CARDIOVASCULAR FINDINGS IN FAMILIAL HYPERCHOLESTEROLEMIC CHILDREN

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Four child patients (1 male and 3 females) with homozygous familial hypercholesterolemia (FH) were examined. They were 4y4m to 9y8m of age on admission. A female patient at age 5y7m on admission had already experienced anginal attacks. Ischemic change was found on exercise ECG in 2 patients. Grade 1/6 to 3/6 (Levine) systolic ejection type murmur was audible in all patients. Cardiac catheterization was carried out in all patients. Supravalvular aortic stenosis was found and so-called atherosclerotic wall thickening was also noticed in 3 of them. Narrowing of the coronary arteries was found in only 1 patient who complained of anginal pain. Supravalvular aortic stenosis was more prevalent than coronary artery disorders in FH children and this lesion was also detected by echocardiography. Therefore, follow-up by echocardiography seems to be very useful in assessing the progression of atherosclerosis in patients with severe hypercholesterolemia.

ATHEROSCLEROSIS in familial hypercholesterolemia (FH) is considered to be a typical example of vascular lesions associated with pure hypercholesterolemia. Among them, homozygous FH is peculiar because very high plasma cholesterol levels above 500 mg/dl have been sustained since childhood. Atherosclerosis developing in such a special situation seems to be considerably different from ordinary cases of atherosclerosis in the general population in regard to the distribution, extent, and the appearance of symptoms and signs. The cardiovascular symptoms of homozygous FH children have not been reported in detail because of the scarcity of the cases. What is the typical cardiovascular findings of this disease in relation to a child age? Which method is suitable to assess its severity? We examined 4 patients with homozygous FH at the National Cardiovascular Center Hospital and attempted to find its characteristics in cardiovascular lesions.

METHODS

Four child patients with homozygous FH were the subjects of the present study. There was one male and three females, aged 4 years and 4 months (4y4m) to 9y8m. The diagnosis was tentatively made based on family history, serum cholesterol levels, and clinical findings. It was confirmed by the assay of $^{125}$I-low density lipoprotein (LDL) binding to cultured skin fibroblasts. In 2 cases parents were cousins and in another

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Plasmapheresis

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TABLE I CLINICAL SYMPTOMS AND THE DATA OF THE CARDIOVASCULAR EXAMINATIONS IN OUR PATIENTS

<table>
<thead>
<tr>
<th>PATIENT</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>5Y7M</td>
<td>9Y4M</td>
<td>4Y4M</td>
<td>9Y8M</td>
</tr>
<tr>
<td>Sex</td>
<td>F</td>
<td>M</td>
<td>F</td>
<td>F</td>
</tr>
<tr>
<td>Xanthoma</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Angina</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Hypertension</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Neck Bruit</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>ECG: ST Change (at rest)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>ECG: ST Change (exercise)</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>ECG: abnormal Q</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Chest X−P:CTR (%)</td>
<td>51.8</td>
<td>52.6</td>
<td>50.6</td>
<td>49.0</td>
</tr>
<tr>
<td>Perfusion Defect (TI Scintigraphy)</td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CTR=Cardio-Thoracic Ratio, TI=Thallium

TABLE II LABORATORY BLOOD CHEMICAL FINDINGS IN OUR PATIENTS

<table>
<thead>
<tr>
<th>PATIENT</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Cholesterol</td>
<td>780</td>
<td>491</td>
<td>692</td>
<td>532</td>
</tr>
<tr>
<td>HDL-cholesterol</td>
<td>20</td>
<td>32</td>
<td>30</td>
<td>23</td>
</tr>
<tr>
<td>Ester Cholesterol</td>
<td>551</td>
<td>293</td>
<td>488</td>
<td>382</td>
</tr>
<tr>
<td>TG</td>
<td>187</td>
<td>50</td>
<td>78</td>
<td>85</td>
</tr>
<tr>
<td>Phospho Lipid</td>
<td>512</td>
<td>454</td>
<td>456</td>
<td>353</td>
</tr>
<tr>
<td>Free Fatty Acid</td>
<td>809</td>
<td>879</td>
<td>1399</td>
<td>301</td>
</tr>
<tr>
<td>Beta Lipoprotein</td>
<td>715</td>
<td>592</td>
<td>1742</td>
<td>1295</td>
</tr>
<tr>
<td>VLDL</td>
<td>190</td>
<td>45</td>
<td>107</td>
<td>28</td>
</tr>
<tr>
<td>LDL</td>
<td>2008</td>
<td>1584</td>
<td>1591</td>
<td>1201</td>
</tr>
<tr>
<td>Chylomicron</td>
<td>18</td>
<td>16</td>
<td>10</td>
<td>23</td>
</tr>
</tbody>
</table>

