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A case of familial hypercholesterolemia; secession from LDL-apheresis by the drug treatment with potent statin and resin

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Low density lipoprotein (LDL)-apheresis is a useful tool for the treatment of familial hypercholesterolemia (FH) with coronary artery disease (CAD). However, it gives economic, physical and mental burdens for the patients. We reports a case of FH in whom LDL-apheresis treatment was seceded with drug treatment with a potent statin and bile acid-sequestering resin.

A 54-year-old woman was admitted for evaluation of atherosclerotic lesion after 4 years of LDL-apheresis and 1 year of drug medication with a potent statin, atorvastatin and resin, cholestimide with coronary angiography. She had been diagnosed as heterozygous FH when she was 46 years old. Oral medication was initiated at the outpatient clinic. LDL-cholesterol (C) level was not successfully controlled despite the administration of a statin, pravastatin, a fibrate, clinofibrate and probucol at maximum doses Concomitantly. Therefore, as combination therapy, LDL-apheresis was introduced in May 1997. However, the patient strongly complained of the economic, physical, and mental burdens of LDL-apheresis and requested discontinuation of apheresis. Therefore, LDL-apheresis was discontinued in July 2000, and oral medication was subsequently changed to a combination of atorvastatin and cholestimide, resulting in successful control of serum LDL-C level by oral medication alone. we compared coronary arteriographic findings between 1997 and 2001. No advancement of lesions was observed. We think that strong drug treatment can secede from the LDL-apheresis for treatment of patients with FH.

Key words: Familial hypercholesterolemia, low-density lipoprotein (LDL)-apheresis, atorvastatin, cholestimide

INTRODUCTION

Familial hypercholesterolemia (FH) is a genetic disease frequently complicated by high serum low density lipoprotein (LDL), xanthoma and coronary artery disease (CAD) [1]. With regard to the etiology of FH, LDL receptor abnormalities decrease the uptake of LDL into cells, particularly into the liver, from the blood, resulting in the increase of serum LDL-choresterol. The incidence of homozygous FH is markedly low, and it occurs in 1 of 1,240,000 people [2]. However, heterozygous FH occurs in 1 of 500 people, and is frequently detected by routine medical health check. The incidence of acute myocardial infarction (MI) linearly increases according to the age in male patients with heterozygous FH who are 30 years old and over. In addition, the incidence of acute MI also increases in female patients with heterozygous FH after menopause [3]. LDL-apheresis was accepted as a useful tool for the treatment of FH with CAD. On the other hand, this treatment gives economic, physical and mental burdens for the patients. In this study, we demonstrate a patient with heterozygous FH with CAD in whom LDL-apheresis could be seceded with drug treatment with a potent statin and resin.

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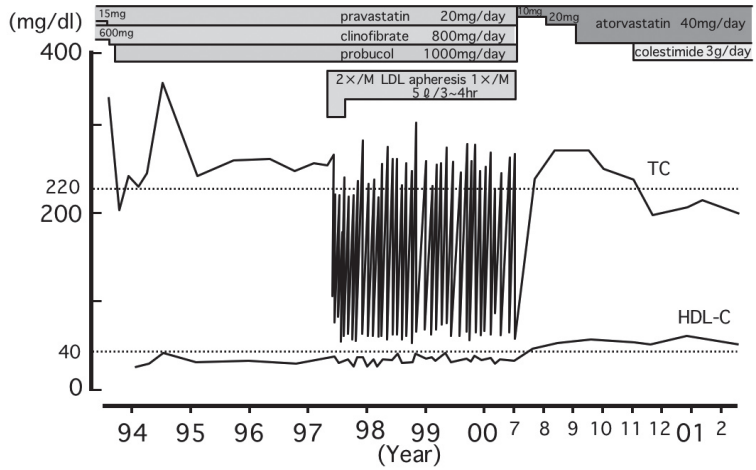

