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CASE REPORT

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Living-donor liver transplantation for homozygous familial hypercholesterolemia from a donor with heterozygous hypercholesterolemia

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Abstract Familial hypercholesterolemia is a rare inherited disease with an incidence of approximately one per million. Severe hypercholesterolemia is observed from the time of birth onwards. It is associated with severe atherosclerosis in childhood, leading to death from myocardial infarction before the age of 20 years. Liver transplantation is the only effective treatment for this disease. We experienced the case of an infant aged 2 years 5 months who had homozygous familial hypercholesterolemia and who received a liver graft from his father, who had familial heterozygous hypercholesterolemia. The pre-operative plasma cholesterol level was >800 mg/dl. After liver transplantation, the recipient's cholesterol level decreased to 250 mg/dl after we administered the HMG-CoA reductase inhibitor. At present, 6 months after transplantation, the patient is doing well and free from a special diet. We can thus conclude that the combination therapy of liver transplantation from a donor with heterozygous familial hypercholesterolemia on cholesterol-lowering drugs is an effective therapy for a patient with the homozygous type of hypercholesterolemia.

Keywords Homozygous familial hypercholesterolemia · Liver transplantation · Donor with heterozygous hypercholesterolemia

Introduction

Homozygous familial hypercholesterolemia (HFH) is a rare, inherited disease with an incidence of approximately one per million. This metabolic disorder is caused by mutations or defects of the genes that encode the information for the synthesis of the low-density lipoprotein (LDL) receptor. Severe hypercholesterolemia is observed from the time of birth. The plasma cholesterol level is usually >550 mg/dl, leading to severe atherosclerosis in childhood and death due to myocardial infarction before the age of 20 years. No drug therapy is effective in HFH because patients cannot synthesize the LDL receptor. The liver contains approximately 70% of the total body LDL receptor, therefore, cadaveric liver transplantation has been carried out to treat this metabolic disorder, and there have been several reports describing its effectiveness [2, 4, 7, 10, 11, 14].

In Japan, living-donor liver transplantation is usually performed, cadaveric liver transplantation being infrequent. The donor is generally a close relation of the patient. Parents of HFH patients always have heterozygous familial hypercholesterolemia. Drug therapy is effective for patients with heterozygous familial hypercholesterolemia. We performed living-donor liver transplantation on a patient with HFH. The donor was his father, who had heterozygous familial hypercholesterolemia. After transplantation the cholesterol level of

the patient decreased but remained slightly higher than the normal upper limit, therefore, he was administered a cholesterol-lowering drug, and the level normalized. We think liver transplantation, even from a donor with heterozygous familial hypercholesterolemia, is an effective treatment.

Case report

The patient, a Japanese infant aged 2 years 5 months, had small orange cutaneous xanthomas in both ankles and wrists (Fig. 1). His parents were healthy and not consanguineous, but had high blood cholesterol levels and were taking cholesterol-lowering drugs. The results of the child's clinical examinations were normal. Biochem-

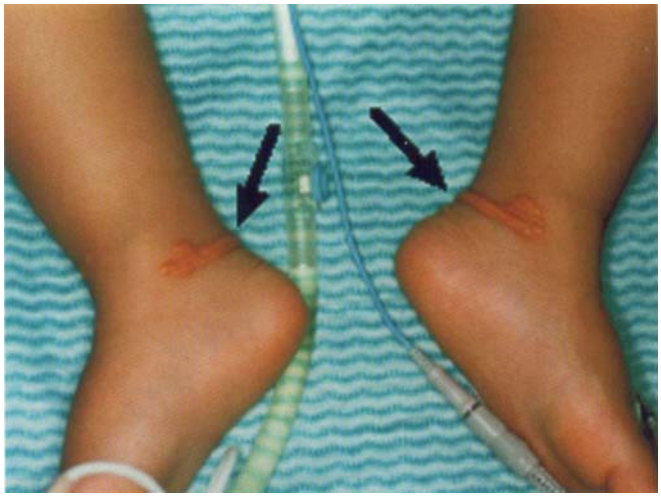

Fig. 1 Orange cutaneous xanthomas were observed in the ankles and wrists. *Arrows* point to the xanthomas in the boy's ankles