LDL receptor of fibroblast
(125I-LDL binding % of the normal control) negative
(8%) negative (7%) negative (1%) negative (7%)

PT(%) | 74 | 70 |
PTT(SEC) | 32 |
Fibrinogen(mg/dl) | 365 | 160 |
Platelet count (million) | 21.6 | 25.2 |
Bleeding Time (minutes) | 14.0 | 9.5 |

HDLL=High Density Lipoprotein, TG=Triglyceride,
VLDLL=Very Low Density Lipoprotein; LDL=L Low Density Lipoprotein; PT=Prothrombin Time;
PTT=Partial Thromboplastin Time

experienced only by the 5y7m old female patient. Their blood pressures were all in the normal range. The neck “bruit” was audible in all patients. The systolic ejection type murmur (grade 1/6 to 3/6 Levine) was audible at the upper left sternal border in all patients (Table I).

2) Laboratory Data

On admission, serum cholesterol levels ranged from 491 to 780 mg/dl. These had already been reduced by 100—200 mg/dl with dietary management during the time they had been treated as our outpatient. Phospholipid was also increased and LDL ranged from 1201 to 2008 mg/dl. Free fatty acid was higher in 3 patients and HDL-cholesterol was decreased in all patients. $^{125}$I-LDL binding to fibroblasts was below 10% in all patients, i.e. the defect in LDL receptors was of receptor negative type, although the normal sized receptor protein and its precursor was detected at very low levels by $^{35}$S-methionin labelling and antibody precipitation in one patient (K.M., 9y4m boy) (Table II).

No remarkable change was found on resting ECG in any patient. But, ST change was noticed on exercise ECG in 2 patients. Their chest X rays did not show any abnormalities. TI myocardial scintigraphy was carried out in 2 patients but no abnormalities were found. Echocardiography revealed supravalvular aortic narrowing in 3 patients (Table I).

3) Therapy

Compactin (ML-236-B), cholestilamine, and probucol were given as anticholesterolmic drugs in single or combined regimens. Cholestilamine was ineffective and a very large dose of compactin was necessary to reduce serum cholesterol to a significant extent as was usually achieved in heterozygous FH.
patients. Probucol was the only drug which was effective at a usual dosage. Intravenous alimentation was tried in one of the patients and it decreased serum cholesterol to a level around 450 mg/dl.

Plasmapheresis is the only procedure which can reduce cholesterol to a level where we can expect to prevent the progression of atherosclerosis, and therefore this procedure has been repeated up to date in all patients in combination with probucol as an oral antilipidemic drug.

4) Cardiovascular Findings in Individual Patients

Patient 1 (5y7m old female)
She had experienced anginal attack already before admission. Based on hearing from her mother about the peculiar signs shown by the patient, it was presumed that the anginal attack started at her age of 2 1/2 years. During the attack, ST depression was noted in I, II, and V3–6 on ECG. The same change was found during a Treadmill exercise test (stage 1 of Bruce’s protocol). Supravalvular aortic narrowing (SVAS) was detected in long axis view of echocardiography (Fig. 1) and it was confirmed by angiography. Grade 2/4 (Kohn) aortic regurgitation was also detected (Fig. 2). The pressure gradient between left ventricle (LV) and ascending aorta was 23 mmHg. Her left coronary artery (LCA) was very weak. Its wall was irregular and the so-called run off of the medium was poor. The left circumflex branch (LCX) was almost completely obstructed. On the other hand, the right coronary artery (RCA) was intact (Fig. 3). Her anginal attack was lessened following 2 years of plasmapheresis treatment, but even after 3 years of the therapy ischemic change was still found on exercise ECG. A selective angiography of RCA carried out later, at the age of 12 years, showed a prominent development of collaterals from right to left (Fig. 3).