Fig. 1 Course of treatment

CASE REPORT

The patient was a 54-year-old female with a chief complaint of hypercholesterolemia and xanthoma who was a staff member of a home for the aged. In August 1989, the development of hypercholesterolemia was initially detected by medical health check. Since 1991, the patient had received oral medication prescribed by a local physician for 2 years, but serum LDL-C levels were around 300 mg/dl. In August 1993, the patient was referred to the Tokai University Hospital for further examinations and treatment. Plasma lipid levels at the initial consultation were as follows: total cholesterol (TC), 396 mg/dl; LDL-choresuterol (LDL-C), 333 mg/dl; triglycerides (TG), 68 mg/dl; and high density lipoprotein-cholesterol (HDL-C), 49 mg/dl, suggesting heterozygous FH. Oral combinatinal medication was initiated at the outpatient clinic, however, serum LDL-C level was not successfully controlled despite the administration of pravastatin (20 mg/day), clinofibrate (800 mg/day), and probucol (1,000 mg/day) at maximum doses we can use in Japan. Therefore, as combination therapy, LDL-apheresis was introduced in May 1997. Briefly, LDL-apheresis was performed using 2 150-ml dextran sulfate cellulose columns (LIPOSORBER, LA-15, Kaneka, Tokyo) [4], and 5,000 ml of plasma was treated during 1 course of apheresis treatment over approximately 4 hours. Since May 1997, LDL-apheresis has been performed twice a month, and has been continued at a frequency of once a month since September 1997. However, the patient strongly complained of the economic, physical, and mental burdens of LDL-apheresis and requested discontinuation of apheresis. Therefore, LDL-apheresis was discontinued in July 2000, and the therapeutic strategy for this patient was changed to oral medication with atorvastatin (40 mg/day) and cholestimide (3 g/day), which was continued thereafter [5, 6]. Serum TC and HDL-C levels are shown in Fig. 1. Plasma TC and HDL-C levels were well controlled with the drug treatment. In January 2001, the patient was admitted to our hospital for coronary arteriography to evaluate the therapeutic value of this pharmacotherapy.

Past history: The patient underwent tumorectomy in the right elbow joint when she was a junior-high school student. She also underwent surgical resection of a thymoma at the age of 29. At the age of 30, the patient developed arthritis in the right foot, when hypertrophy of the Achilles tendon was detected. The patient did not have any drinking or smoking habits.

Family history (Fig. 2): Briefly, her father was killed in an accident (details unknown), and her mother died of bladder cancer at the age of 70. Both her brothers had xanthoma, and her sister died suddenly during the course of treatment for FH in our hospital. Her brothers died of cerebral and myocardial infarctions, respectively. Her second daughter

