stenosis was achieved, but nothing was done at segment 1.

After 5 months, at the age of 47 years, a fifth angiography disclosed totally occluded segment 6 and collateral arteries were well developed from the RCA to the LAD (**Figs. 1–K, L**). PTCA was tried again for the stenotic segment 6, but the guidewire could not be passed through the occluded lesion. He felt chest oppression and chest pain both with and without exercise. Coronary artery bypass graft (CABG) surgery was conducted. The right internal thoracic artery was grafted to the RCA and the left one was grafted to the LAD, and the bypass grafts were confirmed to be patent by a recent angiography. No symptoms were observed after the surgery.

He was treated for hypercholesterolemia as mentioned above. Serum total cholesterol was decreased to <280 mg/d*l* and high-density lipoprotein (HDL) cholesterol decreased to 20–22 mg/d*l* by probucol plus niceritrol. To reduce total cholesterol further, pravastatin was administered for another 15 months (10 mg/day), and the levels decreased to <250–260 mg/d*l* without affecting serum HDL cholesterol

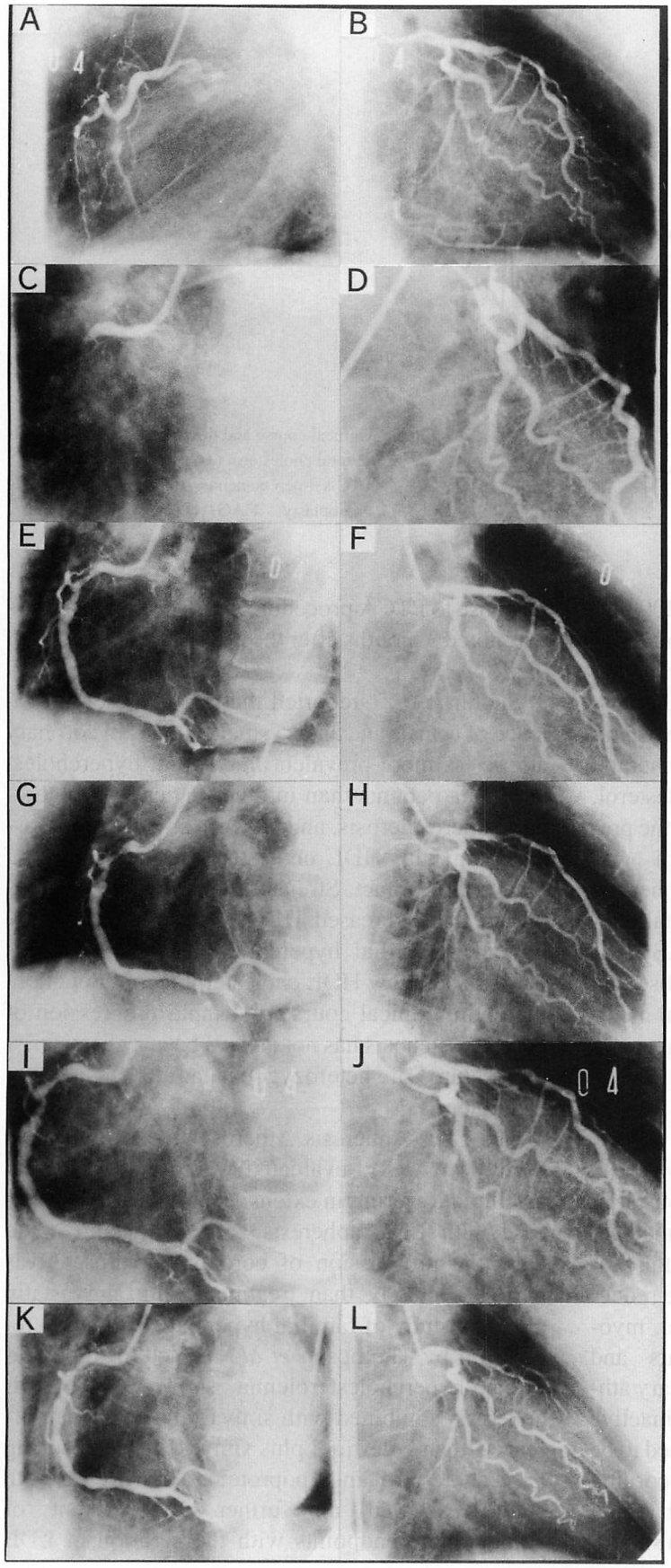

Fig. 1 Angiograms of the right coronary artery (*left column*) and left coronary artery (*right column*)

A, *B*: The first coronary angiography showed severe stenosis (99% with delay) at segment 1 of the RCA, and 50% stenosis was observed at segment 6 of the LAD. Collateral arteries from the LAD and LCX to the RCA were well developed. PTCA at segment 1 achieved 50% stenosis.

