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CASE REPORT

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Successful living-related liver transplantation for familial hypercholesterolemia in the Middle East

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Abstract Familial hypercholesterolemia (FH) is an autosomal dominant inherited metabolic disorder resulting in advanced vascular atherosclerosis and premature death, primarily from coronary artery disease. The primary defect is a mutation in the gene encoding for the plasma LDL receptor located on the short arm of chromosome 19. Liver transplantation is currently the most effective method of treating this disorder. Living-related liver transplantation (LRLT) has become an excellent modality for treating children, including those with inherited metabolic diseases. In this paper, we describe the first report of a LRLT for familial hypercholesterolemia and review FH and the role of liver transplantation.

Keywords Cholesterol · Inborn error of metabolism · Genetic · Pediatric

Introduction

Familial hypercholesterolemia (FH) is one of the most common inborn errors of metabolism resulting in profound elevation of plasma cholesterol levels, advanced vascular atherosclerosis, and premature death. It was not until the early 1970s, however, that Brown and Goldstein [1] elucidated the mechanism of FH and therefore the role of low-density lipoproteins (LDL) in cholesterol homeostasis. They demonstrated that FH results from mutations in a gene coding for the receptor that transports LDL into cell. Traditionally, treatment options for FH have included diet and pharmacological therapy, apheresis and, in some cases, ileal bypass surgery to promote increased intestinal loss of bile acids and secondary depletion of hepatic cholesterol stores. These treatments have, however, been suboptimal and inconsistent with achieving acceptable cholesterol levels in patients with homozygous FH. To date, liver transplantation remains the most effective method for altering plasma lipoprotein in such patients. The optimal timing of transplantation is unclear but should precede the onset of cardiovascular complications. In addition, another limiting factor is the availability of suitable organs for pediatric transplantation.

The success and acceptability of living-related liver transplantation (LRLT) in children and adults has

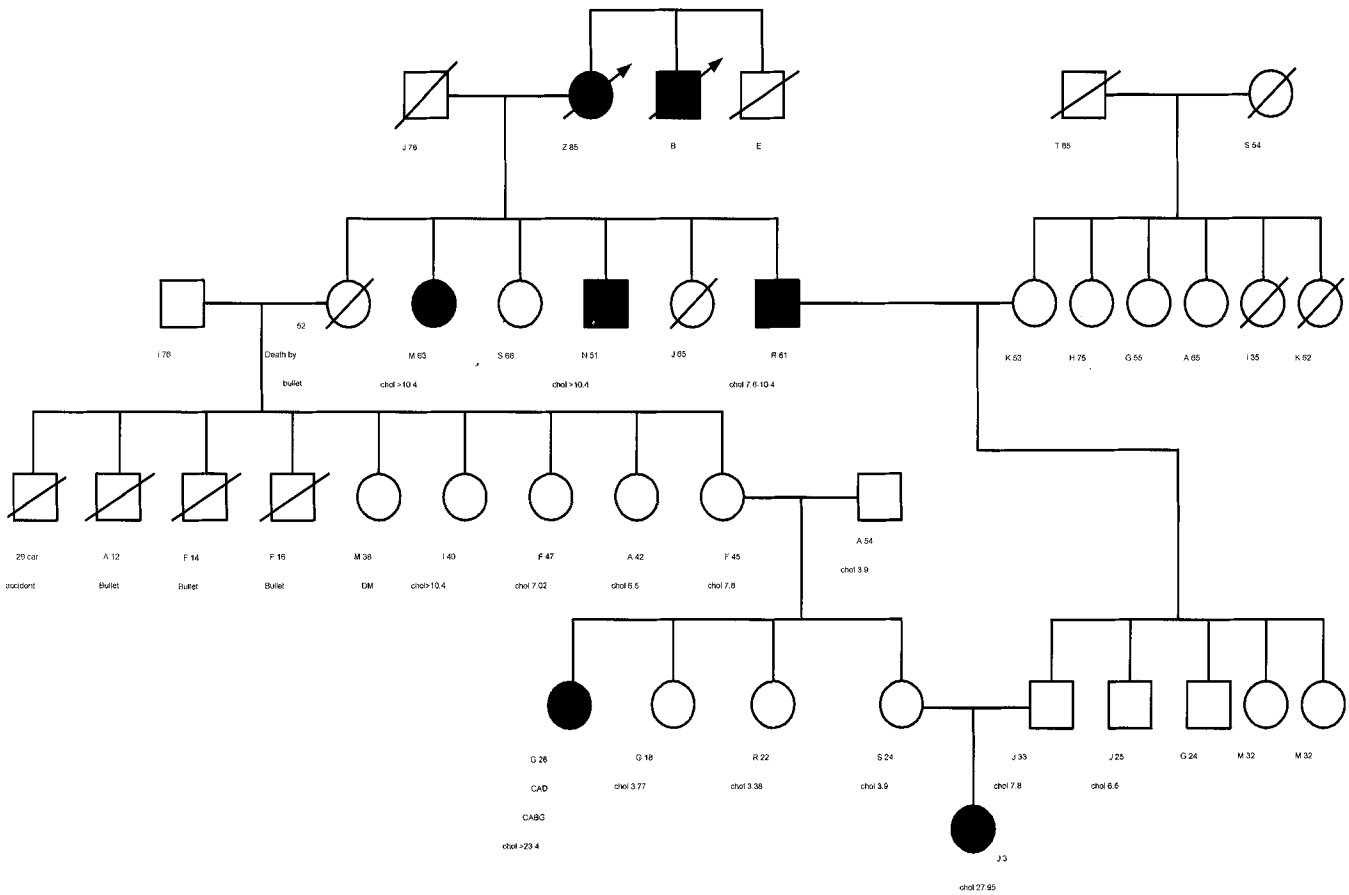
helped overcome the problem of cadaveric donation. In particular, LRLT has been useful in countries where cadaveric donation and organ procurement are unable to meet the demand for patients with liver disease. There are no reports to date of LRLT for patients with homozygous FH. In this paper, we describe a patient with homozygous FH who underwent successful left lobe liver transplantation from her mother. Treatment options for FH and the role of liver transplantation and post-operative management of hypercholesterolemia are reviewed.