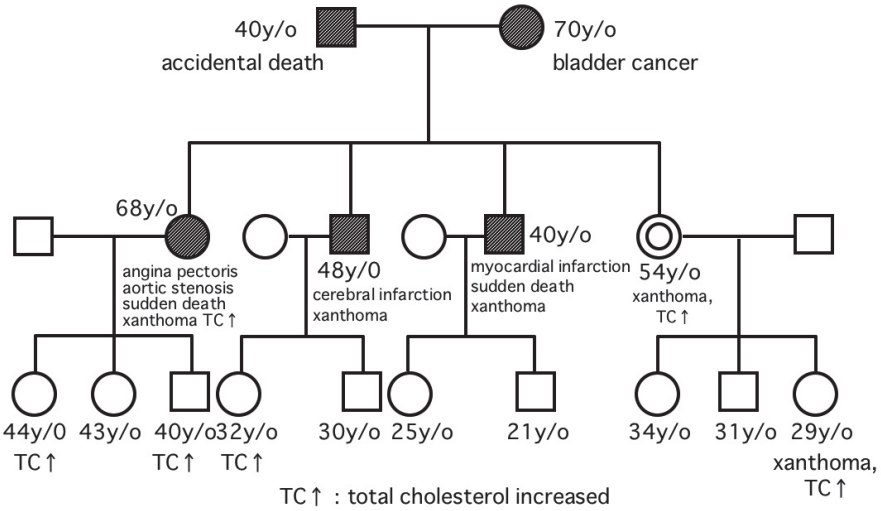

Fig. 2 Family history

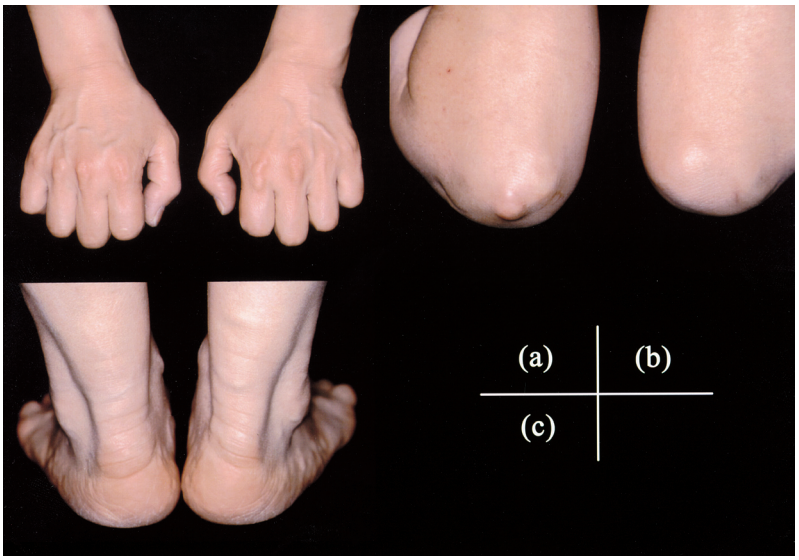

Fig. 3 Xanthomas of the patient
a) extensor tendons xanthoma of hands, b) tuberous xanthoma of elbows, c) Achilles tendon xanthoma

also had xanthoma and hypercholesterolemia. Physical findings: height, 154 cm; weight, 54 kg; body temperature, 36.2°C; blood pressure, 130/68 mmHg; pulse rate, 54/min, regular; anemia, (−); jaundice, (−); lung fields, clear; heart sound, clear without murmur; abdomen, soft; liver and spleen, non-palpable; edema in the lower extremities, (−). However, xanthoma in the bilateral dorsal extensors of the hand, tubercus xanthoma in the bilateral elbows, tubercus xanthoma in the bilateral knees, and xanthoma in the bilateral Achilles tendons were noted (Fig. 3). Although it is not shown in a figure, xanthelasma was also noted in the bilateral eyelids. Soft X-rays for the Achilles tendons revealed that the thickness of the right and left Achilles tendons were 21 mm and 23 mm, respectively [7, 8] (Fig. 4). Table 1 shows clinical laboratory findings on admission. After oral administration of atorvastatin (40 mg/day) and cholestimide (3 g/day), serum lipid levels

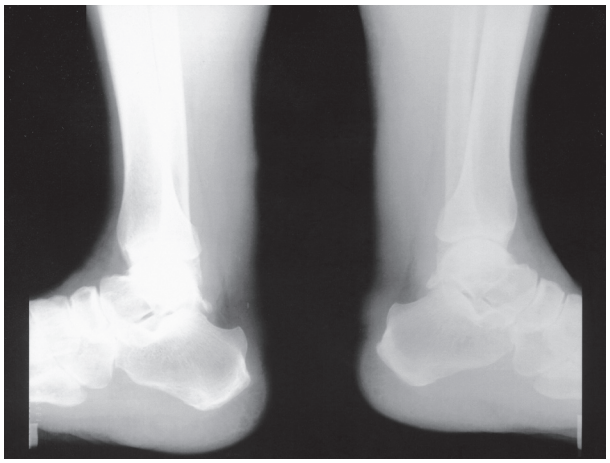

Fig. 4 Soft X-rays for the Achilles tendons revealed that the thickness of the right and left Achilles tendons were 21 mm and 23mm, respectively

