Supravalvular and Valvular Aortic Stenosis in Homozygous Familial Hypercholesterolemia

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SUMMARY
Premature atherosclerosis with a particular predilection to the coronary arteries is a well-known complication of homozygous familial hypercholesterolemia. However, well documented involvement of the aortic root and valve with aortic stenosis has not been recognized frequently antemortem. Clinical, echocardiographic, hemodynamic and angiographic features of a case with valvular and supravalvular aortic stenosis secondary to homozygous familial hypercholesterolemia are described. Surgical relief of the left ventricular outflow obstruction was not attempted because of the patient's refusal.

Additional Indexing Words:
Familial hypercholesterolemia Xanthomas Aortic stenosis

HOMOZYGOUS familial hypercholesterolemia is a rare autosomal dominant disease characterized by very high plasma levels of cholesterol, the development of xanthomas early in childhood and accelerated atherosclerosis, particularly of the coronary arteries.1) Premature coronary artery disease resulting in early death is well recognized in this disorder.2,3) However, involvement of the aortic root and valves giving rise to left ventricular outflow obstruction appears to be another important complication.4–6) Until recent years the diagnosis of aortic stenosis has usually been established clinically or at autopsy.5) Nevertheless, recently a small number of cases have been diagnosed hemodynamically and angiographically and surgical correction has been successfully carried out in a few.7–14)

We describe the clinical, echocardiographic, angiographic and hemodynamic features of both supravalvular and valvular aortic stenosis secondary to homozygous familial hypercholesterolemia in a girl.
CASE REPORT

A 19-year-old girl was referred to the Cardiology Unit of the Hacettepe Medical Faculty in January, 1986 because of widespread xanthomatosis and a heart murmur. The patient had first been seen at the Department of Pediatrics of the Hacettepe Medical Faculty when she was 7 years old. At that time, it was noted that she had xanthomas on the elbows, toes and interdigital areas, but no cardiac murmur was heard on cardiac examination. She was found to have an elevated serum cholesterol level of 700 mg/dl and was started on therapy with a low saturated fat diet and hypolipidemic agents. However, no consistent fall in cholesterol levels was observed during several irregular follow up visits.

When the patient presented to be investigated at the Cardiology Unit in January, 1986, she complained of shortness of breath on severe exertion but denied chest pain, dizziness or syncope. She was the fourth child of a family of 8. Her parents were first cousins and both had moderately elevated serum cholesterol levels confirmed on several occasions. The youngest sibling of the family (an 8-year-old girl) had similarly suffered from xanthomatosis and had very high serum cholesterol levels since the age of 5. The other siblings (excluding the two who could not be investigated) were found to be normal by physical examination and laboratory tests (Fig. 1).

On examination, the blood pressure was 120/75 mmHg and the pulse was 100/min and regular. The peripheral pulses were all present and were of normal volume. She had numerous impressive xanthomas on the elbows, dorsum of the hands, fingers, toes, knees, buttocks, Achilles tendons and the interdigital areas compatible with the homozygous state (Fig. 2). Marked bilateral corneal arcus (juvenilis) was present (Fig. 2). Cardiovascular examination revealed a systolic thrill in the first right interspace, in the suprasternal notch and in both carotid arteries. A grade 4/6 systolic ejection

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**Fig. 1.** Family tree of our homozygous familial hypercholesterolemic patient. square: male, circle: female, white: normal, half black: heterozygote, black: homozygote. Pt = patient. * lipid profiles unknown.
murmur maximal at the first right interspace and radiating to both carotids and down the left parasternal border was audible. No ejection click was heard and the aortic component of the second sound was normal. Bruits were noted over the abdomen, bilateral carotid and femoral arteries.

The chest radiograph was normal. The resting ECG revealed a mean frontal QRS axis of 70° and mild ST segment depressions in leads V₃ to V₆. The exercise ECG was strongly positive with marked ST segment depressions over the chest leads (Fig. 3). The serum chemistries were as follows: total cholesterol 570 mg/dl (normal <200 mg/dl), high density lipoprotein
cholesterol 27 mg/ml (normal >35 mg/dl), low density lipoprotein cholesterol 533 mg/dl (normal <140 mg/dl) and triglyceride 70 mg/dl (normal <124 mg/dl). Other serum chemistries including the thyroid hormones were within normal limits. An echocardiogram (M-mode) demonstrated a narrow and thickened aortic ring and supravalvular narrowing of the aortic root.

Cardiac catheterization and coronary angiography were performed. The left ventricular pressure was 166/4 mmHg and the aortic systolic pressure was 122 mmHg with a mean of 90 mmHg. Two systolic pressure differences were observed on withdrawal from the left ventricle to the aorta. A 26 mmHg
systolic gradient was found across the aortic valve, while a second 18 mmHg systolic gradient was noted between the proximal and distal ascending aorta (Fig. 4). This resulted in a total systolic pressure difference of 44 mmHg between the left ventricle and distal aorta. Aortography showed both funnelling and narrowing of the aortic root and thickening in the aortic valve cusps (Fig. 5). Mild aortic regurgitation was observed. Coronary angiography demonstrated narrowing in the right coronary ostium. The left main, left anterior descending and circumflex arteries were normal. Digital subtraction angiograms of the carotid and femoral arteries and abdominal aorta were with normal limits except for slight irregularities of the vessel contours.