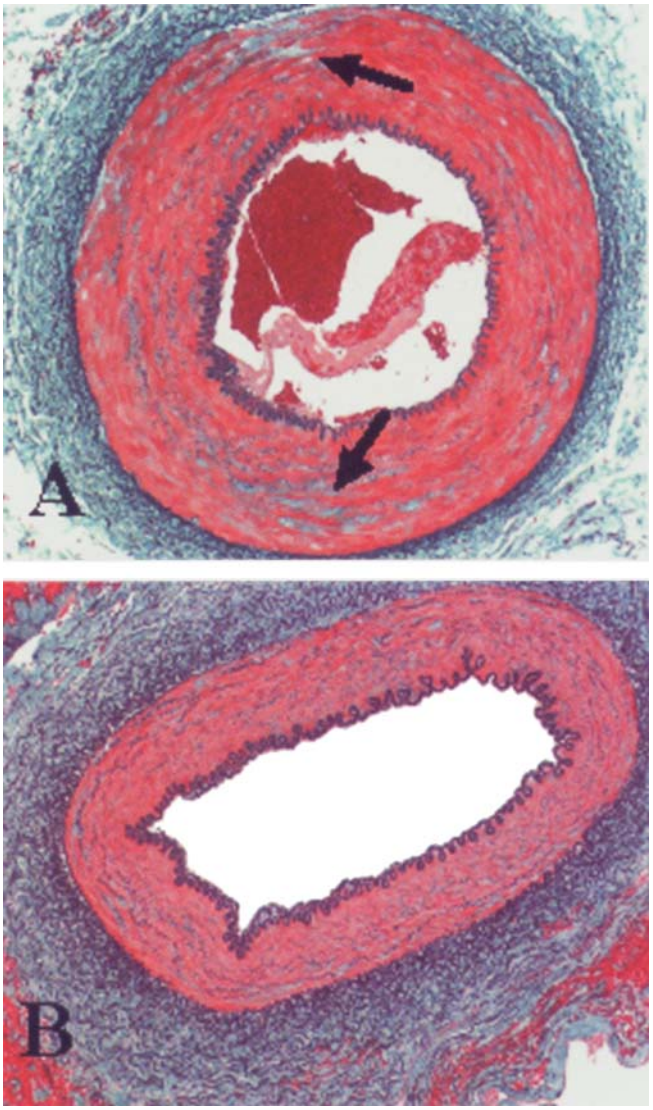

Fig. 3 Light microscopic examinations of the recipient's (**A**) and the donor's (**B**) hepatic arteries (Elastica Goldner staining). **A** Slight elastic changes (*arrows*) of the middle membrane were observed. No severe atherosclerotic changes were observed. **B** Neither elastic nor atherosclerotic changes were observed

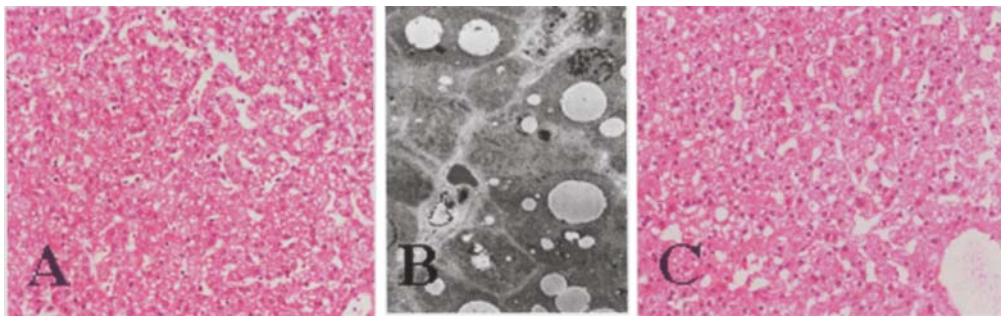

Fig. 2 A Light microscopic examination of the recipient's native liver (HE staining). More than 60% of microvesicular steatosis and high fatty change were observed. **B** Electron microscopic examination of the recipient's native liver. Microvesicular steatosis was observed in hepatocytes. No inflammatory changes were observed in Glisson's capsule. **C** Light microscopic examination of the graft liver (HE staining). Mild macrovesicular steatosis and slight fatty change $< 30\%$ were observed. This graft was suitable for the liver transplantation

