Surgical strategies for severe calcifications of the aorta (porcelain aorta) in two patients with homozygous familial hypercholesterolemia

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Homozygous familial hypercholesterolemia (HzFH) is a rare genetic defect caused predominantly by mutations at the low-density lipoprotein receptor. Until recent advances in the management of this complex disorder, patients affected by HzFH rarely survived beyond 30 years of age. Two patients with HzFH who survived to adulthood and developed cardiovascular complications requiring surgery are reported. In these patients, a porcelain aorta complicated surgical management. Lipid profile, mutational analysis and pathological assessment of the aorta were performed in two patients referred for cardiac surgery. The first patient was a 46-year-old man with a history of coronary artery bypass grafting (CABG) and recurrent severe angina who, because of a heavily calcified ascending aorta, required a complex repeat CABG. The second patient was a 42-year-old woman who underwent CAGB at 28 years of age and presented 13 years later with aortic stenosis. The extensive calcifications of the whole aortic root required performance of a modified Cabrol procedure. A porcelain aorta appears to be a feature of HzFH. This has an important impact on surgical planning and management and on possible pathophysiological processes related to the cardiovascular complications of HzFH.

Key Words: *Homozygous familial hypercholesterolemia; Porcelain aorta; Surgery*

Les stratégies chirurgicales en cas de graves calcifications de l'aorte (aorte porcelaine) chez deux patients atteints d'une hypercholestérolémie familiale homozygote

L'hypercholestérolémie familiale homozygote (HFHo) est une anomalie génétique rare causée en grande partie par des mutations du récepteur de lipoprotéines de faible densité. Jusqu'aux récents progrès dans la prise en charge de ce trouble complexe, les patients atteints d'une HFHo survivaient rarement après 30 ans. Les auteurs font état de deux patients atteints d'une HFHo qui ont survécu jusqu'à l'âge adulte et développé des complications cardiovasculaires exigeant une opération. Chez ces patients, une aorte porcelaine compliquait la prise en charge chirurgicale. Les auteurs ont procédé au profil lipidique, à l'analyse mutationnelle et à l'évaluation pathologique de l'aorte chez deux patients aiguillés en chirurgie cardiaque. Le premier patient était un homme de 46 ans qui avait déjà subi un pontage aortocoronarien (PAC) et avait des antécédents d'angine grave récurrente et qui, à cause d'une aorte ascendante très calcifiée, a dû subir un nouveau PAC complexe. Le deuxième patient était une femme de 42 ans qui avait subi un PAC à 28 ans et avait consulté 13 ans plus tard à cause d'une sténose aortique. Les calcifications étendues sur tout l'anneau aortique ont exigé la tenue d'une intervention de Cabrol modifiée. L'aorte porcelaine semble être une caractéristique de l'HFHo. Ce trouble a un effet important sur la planification et la prise en charge chirurgicales et sur les processus physiopathologiques éventuels reliés aux complications cardiovasculaires de l'HFHo.

Familial hypercholesterolemia is a genetic lipoprotein disorder resulting in severe cardiovascular complications. In the present paper, we report two patients with homozygous familial hypercholesterolemia (HzFH) who were referred for second cardiac operations and in whom we also proceeded with genetic analysis of the *LDLR* gene mutation. In both patients, severe calcification of the aortic root and ascending aorta (porcelain aorta) complicated surgical management and led to a need for a complex surgical procedure.

The reported patients include a 46-year-old man from Honduras (patient 1) referred for repeat coronary revascularization and a 42-year-old woman of Hungarian descent (patient 2) referred for aortic valve replacement. Plasma cholesterol, triglycerides, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol, apolipoprotein B and apolipoprotein A-I measurements were performed using standardized methods. LDL-C was calculated by the Friedewald formula (1). The *LDLR* gene mutation in patient 1 was identified as previously described (2), and direct sequencing of the *LDLR* genes was performed in patient 2.

