Plasma Lipoproteins in Cortical Versus Lacunar Infarction

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We investigated the relation of plasma lipids to the risk for ischemic stroke by comparing clinical and biochemical characteristics of survivors of cortical (n=48) and lacunar (n=36) brain infarction. By analysis of variance, no differences were observed in the concentrations of total cholesterol, triglycerides, low density lipoprotein cholesterol, very low density lipoprotein cholesterol, or apoproteins A1 and B. Patients with lacunar infarction, however, had higher concentrations of high density lipoprotein (HDL)-cholesterol than patients with cortical stroke. This HDL-cholesterol difference was due primarily to a strikingly low HDL-cholesterol content in white patients with cortical stroke. These data suggest that previously demonstrated differences in HDL-cholesterol concentrations between patients with ischemic stroke and control subjects without stroke may apply to patients with cortical but not lacunar infarction. Separation of cerebral infarction into subtypes based on mechanism may help clarify lipid-related risk factors in cerebrovascular disease.

A number of investigations of lipid-related risk factors in cerebrovascular disease have been reported.1-11 These studies have varied greatly in their definitions of cerebrovascular endpoints, assessments of concomitant risk factors, lipids analyzed, and findings. In the Framingham Study, the level of total serum cholesterol in persons over 65 years of age was inversely related to brain infarction; among lipoproteins, only low density lipoprotein (LDL)-cholesterol was identified, and the association was a negative one restricted to women.12 Other studies have suggested that increased concentrations of total cholesterol10 and/or triglycerides2-7 are related to risk for stroke. In more recent investigations, however, only a low concentration of high density lipoprotein (HDL)-cholesterol has been consistently implicated as an indicator of risk for brain infarction.5-7,9,11 While most previous studies have distinguished brain infarction from intracranial hemorrhage, further classification of ischemic stroke into subtypes based on presumed mechanism has generally not been attempted.

If the relation of plasma lipids to stroke risk parallels that of coronary artery disease, lipid abnormalities would be most likely encountered in patients with stroke due to large-vessel atherosclerosis rather than infarction caused by cardiac embolism or lacunar infarction. Clinical and radiographic data can be used to infer stroke mechanism during life.13 When patients with cortical artery distribution infarcts were compared to a cohort with "perforating artery" ischemic lesions (primarily lacunes) in a Japanese population, HDL-cholesterol concentration was found to be lower in the former group.14 These data suggest that separation of ischemic stroke into subtypes based on the relative likelihood of large-vessel atherosclerosis may help clarify lipid-related risk patterns in stroke. We performed a similar study in a racially mixed American population to determine if differences in the concentration of HDL-cholesterol (or other lipids) could be demonstrated between survivors of cortical infarction and a cohort of patients with isolated lacunar stroke.

Subjects and Methods

A prospective study was conducted over 18 months using the occurrence of stroke as the end point defining the study groups. Group I comprised patients evaluated by the Neurology Service at the Medical College of Georgia with cortical infarction. Inclusion criteria were 1) clinical evidence of stroke with cortical deficits (aphasia or nondominant hemi-
sphere symptoms); 2) cranial computed tomography (CT) consistent with ischemic stroke hemorrhage involving the cortex without evidence of primary intraparenchymal, intraventricular, or subarachnoid hemorrhage or coincident lacunar infarct; and 3) absence of major factors predisposing to cardiogenic stroke including atrial fibrillation, valvular heart disease, prosthetic heart valves, acute (<2 weeks) myocardial infarction, or ventricular aneurysm. Group II comprised patients with isolated (no evidence of stroke by other mechanisms) lacunar infarction, selected according to these criteria: 1) symptoms of lacunar stroke consisting of one of the recognized lacunar syndromes (pure motor stroke, clumsy hand-dysarthria, ataxic hemiparesis, pure sensory or sensorimotor stroke) in the absence of cortical deficits, 2) cranial CT showing either lacunar infarct or no vascular lesion, and 3) absence of a cardiogenic source of embolus (see above).

All patients were examined by a neurologist. All patients had cranial CT scans (GE 8800 or 9800, Milwaukee, Wisconsin) performed 1–180 days after the onset of symptoms, which were reviewed by the investigators. Patients who were comatose, severely ill, tube-fed, receiving hyperalimentation, or who had a systemic malignancy were excluded.

Clinical information including age, sex, race, history or current evidence of hypertension (HBP), ischemic heart disease (IHD), diabetes mellitus (DM), and recent smoking history (>6 cigarettes or 2 cigars/day within the previous 3 months was considered a "positive" history) was recorded for all subjects. We restricted smoking history to the previous 3 months to control for the relatively acute effects of smoking on HDL-cholesterol, not to assess the impact of chronic tobacco use on stroke risk. Patients without a history of HBP but with consistently elevated blood pressure (>140 mm Hg systolic or >90 mm Hg diastolic) in the hospital were considered to have HBP. Similarly, patients without known IHD but with electrocardiographic evidence of myocardial infarction were classified as having IHD. Patients with persistently elevated blood glucose concentrations (>130 mg% fasting) were considered to have DM. All medications were noted, but drug therapy (except antihyperlipidemic agents) was not grounds for exclusion from the study.