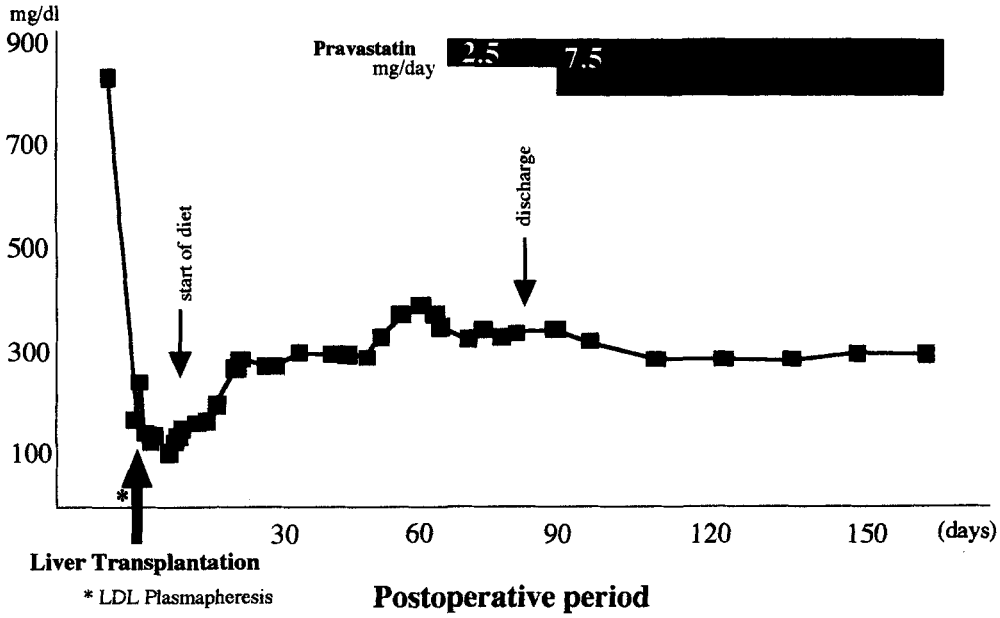

Fig. 4 Plasma cholesterol levels before and after liver transplantation. The plasma cholesterol level before transplantation was >800 mg/dl. We performed selective LDL plasmapheresis before transplantation to prevent post-operative vascular troubles. Immediately after liver transplantation plasma cholesterol decreased to a value within the normal range. The cholesterol level rose to approximately 400 mg/dl in proportion to the amount that the infant's dietary intake increased. Therefore, the HMG-CoA reductase inhibitor, pravastatin was administered, and the cholesterol level decreased to approximately 270 mg/dl

ical values showed normal liver enzymes and no cholestasis. A plasma lipidogram showed that the total cholesterol level was 893 mg/dl, LDL cholesterol was 898 mg/dl and that of triglycerides 60 mg/dl.

The electrocardiogram and the cardiac ultrasonograph showed no abnormal findings. The boy and his parents were genetically diagnosed. The boy and his father had the same gene mutation type of the LDL receptor, but the gene mutation type of his mother was unclear.

