Familial Hypercholesterolemia Patients Treated With Statins at No Increased Risk for Intracranial Vascular Lesions Despite Increased Cholesterol Burden and Extracranial Atherosclerosis

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Background and Purpose—To correlate known vascular disease risk factors and the signs of extracranial and intracranial changes of vascular origin in young patients with heterozygous familial hypercholesterolemia (FH).

Methods—39 DNA test-verified heterozygous FH North Karelian patients (FH-NK), aged 6 to 48, 28 of them treated with statins, and 25 healthy controls underwent brain magnetic resonance imaging (MRI) and carotid ultrasound.

Results—Common carotid intima-media thickness was significantly greater in the patients ($P = 0.005$). MR angiography showed no pathological changes, other than 1 incidental aneurysm. The number and size of white matter hyperintensities on T2-weighted MR images, considered as markers of microvascular alterations, did not differ between patients and controls.

Conclusions—FH-NK patients treated with statins seem to be at no increased risk for brain infarcts or other brain lesions of vascular origin when younger than age 50. (Stroke. 2005;36:1572-1574.)

Key Words: arteriosclerosis ◼ hypercholesterolemia ◼ magnetic resonance imaging ◼ ultrasonography

Heterozygous familial hypercholesterolemia (FH) is one of the most common inherited metabolic diseases with an average worldwide prevalence of $\approx$1 in 500 individuals.

Kaste et al reported a 20-fold increase in risk for fatal or nonfatal stroke in a 10-year-follow-up of 54 heterozygous FH patients compared with that of the general population.1 A recent epidemiological 8-year-follow-up study of 2871 heterozygous FH patients aged 31 to 60 years at entry treated with statins showed no difference in stroke mortality between patients and the general population.2

Magnetic resonance imaging (MRI) can reveal even clinically silent lesions in the brain. White matter hyperintensities (WMHIs) such as the leukoaraiosis seen in T2-weighted images are a sign of possible vascular or circulatory alteration. The cause of the WMHIs is incompletely understood, but the main hypothesis is that they result from brief and repeated episodes of hypoperfusion of small vessels and hypotension-induced ischemia.3 Hypercholesterolemia4 and carotid atherosclerosis5 may be risk factors for WMHIs. No studies with modern imaging techniques exist in statin-treated FH patients.

The purpose of this study was to assess brain alterations of vascular origin with MRI in a sample of young and middle-aged heterozygous FH patients, most of them treated with statins. Findings were related to extent of extracranial atherosclerosis assessed with ultrasound and to cardiovascular risk factors.

Materials and Methods

All FH North Karelia (FH-NK) patients younger than 50 years who had children and who were registered at the lipid clinic of the North Karelia Central Hospital were invited in the study; 39 patients (6 to 47 years) enrolled. Two patients had ischemic heart disease, and none had neurological symptoms. Eleven patients received no statin medication, 9 of whom were aged 15 or younger. Patients receiving the medication were 27 years old, on average, at the beginning of statin treatment (mean duration, 10 years). The control group (12 to 50 years) comprised 13 family members of patients without the FH-NK mutation and 12 other Finnish controls. None of the controls had history of atherosclerosis, diabetes or neurological disorders. Subject characteristics are shown in Table 1. The study was approved by a local ethics committee. Informed consent was obtained from all subjects.

MRI was performed at 1.5 T. An axial fluid-attenuated inversion recovery sequence and a coronal turbo spin-echo T2-weighted sequence were obtained. The intracranial arteries were studied with routine MR angiography (MRA), using a 3-dimensional time-of-flight sequence. All parenchymal and vaso-
cular abnormalities were recorded and rated independently by 2 experienced radiologists (T.A., R.R.) blinded to the clinical and laboratory data. The size and number of the earlier infarcts, including lacunes, and of the WMHIs were recorded. Only hyperintensities seen by both radiologists in the highly T2-weighted fluid-attenuated inversion recovery images were taken into account. These hyperintensities were rated in 2 categories: ≤5 mm and >5 mm, because even healthy young people may have small (≤5 mm) incidental WMHIs.6 Lumen diameter and wall contour of the vessel walls were assessed from the MRA. 13.6 30.6

Results

No infarcts were detected. Six patients (16%) and 6 controls (24%) had 1 or more WMHIs. Twenty-eight WMHIs were found; none was >5 mm in diameter. No statistical difference (P=0.44) in occurrence of hyperintensities appeared between patients and controls. MRA showed normal lumen diameter and smooth wall contour for all vessels except for 1 aneurysm in 1 patient.

