Case Report

Valvular and Supravalvular Aortic Stenosis in Heterozygous Familial Hypercholesterolemia, A Case Report

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Familial hypercholesterolemia (FH) is an autosomal dominant disorder characterized by a high level of LDL-cholesterol and frequent coronary atherosclerosis. We studied a 64 year old woman with heterozygous (hetero) FH, who showed symptoms of chest pain and dyspnea with no other coronary risk factors than post-menopause and hypercholesterolemia. Although her coronary symptoms didn't reveal significant stenosis on coronary angiography, she had severe aortic valvular and supravalvular stenosis at the ascending aorta, which qualified her for aortic valve replacement. Moreover, a coronary flow study revealed functional ischemia with a reduction of the coronary flow reserve. We report a case of valvular and supravalvular aortic stenosis corrected by aortic valve replacement, a rare complication of hetero FH. *J Atheroscler Thromb*, 2005; 12: 289–293.

Key words: Heterozygous hypercholesterolemia, Valvular aortic stenosis, Supravalvular aortic stenosis, Aortic valve replacement

Introduction

Familial hypercholesterolemia (FH) is an autosomal dominant disorder in which the primary defect is a mutation in the low-density lipoprotein (LDL) receptor. FH is characterized by a high level of LDL-cholesterol, and increased risk of premature coronary artery disease (CAD). Approximately 85 % of males and 50% of females suffer coronary events before 65 years old if they are not treated (1).

Hypercholesterolemia affects not only the coronary artery, but also the aortic root and/or valve. Aortic stenosis is critical in the prognosis for most patients with homozygous (homo) FH, whose aortic valves are damaged by extreme hypercholesterolemia in a relatively short period

of time. However, in heterozygous (hetero) FH patients who require surgical replacement, additional risk factors such as high blood pressure, smoking and/or diabetes mellitus contribute to the aggravation of aortic valvular dysfunctions caused by underlying hypercholesterolemia (2), and damage to the valves occurs over an intermediate period of time.

FH is one of the most frequent monogenic hereditary disorders in the general population. Although the frequency of heterozygotes is approximately one per 500 individuals in most countries, severe valve involvement by atheromatous lesions is rare in hetero FH. Here, we report a patient with hetero FH without other major risk factors, who needed valve replacement therapy due to severe valvular and supravalvular aortic stenosis. We also review cases of valvular and supravalvular aortic disease in FH.

Case Presentation

A 64 year old female was admitted with two-month-old symptoms of chest pain and dyspnea on exertion. The

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patient had been diagnosed as suffering from FH about 20 years ago, when her serum cholesterol level was 15.1 mmol/l (585 mg/dl). Figure 1 shows her family pedigree, which indicates a high prevalence of hypercholesterolemia and CAD or sudden death at a young age. In particular, her elder brother had both aortic valve stenosis and CAD.

On admission, the patient was suffering from mild limitation of exertion, and was defined as NYHA functional class II. The patient's height was 150 cm, body weight was 47.6 kg, blood pressure was 120/58 mmHg (no laterality), and pulse rate was regular (66 beats/min). On cardiac examination, an increased aortic second heart sound and a systolic ejection murmur (Levine III/VI) were heard in the second intercostal space on the right sternal border, which was radiated to the neck. The patient had xanthoma (20 mm radius) at the right elbow and thickened Achilles' tendons (right: 24 mm with small calcification, left: 23 mm). All other physical examinations were normal. Routine laboratory examinations with a prescription of a HMG-CoA reductase inhibitor (simvastatin 10 mg/day) and anion-exchange resin (colestyramine 18 g/day), indicated normal findings except for the lipid profile, which consisted of a high level of LDL-cholesterol (7.0 mmol/l, 270 mg/dl), a low level of HDL-cholesterol (0.9 mmol/l, 36 mg/dl), normal levels of triglyceride (1.6 mmol/l, 142 mg/dl) and lipoprotein (a) (12 mg/dl). The activity of LDL receptors was reduced to 32% in the lymphocyte assay, a normal value being more than 80% (3, 4). The serum total homocysteine level was 8.6 nmol/ml (normal range < 10 nmol/ml). A 12-lead electrocardiogram indicated a sinus rhythm of 76 beats/min and left ventricular hypertrophy with strain patterns. Chest x-rays