C, *D*: When acute myocardial infarction occurred again at the age of 45 years (more than 7 years after the first attack), the second coronary angiography showed 100% stenosis of the RCA (segment 1), and 50% stenosis was observed at segment 6 of the LAD.

E, *F*: Then, direct PTCA achieved 50% stenosis and revascularization. The 50% stenosis observed in segment 6 remained unchanged.

G, *H*: The third coronary angiography 3 months after the second, showed 75% stenosis at segment 1 and 50% stenosis at segment 6. No intervention was conducted at segment 1, since no symptoms were observed.

I, *J*: The fourth coronary angiography at the age of 46 years showed 75% stenosis at segment 1 and 90 % stenosis at segment 6. PTCA was performed in segment 6, and 50% stenosis was achieved.

K, *L*: The fifth coronary angiography revealed total occlusion of segment 6. The collateral arteries from the RCA to the LAD were well developed. PTCA was attempted for the segment 6, but the guidewire could not be passed through the occluded lesion.

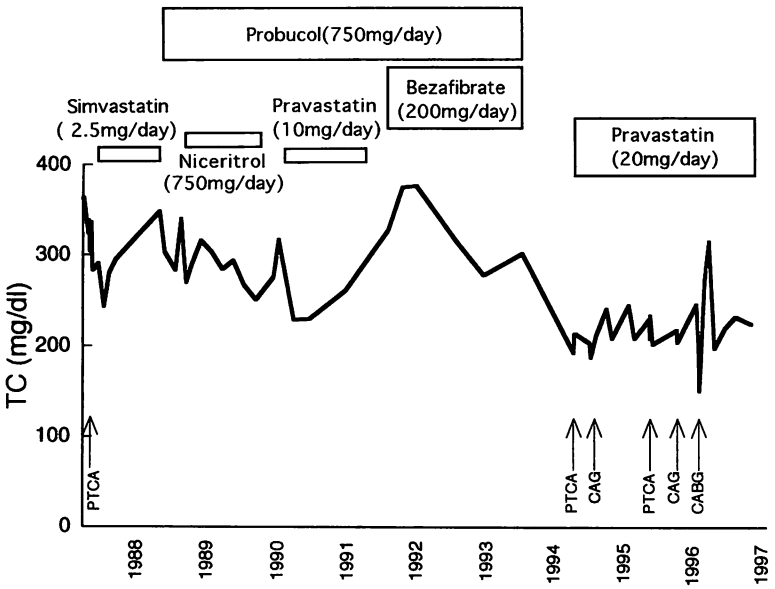

Fig. 2 Clinical course and the changes of serum levels of total cholesterol (TC)
PTCA = percutaneous transluminal coronary angioplasty; CAG = coronary angiography.

levels. Bezafibrate was then administered (200 mg/day) instead of pravastatin along with probucol to raise the low HDL cholesterol caused by probucol. After one and half year of this combination therapy, both drugs were discontinued and only pravastatin was administered, as the combination drug therapy only very mildly reduced serum total cholesterol. The HDL cholesterol level then increased to the pre-combination therapy levels as probucol was stopped. The patient consented to LDL apheresis therapy to achieve a further reduction of total cholesterol, and to prevent restenosis of the CABG, although no clinical symptoms had been observed since the CABG was performed. Antianginal medication and aspirin were continued at the same doses after the CABG.

DISCUSSION

This patient was treated with either simvastatin, probucol, probucol with niceritrol/pravastatin/bezafibrate or pravastatin for 9 years. These medications produced mild reductions in serum total cholesterol levels, as shown in **Fig. 2**, and these reductions were maintained for 9 years. However, myocardial infarction recurred after 7 years and angiography demonstrated significant coronary atherosclerosis progression after a 7-year inactive phase in segment 6 of LAD. The lesion seemed to be "rapidly progressive coronary stenosis" according to Bauters *et al.*[18] Although they reported that both rapidly progressive and stable lesions have a similar response to PTCA procedure, in this case, restenosis was noted 3 months after the PTCA for segment 1 of the RCA.