Case report

A 4-year-old girl was diagnosed to have homozygous FH at the age of 1 year when she started developing multiple cutaneous xanthomas and was found to have a cholesterol level of 24 mmol/l. Her parents were first-degree cousins and a maternal aunt (28 years old) had homozygous FH when diagnosed at a similar age to our patient, and underwent coronary artery bypass grafting at the age of 18 and remains on medication for high cholesterol levels (Fig. 1).

On physical examination there were diffuse xanthomas over the hands, knees, buttocks and ankles. Serum cholesterol level was in excess of 26 mmol/l. Echocardiography and coronary angiography were normal. Because of the marked shortage in cadaveric organ donors in Lebanon, her mother was evaluated for left lateral segment liver donation and was found to be healthy with a total cholesterol level of 3.7 mmol/l (LDL 2.4 mmol/l). The patient underwent a LRLT from her mother. The postoperative course was unremarkable except for an episode of acute cellular rejection treated with the addition of mycophenolate mofetil. Her plasma cholesterol level dropped on the second postoperative day to 9.36 mmol/l and then reached a level of 6.5 mmol/l (Fig. 2). She remains well on tacrolimus and mycophenolate mofetil. Her cutaneous xanthomas have gradually disappeared (Fig. 3) and 1 year post-transplantation, her cholesterol level was still between 6.5 mmol/l and 7.54 mmol/l. She was put on simvastatin (5 mg/day) and her last cholesterol level was around 6 mmol/l.

Fig. 1 The pedigree of the family: *black* propositus with homozygous FH, *white* normal, *dashed* deceased



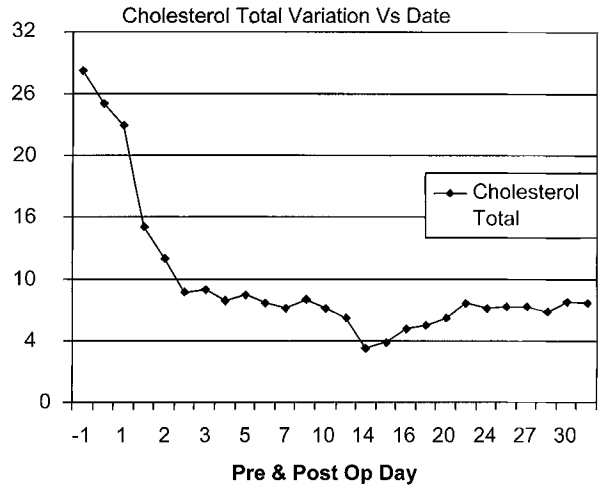


Fig. 2 Plasma or serum cholesterol level before and after liver transplantation

Discussion

FH is an inherited disorder characterized by a mutant gene for the LDL receptor that leads to hypercholesterolemia and accelerated atherosclerosis. The gene is located on the short arm of chromosome 19. When LDL receptors are deficient, the rate of removal of LDL from plasma declines, and the level of LDL rises in inverse proportion to the receptor number. The excess plasma LDL is deposited in scavenger cells and other cell types which produce xanthomas and atheromas.

Transmission of FH follows Mendelian genetics with an autosomal dominant inheritance pattern. The frequency of the FH homozygote is 1 in 1,000,000 while that of the heterozygote state is 1 in 500 with a gene dosage effect with highly varying clinical manifestations or phenotype. The earliest manifestation in the heterozygote type is hypercholesterolemia, which may be present at birth and may remain as the only clinical finding throughout the first decade. Tendon xanthomas and arcus corneae appear at the end of the second decade, and by the third decade each is present in about half of all heterozygotes.