revealed a cardiothoracic ratio (CTR) of 50.2%, normal pulmonary arteries and clear lung fields. Echocardiography demonstrated thickened high-echogenic leaflets of the aortic valve, which were limited to the opened phase (Fig. 2). The pressure gradient across the aortic valve was 126 mmHg and the aortic valve area was also calculated to be 0.41 cm². The mitral valve also looked mildly high-echogenic and thickened. The left ventricular wall revealed diffuse hypertrophy, and measured 12.5 mm. Similar to the echocardiographic findings, computed tomography demonstrated the presence of thickened and calcified leaflets in the aortic valve and atheromatous changes of the wall of the ascending aorta. In cardiac catheterization, coronary flow reserve by Doppler flow wire was decreased to 1.10 using 50 µg of ATP administered by intracoronary injection. The coronary arteriogram showed no significant stenosis (Fig. 3A, top: left coronary artery, bottom: right coronary artery) and the aortogram revealed a stenotic lesion at the ascending aorta (Fig. 3B). The pressure gradient across the left ventricle and the aorta was estimated to be 103 mmHg (Fig. 3C). Following these examinations at admission, the patient was diagnosed with aortic valve stenosis and supravalvular stenosis of the atheromatous ascending aorta. Since she also had mild left ventricular hypertrophy, she was suffering from functional angina, despite no significant coronary stenosis.

To treat the aortic stenosis, the patient underwent an aortic valve replacement with a prosthetic valve (Saint Jude Medical 19 mm). A larger valve could not be used because the aortic wall was unable to be widened. Figure 4 shows microscopic findings in a specimen of resected leaflet. At low magnification (Fig. 4A), the athero-

Fig. 1. Family pedigree of the patient (arrow). The closed circle and squares indicate familial hypercholesterolemia. Oblique lined squares indicate that they were diagnosed with hypercholesterolemia, but no evidence is available now. The numbers refer to age (years), serum LDL-cholesterol/HDL-cholesterol/triglyceride (mmol/l). SD: sudden death, AS: aortic valve stenosis, CAD: coronary artery disease, CC: colon cancer, * death at both, details unknown.

After replacement with the prosthetic aortic valve, the

angina disappeared. However, treatment with the beta-blocker metoprolol was continued to control the remaining aortic stenosis and LDL apheresis therapy with a HMG-CoA reductase inhibitor (simvastatin 20mg/day) was also pursued to treat the hypercholesterolemia.

Fig. 4. Microscopic observations of a specimen from an excised cusp from the aortic valve (H&E stain). Low magnification ($\times 10$) (A) and high magnification ($\times 75$) (B), fibrous tissue (arrow) and foam cells (arrow head) were seen on the aorta sides.

Discussion

Hetero FH is diagnosed by the existence of primary hypercholesterolemia (total cholesterol more than 250 mg/dl), skin xanthoma or a thickened Achilles' tendon, and decreased activity of the LDL receptor (5). Our patient was diagnosed as a heterozygote because primary hypercholesterolemia was recognized in only one of her sons. Moreover, the initial total cholesterol level without therapy was 15.1 mmol/l (585 mg/dl) and the activity of the LDL receptor was weak in the lymphocyte assay.

Supravalvular aortic stenosis is a characteristic feature of homo FH (6). Lipid infiltration with consequent thickening of the aortic cusps is considered to be a unique feature of homozygotes and can affect the valve's mobility (7). Summers *et al.* (8) found that 41% of homo FH patients had supravalvular aortic stenosis by evaluating the aortic root using magnetic resonance imaging. Beppu

et al. (9) also indicated following echocardiography that all homo FH patients had severe aortic root lesions in Japan.

