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Aortic Valve Replacement in Familial Hypercholesterolemia: Not an Ordinary Procedure

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ABSTRACT

Familial hypercholesterolemia is an inherited disorder with incidences of approximately 1:500 and 1:1,000,000 in heterozygous and homozygous form respectively. Affected patients usually show early coronary artery disease and severe aortic root calcification, despite optimization of therapy. We report a case of a 64-year-old woman affected by heterozygous familial hypercholesterolemia which presented dyspnea and anginal symptoms due to a severely calcified aortic root causing valve stenosis and narrowed sinotubular junction. Aortic valve replacement and aortic root enlargement were performed using the Manougian procedure. Even for experiences surgeons, this surgery could prove challenging for this group of patients due to aggressive degenerative tissue calcification of the aortic root, which often presents an extremely calcified aortic valve with a small annulus associated to a narrowed sinotubular junction.

CASE REPORT

We report the case of a 64-year-old woman with a history of heterozygous familial hypercholesterolemia treated by apheresis every 20 days and statins. She presented with dyspnea and chest pain associated with mild exercise. Auscultation revealed an ejection systolic murmur. Doppler ultrasound of supra aortic trunks showed severe atheromatous disease without significant stenosis and there was no history of neurological events. Transthoracic echocardiogram showed severe calcified aortic stenosis with a mean gradient of 70 mmHg.

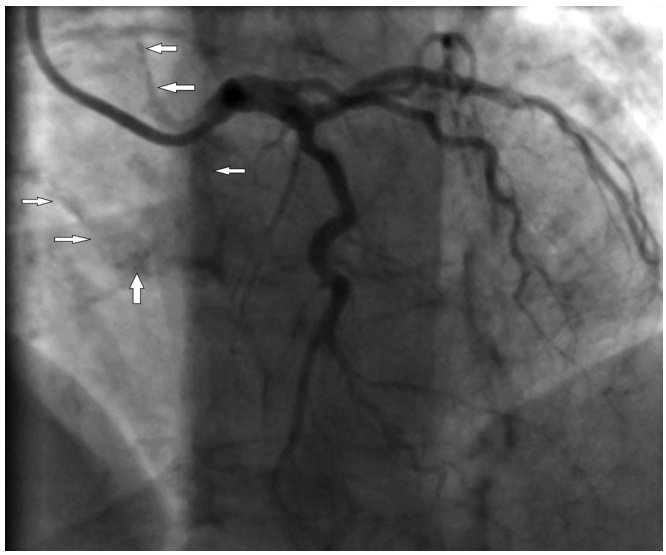
The coronary angiography revealed moderate coronary artery disease with no significant lesions and catheterization showed a mean gradient of 69 mmHg across the aortic valve. The angiography also showed an extremely calcified aortic root (Figure).

Considering the severe aortic stenosis and the symptoms of the patient we decided to perform an urgent cardiac surgery.

After sternotomy we found a heavily calcified aortic root as showed in the angiography. The distal part of the ascending aorta appeared free from calcifications at the digital palpation and we were able to perform the arterial cannulation close to the aortic arch. The cardiopulmonary bypass was instituted after cannulation of the right atrium and the patient was cooled to 32°C. A left ventricular vent through the right superior pulmonary vein was used. Just after cross-clamping of the ascending aorta a cold crystalloid cardioplegia solution was infused in an antegrade fashion.

We entered the calcified wall of the aorta using oblique aortotomy. Important calcification was observed in the posterior wall of the ascending aorta, in the entire aortic root involving both coronary ostia, and close to the muscular and membranous septum. The sinotubular junction was narrowed, about 15 mm.

After excision of the extremely calcified aortic valve followed by an aggressive decalcification, the aortic annulus appeared to be very small and close to the plane of coronary ostia, less than 5 mm. We decided to perform a Manougian procedure, with incision, made through the commisure between left and non coronary cusps, extended into the subcommissural triangle and anterior leaflet of the mitral valve. The defect created was repaired by a pericardial patch and the diameter of the annulus increased enough to allow insertion of 19 bioprosthesis CE. Considering the narrowed and calcified sinotubular junction, we were able to enlarge the aortic



Angiography showing aortic root calcifications (white arrows).

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root closing the aortotomy using the same patch and Prolene 3-0. The patient was weaned from cardiopulmonary bypass without difficulty.

The postoperative course was uneventful. The patient left the intensive care unit on the first postoperative day and was subsequently discharged home seven days after surgery.