The clinical picture of homozygotes is, on the other hand, remarkably uniform and distinctly different. In severe deficiency states (< 2% of normal receptor activity), cardiovascular death is likely within the first decade of life. In less severe cases (2–30% of normal LDL receptor activity), the disease is likely to produce death due to a cardiovascular problem in the second or third decade of life. The diagnosis of FH in the homozygote usually poses no difficulties. The finding of a plasma cholesterol level exceeding 17 mmol/l in a non-jaundiced child with a normal triglyceride value is virtually pathognomonic. It is difficult clinically to differentiate a severely affected heterozygote from a homozygote that has two LDL receptor mutations that partially impair but do not abolish receptor function [2, 3, 4].

Traditionally, treatment options for familial hypercholesterolemia have included diet and pharmacological therapy consisting of bile acid binding resins, HMG-CoA reductase inhibitors, nicotinic acid, and probucol. Apheresis and plasmapheresis produce regression of tendon xanthomas and some amelioration of atherosclerosis in FH homozygotes but are expensive and the effect is short-lived requiring repeated twice weekly sessions to maintain satisfactory results [5]. Ileal bypass surgery promotes increased intestinal loss of bile acids and secondarily depletes hepatic cholesterol stores but results in a sub-optimal response in homozygotes. Adverse effects on growth and development have also been noted [6, 7, 8]. Portocaval shunt is used as an alternative treatment. The operation was, however, only palliative and hence has never been adopted frequently [9, 10, 11, 12].

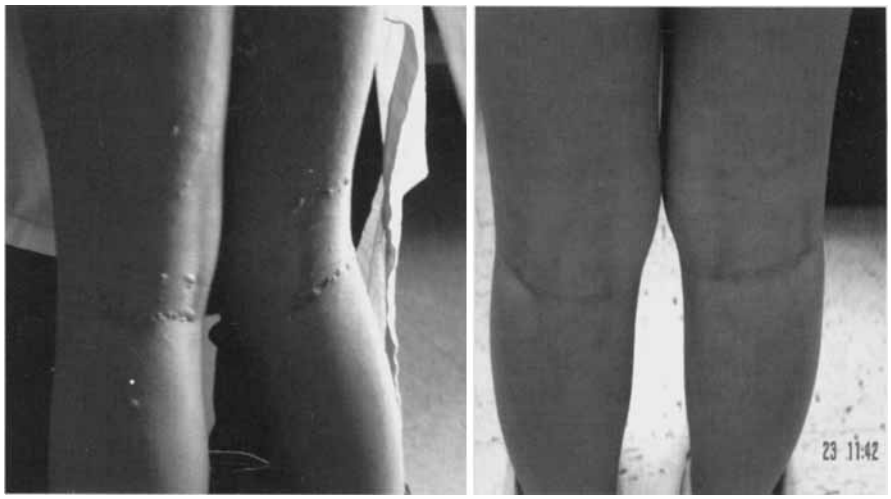


Fig. 3 Preoperative and postoperative xanthomas

Once advanced cardiac disease has occurred, combined heart-liver transplantation is required [13, 14, 15]. In those patients evaluated prior to the onset of significant atherosclerosis, liver transplantation cures the underlying disease because 50–75% of the entire body's LDL receptors exist within the liver. As a result, liver transplantation provides the patient with enough LDL receptors to prevent the onset of clinical disease [16, 17, 18, 19]. As in our case, mild hypercholesterolemia may persist after liver transplantation but can be managed with statins.

To date, all reported cases of liver transplantation for FH have involved cadaveric liver transplantation. The reasons why LRLT has not been considered in FH cases include concern over heterozygosity of the donors and disease progression whilst awaiting a suitable cadaveric donor. Our case is the first report of LRLT for familial hypercholesterolemia, as a result of the shortage of cadaveric organ donation in Lebanon. The limiting factor in liver transplantation continues to be the availability of suitable organs. The discrepancy between the number of patients awaiting liver transplant and the number of organs available, continues to widen because of the increasing number of patients with liver disease being offered transplantation without any increase in organ donation [20]. This problem is more pronounced in the developing world.

The success of liver transplantation in lowering the plasma level of LDL has stimulated efforts to use gene therapy to express recombinant LDL receptors in the liver. The liver cells are retrieved at partial hepatectomy which have been transfected ex vivo with a retrovirus expressing the LDL receptor. The cells were then reintroduced into the liver via the portal vein. The first FH homozygote treated by this approach was a 28-year-old French Canadian whose plasma LDL level fell 16% within 1 month after the procedure. She was then placed on lovastatin with an additional 19% reduction in the LDL cholesterol level. Four further FH homozygotes were subsequently treated using the same protocol and two of the four patients had no significant reduction in their plasma LDL cholesterol levels. Currently, gene therapy does not offer appropriate reduction in serum cholesterol levels and liver transplantation prior to onset of significant heart disease is the preferred mode of therapy [21, 22, 23, 24, 25, 26].

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