

Long-term follow-up of a patient with hypercholesterolaemia treated by liver transplantation

V. O. L. KARUSSEIT, M.B. CH.B., M.F.G.P. (S.A.), M.MED. (SURG.), F.C.S. (S.A.)

C. J. MIENY, M.B. CH.B., CH.M., F.C.S. (S.A.), F.R.C.S. (ENG.), F.R.C.S. (EDIN.)

Department of Surgery, University of Pretoria and Pretoria Academic Hospital

Familial hypercholesterolaemia is a life-threatening inborn error of metabolism characterised by extremely high serum cholesterol levels. The disease manifests clinically as advanced atherosclerosis, cardiovascular disease and premature death. In 1973 Goldstein and Brown¹ described the abnormality causing the hypercholesterolaemia. They described mutations in a gene coding for the receptor responsible for transporting low-density lipoprotein (LDL) into cells. However, no specific treatment has been described and optimal treatment remains elusive. Management includes diet, cholesterol-lowering drugs and apheresis.² Surgical options that have been applied and abandoned are ileal bypass and porto-systemic shunting.^{3,4} Since the 1980s liver transplantation has been successfully applied to this condition. We describe the long-term follow-up of a patient treated successfully with liver transplantation.

Case report

A 13-year-old girl was referred by the endocrine and metabolic clinic to our transplantation unit for consideration for liver transplantation. She was known to suffer from homozygous familial hypercholesterolaemia (HFH). Genetic studies had revealed hetero-allelic mutations in exons 4 and 9 of the gene coding for the LDL receptor. For several years she had been followed up for atherosclerosis and multiple xanthelasma. Several of the latter had been excised, specifically over the knees and elbows. Systolic bruits were audible over both carotid arteries and in the epigastrium, but these were asymptomatic. She had recently developed angina-like chest pain. Angiographical examination revealed stenoses of the carotid arteries and the coeliac trunk, but the coronary arteries were normal. Nevertheless the physicians treating her considered it prudent to refer her for liver transplantation. Conservative treatment with diet and lipid-lowering agents had been singularly ineffective. The serum cholesterol level had been consistently in the region of 20 mmol/l. Apheresis had not been considered appropriate by the doctors treating the patient.

Apart from the abovementioned abnormalities the patient was in good health and she was accepted onto the transplant programme. A cadaver liver was transplanted in 1991. One acute rejection episode was treated successfully with boluses of steroids and there were no other complications. She was maintained on ciclosporin, azathioprine and prednisone immunosuppression.

Serum lipid levels decreased dramatically after transplantation (Fig. 1). The total serum cholesterol level stabilised at about 7 mmol/l and the patient was started on simvastatin. This has maintained the cholesterol level at between 4 and 5 mmol/l ever since.

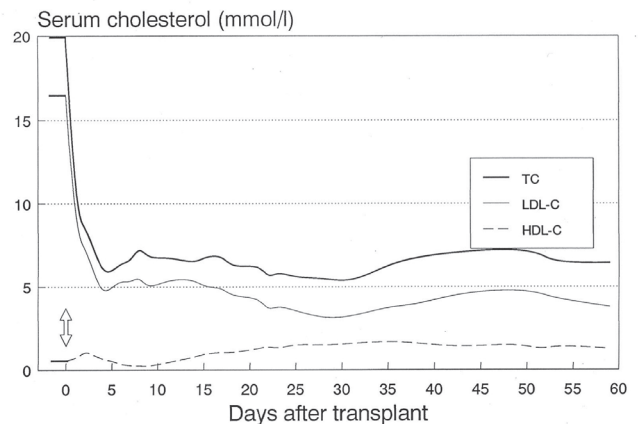


Fig. 1. Change in serum total cholesterol (TC), serum low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C) in the first 2 months after transplantation.

The patient subsequently married a man with a family history of arterial disease. Advice to first have the husband's lipid profile determined and to undergo genetic counselling was not followed, and a child has subsequently been born of the marriage. The child is now 5 years old. It is clinically normal but a lipid profile has not been performed.

The patient is clinically well. The bruits over the carotid arteries are still present but asymptomatic. Liver functions are completely normal.

Discussion

HFH is a universally fatal condition if not treated successfully. Patients with severe receptor deficiency die within the first decade of life, or in the second decade in less severe cases.⁵ Death results from the complications of atherosclerosis. Our patient clearly manifested arterial disease, but complications were not yet evident. It was felt that it would be prudent to attempt to normalise the serum cholesterol levels before any serious sequelae developed. This recommendation was made by Starzl *et al.*⁶ after the first successful combined heart and

liver transplantation in a child with severe coronary artery disease.

The liver contains 50 - 75% of the body's LDL receptors. Liver transplantation provides these receptors and therefore greatly ameliorates the disease.⁷ As in our case, patients require statins to completely normalise serum cholesterol levels. The cases reported in the literature have been cadaveric liver transplantations, but a living related transplant has recently been reported.⁷ Domino transplantation has also been reported.⁸

Apheresis profoundly lowers serum cholesterol levels in hypercholesterolaemia. Recent reviews^{6,9} have recommended apheresis as the treatment of choice for HFH and have stated that apheresis has superseded surgical approaches such as liver transplantation. However, liver transplantation has been successfully applied in many cases and has also been proposed as the treatment of choice.⁷ Both forms of treatment have their advantages and disadvantages. Apheresis is a difficult and hazardous treatment modality and is socially disruptive because of the need for regular long treatment sessions. It also requires permanent vascular access. On the other hand, liver transplantation is a major surgical undertaking with definite mortality and morbidity and exposes the patient to the hazards of lifelong immunosuppression.

The decision regarding treatment modality for HFH should be a consultative one involving the metabolic specialist, the transplant unit, the patient and the family. The precise genetic defect and the state of the patient's cardiovascular system need to be considered. The patient and family then need to make a fully informed decision. Obviously no randomised comparison between treatment modalities has been performed because of the rarity of the condition. It is difficult to glean long-term survival data for the various treatments of HFH from the literature as reports consist of early reports, individual cases and small series.¹⁰⁻¹²

We present a 15-year follow-up of a case of highly successful liver transplantation for HFH. The initial transplant was

uncomplicated and the subsequent course successful in curing the disease. Part of the success of this case is due to the timing of transplantation which was performed before serious sequelae of atherosclerosis had developed.

Despite apheresis being widely and successfully applied in the treatment of familial hypercholesterolaemia, it is our opinion that liver transplantation remains a therapeutic option that should be considered in the management of this devastating disease.

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