In addition to a strict diet and hypolipidemic drug regimen, aortic and coronary artery surgery was recommended in view of the severity of the anatomic lesions. The patient refused the surgical correction because of the high risk involved. The early impression that her hypercholesterolemia was rather resistant to diet and drug therapy suggests that the prognosis is not favorable and, unfortunately, more sophisticated cholesterol lowering therapy such as plasmapheresis is not available at present.

**DISCUSSION**

Homozygous familial hypercholesterolemia characterized by severe hypercholesterolemia (mainly low-density lipoprotein cholesterol) is a rare disorder. In the Western world the incidence of homozygotes is estimated to be one in 1 million persons, and reports from several Asian countries,
including Japan, indicate similar frequencies. It is now known that the genetic defect in this disorder leads to an abnormality in the cell receptors which normally facilitate the cellular uptake and degradation of low-density lipoprotein. When cholesterol cannot be cleared by the normal cellular mechanism, the macrophage scavenger pathway becomes operative, resulting in the formation of xanthomas and a greatly increased tendency to atheroma.

The clinical diagnosis of the homozygous state is strongly suggested by juvenile xanthomatosis, elevated low-density lipoprotein cholesterol levels (generally >500 mg/dl) and an autosomal dominant mode of inheritance. Demonstration of low-density lipoprotein receptor abnormalities in the skin fibroblasts grown in tissue culture confirm the definitive diagnosis. Although low-density lipoprotein receptor abnormalities could not be investigated, our patient possessed all the clinical features of the homozygous state.

The major complication of homozygous familial hypercholesterolemia is accelerated atherosclerosis. Involvement of the coronary arteries is the form widely recognized and with the most dramatic consequences. Actually, coronary artery disease frequently has its clinical onset before age 10 and myocardial infarction has been reported as early as 18 months of age. Characteristically, strictures are commonly seen in the proximal portions or the ostia of the coronary arteries, but the distal vessels are remarkably free of disease. The exercise ECG suggested myocardial ischemia and coronary angiograms disclosed right coronary ostial stenosis in our case, although she had no angina. However, besides the coronary arteries other major arteries may show severe premature atherosclerosis causing significant symptoms and signs. It is suggested that atherosclerosis of the carotid arteries producing symptoms of cerebrovascular insufficiency might be recognized earlier than coronary atherosclerosis. Our patient had bruits over the abdomen and the carotid and femoral arteries but digital subtraction angiograms revealed no significant stenosis in the abdominal aorta and the other mentioned vessels.

Atheromatous and xanthomatous involvement of the aortic root and aortic valve is another characteristic manifestation observed in the homozygote. The proximal aortic root is usually narrowed and shows funnelling towards the aortic valve. This represents the accumulation of atheroma which is most noticeable in the sinuses of Valsalva and extends proximally to involve the coronary ostia and aortic valve cusps. Pressure gradients between the left ventricle and aorta indicating valvular aortic stenosis have been described in the previous reports. In the 7 patients Allen et al evaluated by cardiac catheterization and angiography, all but one were found to have valvular aortic stenosis, although all showed characteristic narrowing of the aortic root. Sprecher et al also had a case with hemodynamically docu-
mented valvular aortic stenosis. Valvular aortic stenosis is presumably due to inadequate valve opening because of atheromatous masses occupying the sinuses of Valsalva rather than atheromatous deposits on the cusps.\textsuperscript{11,12) However, some recent reports emphasize the presence of supravalvular aortic stenosis in addition to a valvular component.\textsuperscript{5,12,13) It is very probable that supravalvular narrowing due to atherosclerosis may add a significant gradient beyond the valvular gradient in some cases. Pressure withdrawal tracings from the left ventricle to the aorta of our patient also demonstrated both valvular and supravalvular systolic pressure gradients. This finding, well documented during life, is very rarely reported in the medical literature.\textsuperscript{5,12)}

Aortography provides the best means of recognizing the typical cardiovascular features of this disorder. Nevertheless, echocardiography (M-mode and two-dimensional) may prove to be useful in most of the cases, demonstrating the thickening and narrowing of the aortic root and distortion of the aortic valve movement,\textsuperscript{11,12,14,19} as observed in our case.

There are several case reports of successful surgical corrections of the left ventricular outflow obstruction in homozygous familial hypercholesterolemia.\textsuperscript{7-13) The usual procedure is replacement of the aortic valve and repair of the supravalvular narrowing. Coronary artery bypass grafting may or may not be necessary as an additional procedure. Transluminal coronary angioplasty has also been employed in one patient with modest benefit, but this technique deserves further evaluation in this disease.\textsuperscript{6)}

Xanthomatous plaques and thickening of the endocardial surfaces of the mitral valve and endocardium have also been observed in the homozygote and may explain the clinical findings of mitral regurgitation and mitral stenosis that are occasionally reported.\textsuperscript{20) Our patient had no clinical features suggesting mitral valve disease.

Diet and drug treatment have been of very limited value in treating homozygous familial hypercholesterolemia. The early encouraging results with newer forms of therapy such as the portacaval shunt operation, plasmapheresis and transplantation of the liver may result in prolonged survival of these patients.\textsuperscript{21,22) These new modes of therapy might be considered for our patient in the future.

It appears that the development of valvular and supravalvular aortic stenosis is a characteristic complication of homozygous familial hypercholesterolemia and is not as rare as had previously been supposed. Since survival of patients may be prolonged by new forms of cholesterol lowering therapy, early recognition and adequate surgical correction of this significant complication gains increasing importance.
REFERENCES


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