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. 


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
The 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-
matous lesion mainly consisted of fibrous tissue. Furthermore, higher magnification (Fig. 4B) showed that a foam cell-rich lesion (Fig. 4, arrow) was located at the aortic surface of the resected leaflet. 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. 2. Two-dimensional echocardiogram showing high-echogenic leaflets of the aortic valve (arrow). Each leaflet was limited in its ability to open but no fusion was recognized among leaflets. LV: left ventricle, LA: left atrium, Ao: ascending aorta.

Fig. 3. Results of cardiac catheterization. No atheromatous lesion was recognized in the coronary arteriogram (A, top: left coronary artery, bottom: right coronary artery). Supravalvular aortic stenosis (arrow) at the ascending aorta was seen in the aortogram (right anterior oblique view) (B). A significant pressure gradient was traced between left ventricular pressure and aortic pressure (LV: left ventricle, Ao: ascending aorta) (C).
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 supraventricular aortic stenosis is lower in hetero FH than in homo FH. Furthermore, the case reported have 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-
The 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 presence of CAD in female FH patients. In the present case, the patient did not show these symptoms or 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