We found no living donors with a normal LDL receptor in his family, and, as there are very few brain-dead donors in Japan, he underwent living-donor liver transplantation with his father as the donor. The father was 29 years old and had heterozygous hypercholesterolemia. We performed selective LDL plasmapheresis before the operation to decrease the viscosity of the blood. The graft was a lateral segment of the liver. The graft weight/recipient standard liver volume ratio was 58%. The duration of the operation was 10.3 h, and the total volume of blood lost during the operation was 320 ml. After transplantation, the child was administered prednisolone combined with tacrolimus as immunosuppressive therapy. Jaundice disappeared and the liver function was normal after the operation. His post-transplant course was unremarkable except for a transient CMV infection. The cholesterol level rapidly normalized. In proportion to the increase in his diet, the cholesterol level rose to approximately 400 mg/dl. He was administered the HMG-CoA reductase inhibitor pravastatin, and his cholesterol level decreased to less than 270 mg/dl. He was discharged from hospital on the 78th post-operative day.

Figure 2A and B show the microscopic and electron-microscopic findings of the recipient native liver and the graft. More than 60% of microvesicular steatosis and high fatty change were observed in the boy's liver. The liver graft showed less than 30% fatty change (Fig. 2C). Neither the recipient nor the donor showed severe atherosclerotic changes in the hepatic artery (Fig. 3). Figure 4 shows the evaluation of post-operative plasma cholesterol levels. Living-donor liver transplantation produced an immediate and remarkable decrease in plasma cholesterol concentration. Administration of pravastatin after liver transplantation resulted in a decrease of the cholesterol level. The resorption signs of the cutaneous xanthomas were evident 6 months after the operation. At present, 6 months after transplantation, the child has no cardiovascular troubles and shows a normal growth pattern, full social rehabilitation, normal psychomotor development and normal liver function.

Discussion

HFH is caused by mutations of the LDL receptor gene. Patients with HFH have severe hypercholesterolemia, xanthomas, and rapidly progressive atherosclerosis. In these patients, the plasma cholesterol level is >550 mg/dl, often >1,000 mg/dl. Cardiovascular disease due to atherosclerosis is usually the cause of death before patients reach the age of 20 years.

Cholesterol-lowering drugs, such as HMG-CoA reductase inhibitors [3, 6, 8], are ineffective because LDL receptors are almost absent in patients with HFH. Selective LDL plasmapheresis can decrease the plasma concentration of cholesterol to approximately 50% of the initial level [1, 9]. However, this treatment is difficult to perform in small children, because of the difficulty presented by maintenance of long-term venous access and the small volume of circulating blood. A portocaval shunt reduces the cholesterol level by altering hepatic cholesterol metabolism [12, 13]. However, this treatment is insufficient to reduce the cholesterol concentration, and major surgery is required. Gene therapy has also been attempted, to improve hypercholesterolemia, but this treatment proved to be inefficient, and the study was stopped [5].

Liver transplantation is effective for HFH because approximately 70% of the total LDL receptors are located in the liver [2, 4, 7, 10, 11, 14]. The transplanted

liver with normal LDL receptors effectively metabolizes cholesterol from plasma, and, early liver transplantation before progression of atherosclerosis prevents death due to irreversible cardiovascular damage.

Since cadaveric donors are scarce in Japan, living-donor liver transplantation has become more common. Donors are usually adults, close relatives of the recipient, almost always the patient's parent or child. The donor must be ABO compatible and healthy. For our patient there was no other donor, except for his father who had familial heterozygous hypercholesterolemia. Medical treatments, such as HMG-CoA reductase inhibitors, are effective for familial heterozygous hypercholesterolemia [3, 6, 8]. We thought that liver transplantation for HFH using a graft from a donor with heterozygous hypercholesterolemia would be effective, together with HMG-CoA reductase inhibitors after the operation. The plasma cholesterol level of the boy normalized immediately after he underwent transplantation. His cholesterol level increased to approximately 400 mg/dl, in proportion to his dietary intake. At treatment with the HMG-CoA reductase inhibitor, pravastatin, his cholesterol level decreased to approximately 270 mg/dl. The child has since been growing up normally, showing no signs of cardiovascular disease.

We can conclude that transplantation of a liver graft from a living donor with heterozygous hypercholesterolemia may prove effective for patients with HFH, and the plasma cholesterol level can be reduced by treatment with cholesterol-lowering drugs after transplantation.

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