Sudhir *et al.*[19] reported that an increased prevalence of ectasis and aneurysmal changes in coronary arteries is more prevalent in familial hypercholesterolemia patients than in other patients with coronary atherosclerosis, and shows a strong inverse association with HDL cholesterol levels and LDL/HDL ratio. In fact, Streja *et al.*[20] and we[21] also reported that decreased HDL cholesterol levels are linked to familial hypercholesterolemia, and this patient had a low HDL cholesterol level throughout the entire clinical course, but rapid progression of coronary stenosis has not always been a characteristic feature of heterozygous familial hypercholesterolemia.

The LDL-Apheresis Atherosclerosis Regression Study (LAARS)[8] evaluated whether very aggressive lipid lowering in extensive coronary artery disease with LDL apheresis and simvastatin could slow the progression of coronary atherosclerosis more effectively than treatment with simvastatin alone. A study of familial hypercholesterolemia regression by Thompson *et al.*[9] in heterozygous familial hypercholesterolemia showed that LDL apheresis combined with simvastatin was more effective than colestipol plus simvastatin in reducing LDL cholesterol and lipoprotein (a). However, both studies showed no further improvement of angiographic endpoints with the addition of LDL

apheresis to conventional lipid-lowering treatment, which means that the lowering of total cholesterol levels is not an important factor in controlling angiographically determined atherosclerosis lesions. Although both lowering serum total cholesterol levels and increasing serum HDL cholesterol levels can actually prevent heart attack[1,2] and by affecting the stabilization of plaque can also have a beneficial effect on abnormal vascular reactivity[22–25], a fundamental functional disturbance is associated with coronary atherosclerosis.

It seems that serum cholesterol levels, including HDL cholesterol levels, may not be determinant factors for the rapid progression of coronary atherosclerosis after a phase of relative inactivity at the lesion. Many detailed case examinations of the backgrounds and angiographic findings of heterozygous familial hypercholesterolemia patients may help to elucidate this important mechanism.

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要　約

家族性高コレステロール血症ヘテロ接合体患者の
冠動脈造影像の長期追跡例

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仁位　隆信　太田　孝男　荒川規矩男

症例は47歳，男性，家族性高コレステロール血症ヘテロ接合体患者で，冠動脈造影所見を9年間追跡した．9年間に2度，急性下壁心筋梗塞を発症し，それは右冠動脈分節1に生じた冠動脈閉塞によるものであった．初回冠動脈造影時より左冠動脈前下行枝分節6に50%の狭窄を認めた．7年間同部位の病変進展はなかったが，8年後に90%狭窄と急速病変進展がみられた．

7年間の不活性病変が急速進展した症例の背景を，抗脂血薬治療，脂質プロフィールの変化から考察した．

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References

1) Yamamoto T, Davis CG, Brown MS, Schneider WJ, Casey ML, Goldstein JL, Russell DW : The human LDL receptor : A cysteine-rich protein with multiple Alu sequences in its mRNA. Cell 1984; **39** : 27–38
2) Goldstein JL, Russell DW : Familial hypercholesterolemia. *in* The Metabolic Basis of Inherited Disease (ed by Scriver CR, Beaudet AL, Sly WS, Valle D), 6th Ed. McGraw-Hill, New York, 1989; pp 1215–1250
3) Brown MS, Goldstein JL : A receptor-mediated pathway for cholesterol homeostasis. Science 1986; **232** : 34–47
4) Hobbs HH, Russell DW, Brown MS, Goldstein JL : The LDL receptor locus in familial hypercholesterolemia : Mutational analysis of a membrane protein. Annu Rev Genet 1990; **24** : 133–170
5) Yamakawa K, Yanagi H, Saku K, Sasaki J, Okafuji T, Shimakura Y, Kawai K, Tsuchiya S, Takada K, Naito S, Arakawa K, Hamaguchi H : Family studies of the LDL receptor gene of relatively severe hereditary hypercholesterolemia associated with Achilles tendon xanthomas. Hum Genet 1991; **86** : 445–449
6) Saku K, Zhang B, Hirata K, Okura Y, Bai H, Liu R, Arakawa K : Combined therapy with probucol and pravastatin in hypercholesterolemia. Eur J Clin Pharmacol 1993; **44** : 535–539
7) Saku K, Zhang B, Jimi S, Bai H, Hirata K, Sasaki N, Liu R, Arakawa K : High-density lipoprotein and apolipoprotein A-I deficiency induced by combination therapy with probucol and bezafibrate. Eur J Clin Pharmacol 1995; **48** : 209–215
8) Kroon AA, Aengevaeren WRM, van der Werf T, Uijen GJH, Reiber JHC, Brunschke AVG, Stalenhoef AFH : LDL-Apheresis Atherosclerosis Regression Study (LAARS) : Effect of aggressive versus conventional lipid lowering treatment on coronary atherosclerosis. Circulation 1996; **93** : 1826–1835
9) Thompson GR, Maher VMG, Matthews S, Kitano Y, Neuwirth C, Shortt MB, Davis G, Rees A, Mir A, Prescott RJ, Feyter P, Henderson A : Familial Hypercholesterolemia Regression Study : A randomized trial of low-density-lipoprotein apheresis. Lancet 1995; **345** : 811–816
10) Frick MH, Elo O, Haapa K, Heinonen OP, Heisalmi P, Helo P, Huttunen JK, Kaitaniemi P, Koskinen P, Manninen V, Maenpaa H, Malkonen M, Manttari M, Norola S, Pasternack A, Pikkarainen J, Romo M, Sjoblom T, Nikkila EA : Helsinki Heart Study : Primary-prevention trial with gemfibrozil in middle-aged-men with dyslipidemia : Safety of treatment, changes in risk factors,

