Extracranial Carotid Arterial Disease in Patients With Familial Hypercholesterolemia and Coronary Artery Disease Treated With Colestipol and Nicotinic Acid

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Carotid bifurcation atherosclerosis was demonstrated in 34 of 108 patients with familial hypercholesterolemia and coronary artery disease by B-scan, continuous-wave Doppler sonography, and intravenous digital subtraction angiography. An intensive combined therapy of diet, colestipol, and nicotinic acid was mounted to control the hypercholesterolemia of these patients. Their serial sonographies and digital subtraction angiographies were evaluated independently by technical specialists who served as coinvestigators. The data obtained suggest that 1) extracranial arterial disease can develop concurrently with coronary artery disease in a significant proportion of patients with familial hypercholesterolemia, and 2) amaurosis fugax, transient ischemic attack, cerebral infarction, and myocardial infarction did not recur during 58–72 months of control of familial hypercholesterolemia in this series of patients. (Stroke 1987;18:716–721)

Familial hyperbetalipoproteinemia is a dominant-trait hereditary disorder characterized by hypercholesterolemia, elevation of low density lipoprotein (LDL), and premature atherosclerosis. Increased susceptibility to premature coronary artery disease (CAD) has been well documented. Scant information about the prevalence of extracranial carotid arterial disease in patients with familial hypercholesterolemia, particularly in those patients with known CAD. Because ultrasonography and intravenous digital subtraction angiography (IV-DSA) have created a safe and reliable means to evaluate extracranial arterial lesions, we used these techniques to determine the possible effect of lowering cholesterol and lipid on the carotid bifurcation pathology in patients with familial hypercholesterolemia. Our goal was to determine whether long-term control of hypercholesterolemia would reduce the excess risk for stroke in a series of familial hypercholesterolemic patients with extracranial carotid arterial disease and premature CAD.

Subjects and Methods

Patient Population

One hundred eight unselected patients with familial hypercholesterolemia and CAD (angina and/or post-myocardial infarction), aged 39–62, were evaluated. Diagnosis of heterozygous familial hypercholesterolemia was established by the demonstration of persistent hypercholesterolemia (serum total cholesterol ≥300 mg/dl, LDL cholesterol ≥190 mg/dl, and triglyceride ≤200 mg/dl); elevated LDL cholesterol that responded minimally to a diet low in cholesterol and saturated fat; demonstration of a similar plasma lipid-lipoprotein abnormality with or without clinical CAD in first-degree family members; and characteristic clinical manifestations of familial hypercholesterolemia including tendinous xanthomas with or without corneal arcus. After obtaining informed consent, 34 patients in whom extracranial carotid arterial atherosclerosis had been demonstrated were enrolled in a diet-drug treatment program for long-term management of hypercholesterolemia. Women of childbearing age and patients with secondary hypercholesterolemia or who were receiving drugs or hormones known to exert significant effects on lipid metabolism were excluded from the study.

Laboratory Determinations

Diagnosis of CAD was established by history, physical examination, electrocardiogram, and a thallium-201 exercise stress test and/or coronary arteriogram. Extracranial carotid arterial disease was documented by the combined use of 1) real-time 7.5-MHz aperture high-resolution ultrasonic B-mode scanner to image
atherosclerotic plaque from anteroposterior, lateral, and posterolateral views; 2) continuous-wave directional 5-MHz Doppler scanner to develop an arterial blood flow velocity map and real-time spectral display at peak frequency sites; and 3) IV-DSA to visualize maximal degrees of cervical arterial obstruction in left and right posterior oblique projections and aortic arch in left posterior oblique projection. Degrees of luminal obstruction revealed by real-time B-scan and continuous-wave Doppler sonography were estimated according to the methods of Wolverson et al and Spencer and Reid. Quantification of arterial stenosis by IV-DSA was made according to the method suggested by Earnest et al. The measurements chosen for analyses were 1) estimates of percent stenosis by B-scan, defined as [(arterial diameter − residual lumen)/artery diameter × 100] and expressed as quartiles (0–24%, 25–49%, 50–74%, and 75–100%); and 2) internal carotid Doppler peak frequency shift in kHz. Data for each side of the neck were analyzed using a two-tailed paired Student’s t test. All ultrasound examinations were performed by one of the experienced medical diagnostic sonographers, one of whom was also responsible for data management and statistical analysis. IV-DSA studies were performed by the University Hospital Radiology Group. The supporting specialists did not participate in the clinical evaluation of these patients.