The incidence of supravalvular aortic stenosis is lower in hetero FH than in homo FH. Furthermore, the case reported here with both severe valvular and supravalvular aortic stenosis is considered to be extremely rare. Rallidis *et al.* (10) reported that two patients (2.6%) had severe aortic valve stenosis and that one of them also had supravalvular stenosis among 78 consecutive hetero FH patients. In the present report, we didn't find any relationship between other factors, therefore we cannot suggest a mechanism for these stenotic complications. Ribeiro *et al.* (11) showed that 4 (12.5%) of 32 hetero FH patients had supravalvular narrowing and no valvular aortic stenosis. Similarly, in Japan, Beppu *et al.* (9) reported that supravalvular aortic stenosis was recognized in 4 (16%) of 25 hetero FH patients and no valvular aortic stenosis was detected.

Aortic stenosis is critical to the prognosis for most homo FH patients. It is also critical for some hetero FH patients (2). However, hetero FH patients who require surgical replacement, show additional risk factors such as high blood pressure, smoking, and/or diabetes mellitus which all contribute to the aggravation of aortic valvular dysfunctions caused by underlying hypercholesterolemia (2). Although the present subject had only post-menopause as an additional risk factor for hypercholesterolemia, she suffered not only from supravalvular stenosis but also from severe valvular stenosis. At present, we cannot clarify the mechanism involved, but the fact that her brother had a similar valvular stenosis that needed valve replacement suggested a relation to genetic defects in the LDL receptor.

Concerning her angina, this patient had no significant coronary stenosis. We suggest that the angina might have been elicited by relative ischemia induced by left ventricular hypertrophy. The decreased coronary flow reserve supported this hypothesis. It has been often pointed out that FH has a direct and firm correlation with CAD. A coronary angiographic study in Japan revealed that the prevalence of significant coronary stenosis in hetero FH was more than 3 times that in non-hetero FH, and, such patients were more likely to develop ectatic lesions compared to patients in western countries (12). Although female gender lessens the risk of atherosclerosis, the prevalence of CAD in female hetero FH patients was reported to range from 13% to 27% (13–15) and varies greatly with age and severity. This clinical variability also occurs among subjects coming from families sharing the same mutations in the LDL receptor gene, indicating that other genetic or environmental factors may play an important role in the development of atherosclerosis in FH (16). Kawashiri *et al.* (17) suggested that gene mutation of serum methylenetetrahydrofolate reductase, a homocys-

teine regulatory enzyme, had some effect on the prevalence of CAD in FH patients. Hill *et al.* (13) also reported that the existence of hypertriglyceridemia and hypertension had a strong association with the prevalence of CAD in female FH patients. In the present case, the patient did not show these symptoms nor any signs of other major coronary risk factors. Therefore, the present case had no significant coronary atherosclerosis. However, the reason for the discrepancy between CAD and aortic stenosis in our patient was not elucidated.

CAD is the major cause of death in hetero FH (18, 19). It accounts for about 73% of hetero FH deaths in Japan (20). The rate of death from CAD in heterozygotes was 11 times higher than that in the general population in Japan. Therefore, we should continue an intensive LDL-lowering therapy with apheresis and medication therapy to prevent CAD.