CASE PRESENTATIONS

Patient 1

A 46-year-old man developed angina at 29 years of age and underwent coronary artery bypass surgery (CABG) for severe triple-vessel coronary artery disease; a sequential saphenous vein graft (SVG) was used to bypass the left anterior descending artery (LAD) and first diagonal (D1) (SVG to LAD-D1), and another sequential graft was done on the obtuse marginal (OM) branch of the

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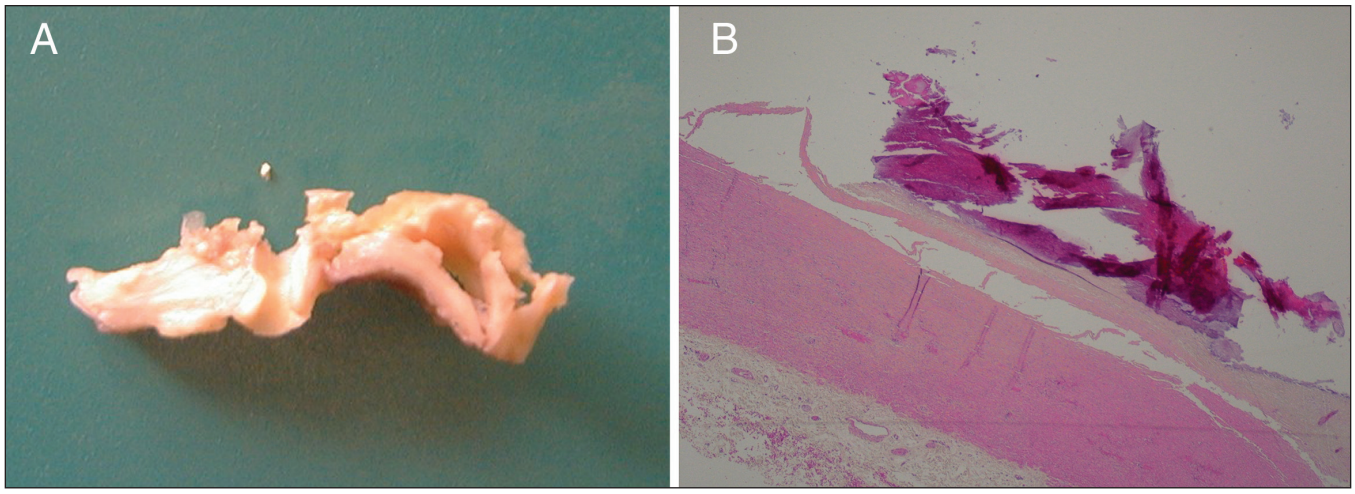

Figure 1) *Pathological specimen of aorta (patient 2) – macroscopic (***A***) and microscopic examination (***B***)*

circumflex coronary artery and the posterior descending artery (PDA) (SVG to OM-PDA) The procedure was complicated by tracheal stenosis. By that time, the patient had already had bilateral carotid endarterectomies and was known to have right subclavian stenosis and peripheral vascular disease. After his first surgery, the lipid profile revealed a total cholesterol level of approximately 18 mmol/L and LDL-C level of 16 mmol/L. The patient was closely followed by his cardiologist and placed on different cholesterol-lowering agents, including simvastatin and cholestyramine, which had marginal benefits on his total cholesterol and LDL-C levels. LDL-selective plasma filtration was initiated in 1992 and was associated with an approximate 45% decrease in time-averaged plasma LDL-C levels. The addition of atorvastatin in 1996 reduced his LDL-C by an additional 15%. The LDL-selective filtration treatment was discontinued for nearly three years because of unavailability of the filters. In 2002, selective plasma filtration was initiated using the Heparin-induced Extracorporeal Low-density lipoprotein Precipitation technique (Braun Medical, USA). In 2003, the patient presented with Canadian Cardiovascular Society angina classification grade III and underwent multiple percutaneous coronary intervention procedures. The most recent cardiac catheterization demonstrated a severe and completely calcified ascending aorta and arch. The SVG to OM-PDA was patent. However, the SVG to LAD-D1 was heavily diseased and stenosed with a patent distal portion, which included anatomosis to the area of the LAD and D1. The left internal mammary artery was injected and found to be of poor quality. The Allen's test was negative manually and with Doppler in both arms. The patient underwent a complex repeat CABG by performing a sequential LAD-D1 graft using a radial artery with a proximal anastomosis on the hood of the old patent SVG to OM-PDA. The surgery was performed on a beating heart, supported by cardiopulmonary bypass, with femoral artery cannulation. Using the Medtronic Octopus stabilization device (Medtronic Inc, USA), the hood of the old SVG to LAD-D1 was opened and the distal anastomosis was performed with the radial artery in an end-to-side fashion. After obtaining proximal and distal control of the old SVG to OM-PDA, the radial artery was anastomosed proximally to the normal-appearing proximal portion of the old graft. The patient was then successfully weaned from cardiopulmonary bypass and decannulated. Total cardiopulmonary bypass time was 22 min. The postoperative course was complicated by pneumonia and a left leg lymphocoele. The patient left the hospital one month after his surgery.