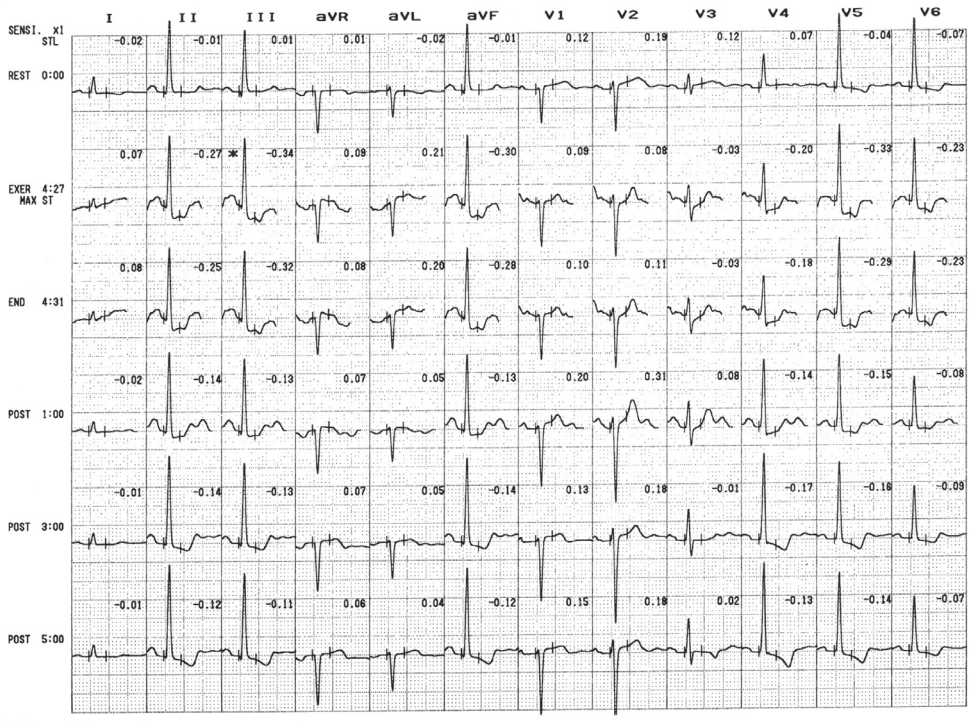

Fig. 5 Treadmill exercise test was performed.
Electrocardiographic ST depressions were observed in II, III, aVF and V3-V6 leads.

were improved as follows: TC, 205 mg/dl; LDL-C, 129 mg/dl; HDL-C, 61 mg/dl; and TG, 61 mg/dl. However, the activity of LDL receptors was as low as 69% (normal range of reference activity: 80-120%). Before admission, Treadmill exercise test was performed up until the Bruce protocol stage 2 (4 min 30 sec) before termination at the target heart rate. Although the patient did not complain of any subjective symptoms, electrocardiographic ST depressions were observed in II, III, aVF, and V_3-V_6 leads (Fig. 5). Figure 6 shows coronary arteriographic findings obtained on March 12, 1997 and January 12, 2001. In 1997, coronary arteriograms obtained at an angle of 30 degrees from the right frontal region of the left coronary artery showed 50% stenosis in the proximal potion of the left

Table 1 Laboratory Data on Admission

Hematology		Biochemistry				Biochemistry	
WBC	4600 /μl	TP	7.3	g/dl	TC	205	mg/dl
RBC	438 ×10⁴/μl	glucose	97	mg/dl	LDL-C	129	mg/dl
Hb	13.0 g/dl	BUN	11	mg/dl	HDL-C	61	mg/dl
Hct	38.8 %	Cr	0.5	mg/dl	TG	61	mg/dl
PLT	18.1 ×10⁴/μl	UA	4.4	mg/dl	ApoA I	134	mg/dl
		GOT	24	U/l	ApoA II	25	mg/dl
		GPT	25	U/l	ApoB	107	mg/dl
Urinalysis		CK	117	U/l	ApoC II	2.9	mg/dl
Protein	(−)	LDH	361	U/l	ApoC III	7.8	mg/dl
Glucose	(−)	γ-GTP	15	U/l	ApoE	4.2	mg/dl
Occult blood	(−)	Na	140	mEq/l	Lp (a)	14	mg/dl
		K	4.0	mEq/l			
		Cl	103	mEq/l	LDL-receptor activity 69%		