References

- (1) Cliveria F: Guidelines for the diagnosis and management of heterozygous familial hypercholesterolemia. *Atherosclerosis*, 173: 55–68, 2004
- (2) Kawaguchi A, Yutani C, and Yamamoto A: Hypercholesterolemic valvulopathy: an aspect of malignant atherosclerosis. *Ther Apher Dial*, 7: 439–443, 2003
- (3) Ranganathan S, Hattori H, and Kashyap ML: A rapid flow cytometric assay for low-density lipoprotein receptors in human peripheral blood mononuclear cells. *J Lab Clin Med*, 125: 479–486, 1995
- (4) Kajinami K and Takekoshi N: Assay for LDL receptor activity (Japanese). *Nippon Rinsho*, Suppl, 2: 827–832, 2001
- (5) Tarui S: Classification and diagnosis criteria of primary hyperlipidemia, Ministry of Welfare, Study Report, pp 26–34, 1988
- (6) Brook GJ, Keidar S, Boulous M, Grenadier E, Wiener A, Shehada N, Markiewicz W, Benderli A, and Aviram M: Familial homozygous hypercholesterolemia: clinical and cardiovascular features in 18 patients. *Clin Cardiol*, 12: 333–338, 1989
- (7) Roberts WC, Ferrans VJ, Levy RI, and Fredrickson DS: Cardiovascular pathology in hyperlipoproteinemia. Anatomic observations in 42 necropsy patients with normal or abnormal serum lipoprotein patterns. *Am J Cardiol*, 31: 557–570, 1973
- (8) Summers RM, Andrasko-Bourgeois J, Feuerstein IM, Hill SC, Jones EC, Busse MK, Wise B, Bove KE, Rishforth BA, Tucker E, Spray TL, and Hoeg JM: Evaluation of the aortic root by MRI: insights from patients with homozygous familial hypercholesterolemia. *Circulation*, 98: 509–518, 1998
- (9) Beppu S, Minura Y, Sakakibara H, Nagata S, Park YD, Nambu S, and Yamamoto A: Supraaortic stenosis and coronary ostial stenosis in familial hypercholesterolemia: two-dimensional echocardiographic assessment. *Circulation*, 67: 878–884, 1983
- (10) Rallidis L, Naoumova RP, Thompson GR, and Nihoyannopoulos P: Extent and severity of atherosclerotic involvement of the aortic valve and root in familial hypercholesterolaemia. *Heart*, 80: 583–590, 1998
- (11) Ribeiro P, Shapiro LM, Gonzalez A, Thompson GR, and Oakley CM: Cross sectional echocardiographic assessment of the aortic root and coronary ostial stenosis in familial hypercholesterolaemia. *Br Heart J*, 50: 432–437, 1983
- (12) Genda A, Nakayamada A, Shimizu M, Nunoda S, Sugihara N, Suematsu T, Kita Y, Yoshimura A, Koizumi J, Mabuchi H, and Takeda R: Coronary angiographic characteristics in Japanese patients with heterozygous familial hypercholesterolemia. *Atherosclerosis*, 66: 29–36, 1987
- (13) Hill JS, Hayden MR, Frohlich J, and Pritchard PH: Genetic and Environmental Factors affecting the Incidence of coronary artery disease in heterozygous familial hypercholesterolemia. *Arterioscler Thromb*, 11: 290–297, 1991
- (14) Gange C, Moorjani S, Brun D, Toussaint M, and Lupien PJ: Heterozygous familial hypercholesterolemia. Relationship between plasma lipids, lipoproteins, clinical manifestations and ischaemic heart disease in men and women. *Atherosclerosis*, 34: 13–24, 1979
- (15) Hirobe K, Matsuzawa Y, Ishikawa K, Tarui S, Yamamoto A, Namabu S, and Fujimoto K: Coronary artery disease in heterozygous familial hypercholesterolemia. *Atherosclerosis*, 44: 201–210, 1982
- (16) Ferrieres J, Lambert J, Lussier-Cacan S, and Davignon J: Coronary artery disease in heterozygous familial hypercholesterolemia patients with the same LDL receptor gene mutation. *Circulation*, 92: 290–295, 1995
- (17) Kawashiri M, Kajinami K, Nohara A, Yagi K, Inazu A, Koizumi J, and Mabuchi H: Effect of common methylenetetrahydrofolate reductase gene mutation on coronary artery disease in familial hypercholesterolemia. *Am J Cardiol*, 86: 840–845, 2000
- (18) Miettinen TA, and Gylling H: Mortality and cholesterol metabolism in familial hypercholesterolemia. Long-term follow-up of 96 patients. *Atherosclerosis*, 8: 163–167, 1988
- (19) Mabuchi H, Koizumi J, Shimizu M, and Takeda R: Development of coronary heart disease in familial hypercholesterolemia. *Circulation*, 79: 225–232, 1989
- (20) Mabuchi H, Miyamoto S, Ueda K, Oota M, Takegoshi T, Wakasugi T, and Takeda R: Causes of death in patients with familial hypercholesterolemia. *Atherosclerosis*, 61: 1–6, 1986