DISCUSSION

The aim of this article is to describe our experience with patients affected by familial hypercholesterolemia. This issue is treated in the literature only through individual case reports.

The familial hypercholesterolemia is an inherited disorder of lipid metabolism characterized by high levels of low-density lipoprotein cholesterol (LDL-C) over a lifetime. The etiology is represented by mutations in the gene of the LDL receptor, the proprotein convertase subtilisin/kexin type 9 gene, the gene of apolipoprotein B or a rare mutation in LDL receptor adapter protein 1 gene.

The heterozygous familial hypercholesterolemia has a prevalence of 1 in 500 and the disease is less severe and more responsive to treatment because of the presence of one functional gene.

The homozygous familial hypercholesterolemia is more aggressive and frequently unresponsive to treatment with a prevalence of 1 in 1,000,000 [Al-Rasadi 2014].

The mechanism of familial hypercholesterolemia is based on a reduction in the number and activity of the low-density lipoprotein receptor localized on the surface of all cells. The cholesterol not transferred into the cells is cleared by macrophage scavenger.

Though single gene disorders have a crucial role in the etiology of familial hypercholesterolemia, polygenic variation together with environmental factors is the leading cause for hypercholesterolemia.

Homozygous familial hypercholesterolemia usually is characterized by cutaneous and tendon xanthomas formation frequently associated with coronary artery disease and aortic root calcification in early age [Jalel 2014].

Heterozygous familial hypercholesterolemia is often asymptomatic in childhood and adolescent years.

The treatment consists in lifestyle changes, cholesterol-lowering medication, and LDL apheresis.

Three novel classes of medication for familial hypercholesterolemia are mipomersen, lomitapide, and PCSK9 (proprotein convertase subtilisin/kexin type 9), which decrease LDL-C production. The first is an antisense oligonucleotide that inhibits the translation of apolipoprotein B-100 and the second is an inhibitor of the microsomal triglyceride transfer protein that prevents the incorporation of triglycerides into lipoprotein. The last is a proprotein convertase subtilisin/kexin type 9 inhibitor that decreases the degradation of the LDL receptor.

LDL apheresis has been shown to be a beneficial treatment in reducing LDL levels in patients who have elevated lipid levels in spite of optimal medical therapy [Varghese 2014].

The patients affected by familial hypercholesterolemia usually showed atheromatous involvement of the aortic root and coronary artery. It appears that exposure to LDL cholesterol concentration in shorter duration but in higher levels, typical of homozygous familial hypercholesterolemia, is the cause of severe involvement in that group of patients, while in heterozygous familial hypercholesterolemia it is principally due to the prolonged exposure time, though low level, of LDL cholesterol [Rallidis 1998].

The histological aspect of valve and aortic root lesions is characterized by foam cells, cholesterol clefts, and fibrocalcific deposits. The intracellular lipid and cholesterol clefts within the cuspal tissues are typical of aortic stenosis in homozygous familial hypercholesterolemia. That could explain why delayed introduction of lipid lowering therapy, removing cholesterol, could convert a lipid-rich aortic cusp into one more rigid fibrotic cusp, worsening the aortic stenosis [Rallidis 1998].

Aortic valve calcification in patients affected by familial hypercholesterolemia is often associated with severe involvement of the aortic root with a small annulus and narrowed sinotubular junction. In view of this aspect, an aortic valve replacement could be a challenging procedure even in skilled hands.

The presence of heavy calcification of the aortic root and ascending aorta may demand temporary hypothermic cardiac arrest and endarterectomy of the ascending aorta as reported by Yasuda [Yasusa 2000].

The presence of a calcified aortic root with a small aortic annulus may require an aortic root augmentation using different techniques like linguiform vascular-graft patch as reported by Saito [Saito 2006].

In the presence of heavy calcification associated with a small aortic annulus, it might be useful to replace the aortic root using an aortic homograft as reported by Elghobary [Elghobary 2006].

We found only moderate disease of the coronary artery but important calcification of the aortic root around the coronary ostium with a narrowed sinotubular junction and an annulus too small to fit a 19 bioprosthesis without performing Manougian procedure.

The therapeutic management of familial hypercholesterolemia is difficult. Our patient was under treatment with apheresis combined with statins, even though she had a severe aortic root calcification.

This aggressive lipid-lowering treatment slows the rate of progression of atherosclerosis, but an early diagnosis is paramount for a timely initiation of therapy. A late setting of the treatment paradoxically could accelerate the valve fibrosis, worsening the aortic stenosis and demanding a more challenging surgery.

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