and incidence of coronary heart disease. N Engl J Med 1987; **317** : 1237–1245

11) Lipid Research Clinics Program : The Lipid Research Clinics Coronary Primary Prevention Trial Results : II. The relationship of reduction in incidence of coronary heart disease to cholesterol lowering. JAMA 1984; **251** : 365–374
12) Scandinavian Simbastatin Survival Study Group : Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease : The Scandinavian Simbastatin Survival Study (4S). Lancet 1994; **344** : 1383–1389
13) Handa K, Sasaki J, Saku K, Kono S, Arakawa K : Alcohol consumption, serum lipids and severity of angiographically determined coronary artery disease. Am J Cardiol 1990; **65** : 287–289
14) Saku K, Jimi S, Sasaki N, Nii T, Shirai K, Koga N, Arakawa K : Reduced coronary vasodilation in patients with familial hypercholesterolemia following intracoronary injection of isosorbide dinitrate. Jpn Circ J 1995; **59** : 808–814
15) Allain CC, Poon LS, Chan CSG, Richmond W, Fu PC : Enzymatic determination of total cholesterol. Clin Chem 1974; **20** : 470–475
16) Eggestein M, Kreuntz FH : Ein neue Bestimmung der Neutralfette in Blutserum und Gewebe : I. Mitt. Prinzip, Durchführung und Besprechung der Method. Klin Wochenschr 1966; **44** : 262
17) Noma A, Nezu-Nakayama K, Kita M, Okabe H : Simultaneous determination of serum cholesterol in high- and low-density lipoproteins with use of heparin, Ca^{2+}, and anion-exchange resin. Clin Chem 1978; **24** : 1504–1508
18) Bauters C, Passart F, Lablanche JM, McFadden EP, Hamon M, Bertrand ME : Restenosis after coronary angioplasty for rapidly progressive coronary stenosis. Eur Heart J 1996; **17** : 1671–1677
19) Sudhir K, Ports TA, Amidon TM, Goldberger JJ, Bhushan V, Kane JP, Yock P, Malloy MJ : Increased prevalence of coronary ectasia in heterozygous familial hypercholesterolemia. Circulation 1995; **91** : 1357–1380
20) Streja D, Steiner G, Kwiterovich PO : Plasma high-density lipoproteins and ischemic heart disease. Ann Intern Med 1978; **89** : 871–880
21) Saku K, Yamamoto K, Sakai T, Yanagida T, Hidaka K, Sasaki J, Arakawa K : Kinetics of HDL-apoA-I in the WHHL rabbit, an animal model of familial hypercholesterolemia. Atherosclerosis 1989; **79** : 225–230
22) Egashira K, Hirooka Y, Kai H, Sugimachi M, Suzuki S, Inou T, Takeshita A : Reduction in serum cholesterol with pravastatin improves endothelium-dependent coronary vasomotion in patients with hypercholesterolemia. Circulation 1994; **89** : 2519–2524
23) Zeiher AM, Drexler H, Wollschläger H, Just H : Modulation of coronary vasomotor tone in humans : Progressive endothelial dysfunction with different early stages of coronary atherosclerosis. Circulation 1991; **83** : 391–401
24) Stark RM : Review of the major intervention trials of lowering coronary artery disease. Am J Cardiol 1996; **78** (Suppl 6A) : 13–19
25) Tatami O, Matsuoka H, Itabe H, Wada Y, Kohno K, Imaizumi T : Single LDL apheresis improves endothelium-dependent vasodilatation in hypercholesterolemic humans. Circulation 1997; **95** : 76–82