The mean intima-media thickness of the far wall of the left common carotid artery was greater in the patients than in the controls (P=0.005) (Table 2). Total cholesterol, low-density lipoprotein cholesterol, and cholesterol-years scores were significantly higher in the patients than in the controls.

Discussion

No signs of intracranial alterations of vascular origin, including clinically silent infarcts, were found in patients’ brain MRI or MRA despite their higher cholesterol-years scores and intima-media thickness, which indicate, respectively, a larger cholesterol burden and a more advanced state of extracranial atherosclerosis.

Kaste et al investigated 21- to 50-year-old heterozygous FH patients from southern Finland,4 where FH Helsinki and FH-NK account for two-thirds of the FH cases. These mutations produce similar phenotypes.9 Our patients are quite comparable to theirs. At that time, statin treatment was unavailable, and total cholesterol of their patients was much higher than that of our patients (13.5 mmol/L versus 5.2 mmol/L). They found that patients without statin treatment are at least at a 20-fold higher risk for brain infarction than the general population.

Because of the effective statin treatment of our patients, we did not expect to find any severe lesions, but at least minor ones, because of their high cholesterol levels before the treatment. Surprisingly, our patients showed no difference in the occurrence of brain infarcts and WMHIs from that of the controls. Thus, statin treatment may protect the vessels of the brain.10 Our results are in line with those of a recent meta-analysis indicating a reduction in incidence of clinical strokes in statin-treated patients in general.11

In conclusion, FH NK patients treated with statins seem to be at no increased risk for brain infarcts or other brain lesions of vascular origin when younger than age 50. However, the risk at older ages should be evaluated with longitudinal studies.

Acknowledgments

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References


TABLE 1. Characteristics of FH-NK Patients and Controls

<table>
<thead>
<tr>
<th></th>
<th>FH-NK (n=39)</th>
<th>Control (n=25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y†</td>
<td>30.0±13.6</td>
<td>30.6±11.3</td>
</tr>
<tr>
<td>BMI, kg/m**</td>
<td>22.3±4.1</td>
<td>23.0±2.4</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg*</td>
<td>120.9±14.8</td>
<td>117.9±11.2</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg*</td>
<td>70.5±11.1</td>
<td>69.0±9.8</td>
</tr>
<tr>
<td>Smokers, no.</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>Statin users, no.</td>
<td>28</td>
<td>0</td>
</tr>
</tbody>
</table>

BMI indicates body mass index; FH-NK, familial hypercholesterolemia North Karelia. Values are means±SD.

For statistical analyses, the t test* and the Mann–Whitney U test† were used.

TABLE 2. Lipids, Cholesterol-Years Scores and IMTs in FH-NK Patients and Controls

<table>
<thead>
<tr>
<th></th>
<th>FH-NK (n=39)</th>
<th>Control (n=25)</th>
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<tbody>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>5.24±1.70</td>
<td>3.89±1.03*</td>
</tr>
<tr>
<td>HDL cholesterol, mmol/L</td>
<td>1.13±0.41</td>
<td>1.19±0.30</td>
</tr>
<tr>
<td>LDL cholesterol, mmol/L</td>
<td>3.68±1.41</td>
<td>2.27±0.82*</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>0.94±0.48</td>
<td>0.93±0.32</td>
</tr>
<tr>
<td>Cholesterol-years score, mmol-ý/L</td>
<td>243±122</td>
<td>137±74*</td>
</tr>
<tr>
<td>IMT, mm</td>
<td>0.57±0.13</td>
<td>0.48±0.13†</td>
</tr>
</tbody>
</table>

HDL indicates high-density lipoprotein; IMT, intima-media thickness; LDL, low-density lipoprotein. Values are means±SD.

*P<0.001.
†P=0.005 compared with all FH-NK patients.


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