Method of Study

Patients were given detailed instructions for a low-cholesterol, low-saturated-fat (therapeutic) diet, patterned after the recommendation of the American Heart Association, as reported previously. Serum lipid-lipoprotein analyses were performed 3 times at 2-week intervals while the patient was on the therapeutic diet to document limited hypocholesterolemic response to diet. After a 6-week dietary modification period, treatment of LDL cholesterol abnormality was augmented by combined administration of 10 g cholestipol before each meal, and 2.0–2.5 g nicotinic acid 3 times a day after meals. Patients were advised to take laxatives to prevent constipation during the initial phase of cholestipol administration and to take aspirin to minimize the flushing reaction to nicotinic acid (starting with 1.5 g/day in divided doses taken after each meal).

Plasma lipid-lipoprotein was analyzed at monthly intervals. Fasting serum cholesterol and triglyceride concentrations were measured with automated procedures and high density lipoprotein (HDL) cholesterol by the heparin-manganese precipitation method. Lipid analyses were standardized for accuracy by the Centers for Disease Control, US Public Health Service. LDL cholesterol was the difference between total cholesterol and HDL cholesterol plus the calculated very low density lipoprotein (VLDL) cholesterol (serum total triglyceride divided by 5). The difference between plasma lipid levels prior to and 58–72 months after diet-drug treatment was analyzed using a paired t test.

Extracranial carotid arterial disease was reevaluated with the same battery of sonography and IV-DSA after 58–72 months’ tight control of hypercholesterolemia.

Results

Plasma Lipids

The patients’ pretreatment plasma concentrations (mean ± SEM) of total cholesterol and LDL cholesterol were 378 ± 14.5 and 285 ± 11.8 mg/dl, respectively. As their total cholesterol and LDL cholesterol were lowered to and maintained at normal ranges (220 ± 7.8 and 140 ± 7.6 mg/dl, respectively) by combined diet-drug treatment, their HDL cholesterol was increased significantly (p < 0.001) from 46.1 ± 1.6 to 55.4 ± 2.1 mg/dl, respectively (Table 1). The HDL cholesterol-to-LDL cholesterol ratio was more than doubled (0.16 vs. 0.40) by diet-drug treatment. The change in HDL cholesterol levels was similar to that previously reported with long-term cholestipol-nicotinic acid administration.

<table>
<thead>
<tr>
<th>Plasma lipids</th>
<th>Baseline (before treatment)</th>
<th>Diet alone (6 weeks)</th>
<th>Diet, cholestipol, and nicotinic acid (58–72 months)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>x ± SEM</td>
<td>Change</td>
<td>p Value</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>378 ± 14.5</td>
<td>344 ± 10.7</td>
<td>-10%</td>
</tr>
<tr>
<td>LDL cholesterol</td>
<td>285 ± 11.8</td>
<td>268 ± 11.8</td>
<td>-6%</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>46.1 ± 1.6</td>
<td>41.2 ± 1.8</td>
<td>-11%</td>
</tr>
</tbody>
</table>

3 readings in each patient (n = 34). LDL, low-density lipoprotein; HDL, high-density lipoprotein; x ± SEM in mg/dl.

Carotid Arterial Disease

Fifty-seven common carotid and/or internal carotid arterial plaques found in 34 patients were estimated to range between 11.4 and 89.4% stenosis by IV-DSA and B-scan and Doppler sonography. Four patients with 60–70% obstruction of the luminal diameter developed transient ischemic attacks (TIAs), and 3 others with estimated luminal obstruction of >45% suffered attacks of amaurosis fugax in the first 2 months of the diet-drug treatment. These 7 patients were promptly treated with a combination of 0.30 g/day acetylsalicylic acid and 150 mg/day dipyridamole for 3–4 months until satisfactory control of LDL cholesterol was achieved by the diet-drug regimen. All 7 patients had no further neurologic or ocular ischemic episodes. No episode of cerebral or ocular ischemia occurred during the long-term diet-drug therapy in the remaining patients.

Follow-up extracranial carotid arterial disease evaluations made with DSA, B-scan, and ultrasonography.
The need for evaluation of carotid arterial disease has stimulated the development of sensitive noninvasive and relatively nontraumatic diagnostic methods to either supplement or replace carotid arteriography for the evaluation of patients with anatomically and hemodynamically significant extracranial carotid arterial disease. Various aspects of noninvasive extracranial carotid arterial disease testing have been reviewed by Weinberger and support the proficiency of noninvasive methods to study carotid arterial disease as demonstrated by Jones et al and Blackwell et al.