Mutational analysis of the *LDLR* gene was carried out. A novel mutation was identified, consisting of a splice-site mutation in exon 7 of the *LDLR* gene (2).

Patient 2

Patient 2 was a 42-year-old woman of Hungarian descent. Both her parents had severe hypercholesterolemia (LDL-C above the 95th percentile for age- and sex-matched subjects). Her only sibling died suddenly at 25 years of age. The patient had an acute myocardial infarction at 21 years of age and underwent quadruple CABG at 28 years of age (in 1991) (SVG to right coronary artery, SVG to OM, right internal mammary artery to OM1 and left internal mammary to LAD). At the time of surgery, the surgeon commented on the severe calcification of the proximal third of the ascending aorta (porcelain aorta). Her total cholesterol level (without treatment) was 13 mmol/L and LDL-C was approximately 11 mmol/L. While taking a combination of simvastatin 80 mg and ezetimibe 10 mg daily, her LDL-C remained in the range of 5.5 mmol/L to 6.0 mmol/L. Recently, the patient developed severe and symptomatic aortic stenosis and was referred for aortic valve replacement. Preoperative cardiac catheterization demonstrated that all grafts were patent, but that the aortic root was extensively calcified. The aortic valve area was 0.52 cm^2, with a peak gradient of 99 mmHg and a mean gradient of 55 mmHg. The patient first underwent a repeat sternotomy. Intraoperatively, the extensive calcifications of the whole aortic root required performance of a modified Cabrol procedure with a mechanical valved conduit. The left coronary ostium was so calcified that it required complete resection. A 7 mm Hemashield graft (Boston Scientific, USA) was anastomosed distally end-to-end to the native distal left main artery and proximally to the valved conduit. The small and extensively calcified aortic annulus was enlarged by a Manoughian aortoplasty procedure so that a size 21 mm St Jude aortic valved conduit (St Jude Medical, USA) could be used. Because the old patent SVG to the right coronary artery was injured during sternal re-entry, a new bypass was constructed and anastomosed proximally to the valved conduit. The patient left the hospital eight days after her surgery.

She was determined to be homozygous for the point mutation A410T (nt G1291A) in exon 9; this allele has been previously reported and is designated FH Algeria-2 (3). The pathological specimen of this subject comprised the aortic valve, root and ascending aorta. It revealed complicated arteriosclerosis consistent with a porcelain aorta (Figure 1).

DISCUSSION

The present report describes two patients with HzFH who survived well into adulthood, both of whom required two cardiac surgical procedures. Both patients were characterized genetically for the mutations at the *LDLR* gene and had a confirmed diagnosis of porcelain aorta. Atheromatous involvement of the aortic valve and root is commonly present in HzFH. Lipid infiltration and subsequent thickening of the aortic cusps leads to aortic stenosis in patients with HzFH (4) and the atherosclerotic involvement of the aortic root typically leads to ostial stenosis and 'supravalvular' aortic stenosis (5). At the present time, it is unclear what effect specific mutations have on the load and the pattern of calcification of the ascending aorta.

In view of recent improvements in medical management of HzFH, including cholesterol-lowering agents and extracorporeal LDL removal, patients affected with this disorder can now survive well into adulthood. They are then at high risk of requiring one or more cardiac surgical procedures. A characteristic feature of these patients is a porcelain aorta, which then complicates surgical management and renders the surgery more challenging. We suggest that thorough preoperative planning be made with particular attention to the type of procedure, the availability of conduits (for revascularization), the presence of comorbid diseases (particularly those affecting the vasculature) and the extent of calcification of the aorta. This will hopefully reduce surgical complications, leading to an overall better survival rate and quality of life.

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