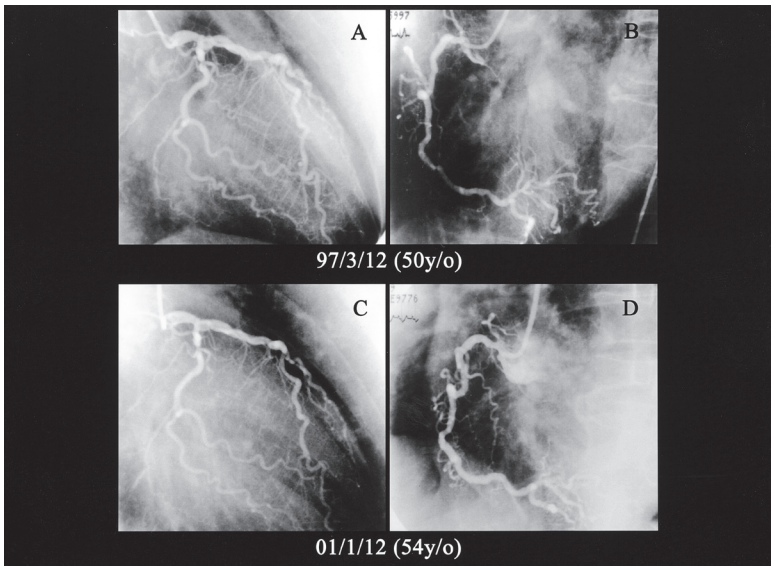

Fig. 6 shows coronary angiographic findings obtained on March 12, 1997 and January 12, 2001. In 1997, atherosclerotic lesion was observed in the proximal portion of the left circumflex branch(approximately 50% in diameter)(A). Findings of the right coronary artery demonstrated the irregular vascular wall, although there was no apparent stenotic lesion(B). In 2001(C,D), Significant progression of atherosclerotic lesions was not observed.

circumflex branch. Coronary arteriograms obtained at an angle of 30 degrees from the left frontal region of the right coronary artery demonstrated the irregular vascular wall, although there was no apparent stenotic lesion. In this study, we compared coronary arteriographic findings between 1997 and 2001. No advancement of lesions was observed. The patient accepted to report her as a case report, except for the publication of a picture of her face.

DISCUSSION

Since most cases of FH are intractable, multi-drug regimens are frequently used at the maximum doses. However, if multi-drug regimens do not exhibit sufficient therapeutic results [9], the LDL-apheresis is used for

treating FH concomitantly [10]. In the United Kingdom, since Thompson introduced total plasma exchange in 1974 [11], the procedures of plasma apheresis have gradually improved. Currently, dextran sulfate adsorption LDL-apheresis is widely used in Japan [4, 12]. That is, selective removal of lipoproteins containing apolipoprotein B from the plasma facilitates the reduction of LDL-C levels without reducing HDL-C levels. Mabuchi *et al.* evaluated the long-term therapeutic value of this procedure over 6 years [13], and reported that the combination of pharmacotherapy and LDL-apheresis facilitated the reduction of LDL-C levels by 60%, and that the incidence of coronary arterial events was significantly decreased in FH patients receiving the combination of LDL-apheresis and pharmacotherapy compared to those treated by pharmacotherapy alone, in whom LDL-C levels were decreased by 30%. Reduction of coronary arterial lesions was also observed in FH patients in whom serum TC levels were decreased to 180 mg/dl or less. Therefore, the maintenance of low serum cholesterol levels is very important. It has been reported that serum cholesterol levels obtained 1 week after the administration of LDL-apheresis were 70% of those before apheresis, and that serum cholesterol levels almost returned to their levels before apheresis 3 weeks later. Therefore, it is ideal to decrease the mean time integral value of total cholesterol levels obtained from the rebound curve of serum cholesterol levels after apheresis [=values immediately after apheresis +0.73 (values immediately before apheresis −values immediately after apheresis)] to 180 mg/dl (targeted value) or below [14]. Since May 1997, LDL-apheresis had been performed in our patient twice a month for 4 months, during which time the mean time integral value of TC was 183 mg/dl. However, LDL-apheresis had been performed once a month since September 1997 because of the desire of patient, and the mean time integral value of TC might have increased to 200 mg/dl or more during that period. Although LDL-apheresis for this patient should have been performed twice or more frequently each month, long-term continuation of LDL-apheresis was difficult even at a frequency of once a month due to increased burdens of apheresis on this patient. Compared to conventional statins, atorvastatin much more markedly decreases LDL-cholesterol levels. Therefore, atorvastatin is useful for treating intractable and severe hypercholesterolemia such as FH [15]. In addition, a combination of atorvastatin and a bile acid-sequestering resin is the most powerful method of treatment for FH [16, 17]. We think that LDL-apheresis can be seceded with this kind of combination drug treatment as shown in this case report. We need further accumulation of data.

CONCLUSIONS

Although LDL-apheresis is useful for treating FH complicated by CAD, it gives economic, physical and mental burdens to the patient. New potent statins have been developed. Thus, we think that we can secede from LDL-apheresis with the treatment with potent drug treatment.

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