Patient 2 (9y4m old male)
ECG abnormality was not found at rest but the ischemic change was noticed on exercise. Even so, no remarkable change was found on coronary angiography. SVAS was noticed and it was also detected on echocardiography. Deformity of the aortic valve (Fig. 4) and irregularity of the descending aorta were found.
**Patient 3** (4y4m old female)

No significant change was found on ECG at rest or during exercise. Echocardiography and angiocardiography did not show any remarkable atherosclerotic change.

**Patient 4** (9y8m old female)

There was no remarkable finding on ECG, but echocardiography showed supravalvular aortic narrowing. Coronary arteries were intact on angiography, although SVAS and grade 2/4 (Kohn) aortic regurgitation were found (Fig. 5). Marked irregularities of the descending aorta were noticed. The most impressive finding of this patient was a tapering change of the abdominal aorta (Fig. 6), but common iliac arteries and their branches were not obstructed. Clinically, the symptoms of the perfusion disturbance of lower extremities were not noticed. These findings of cardiac catheterization and angiography in all patients are summarized in Fig. 7.

**DISCUSSION**

The metabolic basis of FH was demonstrated by Goldstein and Brown to be a defect in LDL receptors. It is a congenital disorder of lipoprotein metabolism inherited as an autosomal codominant trait. The frequency of the heterozygote is one in 500 and that of the homozygote is one in one million in the general population.

Sprecher et al examined 16 Caucasian FH homozygote patients including both children and adults and reported their cardiovascular features. In this study we examined 4 homozygous FH Japanese children. According to the data reported by Sprecher et al, the total cholesterol and LDL cholesterol level were higher in the patients who had experienced episodes of angina than in those patients who did not have such episodes. In our study, the total and LDL cholesterol levels were the highest in Patient 1 (5y7m old female) who had experienced anginal attacks. The patient was a FH homozygote with receptor-negative type and no receptor protein was demonstrated in her fibroblasts.
by using $^{35}$S-methionin labelling followed by a detection with antibody. HDL-cholesterol level was significantly lower and ischemic heart disease appeared more frequently in young patients with the receptor-negative type of FH compared to those with the receptor-deficient type.

Neck bruit and the precordial ejection type heart murmur were detected in all patients, but the age when these symptoms began is not clear. The peak systolic pressure gradients between LV and the ascending aorta were 6–23 mmHg in 3 patients aged 5 to 10 years. Such pressure gradients do not suggest the presence of very severe stenotic regions, and therefore growing atherosclerotic changes do not appear to make a severe SVAS in childhood. None of the patients had hypertension. Blood flow in the renal arteries does not seem to have been seriously disturbed even in a patient who showed a marked narrowing of the abdominal aorta.

Sprecher et al reported that anginal attack happened at a mean age of 13 years. In our cases, only one patient had experienced anginal attack. Coronary angiography revealed no stenotic lesions in the other 3 cases. On the other hand, aortic valve thickening, aortic regurgitation, SVAS, and so called atherosclerotic changes of the aorta were noted in 2 older patients without coronary artery stenosis. It is suggested that atherosclerotic changes in the aorta progress more rapidly than in coronary arteries in childhood. But we have to notice that the thickening of the ascending aorta may cause the stenosis of the orifice of the coronary artery. Selective coronary angiography may fail to reveal the orifice stenosis and aortography is a good aid to assessment.

By echocardiography we could detect the SVAS lesions and assess the thickening of the aortic wall. This non-invasive method is useful for follow up in child patients because
cardiovascular symptoms are rare in early life and SVAS appears earlier than coronary stenotic lesions.

With regard to the treatment, plasmapheresis seems to be the most convenient and efficient method for our homozygous patients. In earlier stage, we used plain plasma exchange. But now, an apparatus equipped with two small (150 ml) columns and a fully automated washing-regeneration system is available and we can selectively remove LDL and VLDL with a very high efficiency. Anginal attack decreased in both number and severity after several repetitions of the plasmapheresis treatment, possibly due to the decrease in blood viscosity. Xanthomas became smaller and some atherosclerotic lesions disappeared after continuous treatment with plasmapheresis combined with the drug therapy with probucol. An angiography carried out recently in patient 2 (9y4m boy) showed that there was no development of coronary atherosclerosis after 5 years treatment with plasmapheresis and probucol (data not shown).

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