In the present study, 3 complementary noninvasive tests were used to obtain anatomic-physiologic data for evaluation of atherosclerotic lesions in the extracranial carotid arterial system. These tests were used to screen 108 patients with familial hypercholesterolemia and CAD. The tests demonstrated extracranial carotid arterial disease in 34 and were used to perform follow-up studies on these patients with both carotid and coronary arterial diseases. By controlling hypercholesterolemia, no ophthalmologic or cerebral ischemic episode developed or recurred during 4-5½ years of observation. Since this study was limited to patients with familial hypercholesterolemia who have both extracranial carotid and coronary artery diseases, it cannot provide information on the incidence or natural history of extracranial arterial disease in familial hypercholesterolemic patients in general, or in patients with other unspecified type(s) of carotid arterial disease.

Currently, the indications for surgical and/or medical treatment to reduce the risk of stroke in patients with extracranial carotid arterial disease are a subject of intense debate. A prime possibility for determining which therapeutic regimen is most beneficial can be provided with noninvasive systems plus clinical trials. The limited information on carotid arterial disease caused by a specific metabolic abnormality has encouraged us to report this series of atherosclerotic patients with familial hypercholesterolemia. Treatment to control the metabolic defect was associated with no new episodes of vascular compromise nor with significant change in the measured atherosclerotic lesions at the carotid bifurcation. Whether this represents the natural history of the disease or an effect of therapy on the reported patients cannot be determined by the present experimental design.

Because patients with familial hypercholesterolemia are predisposed to premature atherosclerosis, it is not
surprising that we and Postiglione et al. detected mild-to-moderately severe extracranial carotid arterial disease in many patients with familial hypercholesterolemia. We found mild-to-severe CAD after sequentially screening 108 patients with familial hypercholesterolemia and CAD. Although this study was not randomized, no TIA or transient monocular blindness has recurred in patients receiving hypocholesterolemic therapy; this is encouraging and deserves further investigation. Seventy-four patients in the series continue to be free of symptoms and signs of carotid arterial disease while receiving the same diet-drug treatment for hypercholesterolemia and CAD as the 34 patients with carotid arterial disease.

The benign course of extracranial carotid arterial disease in this series of patients with familial hypercholesterolemia may be attributed to interruption of the atherosclerotic progression, or suppression of platelet aggregation and activation, or to other mechanisms. Nevertheless, data obtained from the present and other reported studies support the use of diet-drug hypocholesterolemic therapy to stabilize the arterial atherosclerotic lesions rather than surgery to prevent complications. This conclusion is supported by the
Table 3. Comparison of Baseline and Follow-up B-Mode Estimate of Percent Internal Carotid Arterial Stenosis and Doppler Peak Frequency

<table>
<thead>
<tr>
<th>Method of evaluation</th>
<th>Left</th>
<th>Right</th>
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<tbody>
<tr>
<td>Baseline (n = 34)</td>
<td></td>
<td></td>
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<tr>
<td>B-Mode estimate</td>
<td>33.0±20.7</td>
<td>34.3±23.6</td>
</tr>
<tr>
<td>(mean % stenosis)</td>
<td></td>
<td></td>
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<tr>
<td>Doppler peak frequency</td>
<td>4.0±1.8</td>
<td>4.1±1.9</td>
</tr>
<tr>
<td>(mean peak shift, kHz)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Follow-up (n = 34)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B-Mode estimate</td>
<td>34.0±20.5*</td>
<td>35.6±24.7*</td>
</tr>
<tr>
<td>(mean % stenosis)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Doppler peak frequency</td>
<td>3.7±2.18*</td>
<td>4.7±3.4*</td>
</tr>
<tr>
<td>(mean peak shift, kHz)</td>
<td></td>
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</table>

*No significant change compared with baseline value.

References


recent report of Chambers and Norris, who found a low incidence of stroke in 500 patients with carotid artery stenosis followed for an average of 2 years, and by Caplan, who reemphasized screening for identifi-
cation of individuals at excess risk of stroke, followed by control of hyperlipidemia and other risk factors for atherosclerosis.

Acknowledgments

Dr. Stanley L. Malkin of New York Medical Imaging provided us with updated Doppler and B-scan facilities for follow-up examination of our patients and supervised the interpretation of the data. The Upjohn Company gave us a generous supply of colestipol for cholesterol control. CPC International supplied us with corn oil and peanut butter for dietary manage-
ment.

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**KEY WORDS** extracranial carotid arterial disease familial hypercholesterolemia colestipol-niacin treatment
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