A single fasting (>10 hours) venous blood sample was collected in two EDTA tubes between 2 and 90 days after a qualifying stroke, usually within the first 14 days. Blood was placed on ice and processed within 1 hour. All plasma cholesterol and triglyceride analyses were carried out using Gilford System 103 autoanalyzer (Oberlin, Ohio) methodology. HDL-cholesterol concentration was measured in plasma supernatant following precipitation of very low density lipoprotein (VLDL) and LDL by dextran sulfate and magnesium.

Plasma VLDL- and LDL-cholesterol concentrations were determined as follows. VLDL was isolated from the plasma by preparative ultracentrifugation at a plasma density of 1.006 g/ml at 40,000 rpm for 18 hours at 15° C using a Ti 50.3 rotor (Beckman Instruments, Palo Alto, California). The HDL + LDL-cholesterol concentration of the infranatant plasma was determined. VLDL-cholesterol concentration was calculated by subtracting the infranatant plasma HDL+LDL-cholesterol concentration from the total plasma cholesterol concentration. LDL-cholesterol concentration was calculated by subtracting the HDL-cholesterol concentration from the infranatant plasma HDL+LDL-cholesterol concentration.

Apolipoproteins (Apos) A1 and B were quantified by radial immunodiffusion using plates purchased from Tago Diagnostics, Inc. (Burlingame, California). These Apo immunoassay plates contain antisera specific for Apo A1; the Apo B plates detect both Apo B-100 and Apo B-48. To avoid interference from lipids, the lipoproteins were dissociated with detergents during preincubation (Apo B) and during assay (Apo A1).

Statistical analyses included 1) comparison of group means for biochemical values and age using analysis of variance, 2) comparison of group clinical characteristics (nominal data) using χ² analysis, and 3) multiple logistic regression to assess the relation of HDL-cholesterol concentration to clinical characteristics and stroke type (this analysis was performed by using significant [p<0.05] clinical variables and adding HDL-cholesterol concentration; significance was established using analysis of variance).

**Results**

The clinical characteristics of the two groups are shown in Table 1. There was no difference in age between groups, but the percentage of whites was significantly lower in the lacunar stroke group. The groups were comparable with respect to the other clinical characteristics. Among the lacunar stroke patients, the following syndromes were encountered: pure motor stroke in 29, clumsy hand-dysarthria in two, ataxic hemiparesis in two, pure sensory stroke in two, and sensorimotor stroke in

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Mean±SEM</th>
<th>Range</th>
<th>% male</th>
<th>% white</th>
<th>% HBP</th>
<th>% IHD</th>
<th>% DM</th>
<th>% smokers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cortical</td>
<td>48</td>
<td>61±1.5</td>
<td>44–81</td>
<td>75</td>
<td>60</td>
<td>74</td>
<td>42</td>
<td>35</td>
<td>44</td>
</tr>
<tr>
<td>Lacunar</td>
<td>36</td>
<td>62±2.5</td>
<td>37–90</td>
<td>57</td>
<td>36*</td>
<td>72</td>
<td>33</td>
<td>36</td>
<td>36</td>
</tr>
</tbody>
</table>

HBP, hypertension; IHD, ischemic heart disease; DM, diabetes mellitus.

*p<0.05, different from cortical by χ².*
one; cranial CT confirmed lacunar infarction in 81% of the patients.

Biochemical values of the two groups are given in Table 2. Significant differences (p<0.05) were found only in HDL-cholesterol concentration; the cortical stroke group had a lower concentration than the lacunar stroke group. White stroke patients had lower HDL-cholesterol concentrations (37 mg%) than black patients (48 mg%). Apo A1 and Apo B (not shown) were analyzed in 50% of the patients; no significant differences were found between groups.

Drug effects were considered. Three patients were prescribed a thiazide diuretic and two were prescribed propranolol at the time of entry into the study. Since these numbers were small and the patients on these medications were distributed between the groups, the influence of drugs was considered insignificant and was not investigated further.

Discussion

Our principal findings were that HDL-cholesterol levels were lower in whites than in blacks among survivors of cortical and lacunar stroke and that a significant difference in HDL-cholesterol concentration was based on stroke type. Separation of cerebral infarction into cortical and lacunar subtypes and the exclusion of apparent cardioembolic strokes may have allowed differences to emerge even though the cohorts were relatively small. Selection of patients on the basis of relatively specific manifestations of cerebrovascular disease has been advocated by other investigators. Mathew et al. reported a higher incidence of hyperlipoproteinemia (primarily Type IV) in patients with large-artery extracranial disease than in patients with "intracranial small vessel lesions." However, the patients were classified on the basis of angiography, and the criteria for the detection of small-vessel disease were not described. Ueda et al. compared the characteristics of patients with transient ischemic attack (TIA) and extracranial carotid disease to patients with cerebral infarction and no extracranial disease (including 19% with lacunar infarcts); using this approach, cholesterol and triglyceride concentrations were found to be higher in patients with extracranial atherosclerosis. Other authors have documented an association between low concentrations of HDL-cholesterol (but not increased concentrations of total cholesterol and/or triglycerides) and the severity of carotid disease assessed by angiography or ultrasound.

The only other study to directly compare cortical infarction (presumably related to atherosclerosis) and lacunar infarction (in which the role of atherosclerosis is uncertain) was the study of Murai et al. In this Japanese cohort, HDL-cholesterol concentration was lower in patients with cortical infarcts than in patients with lacunar lesions or those without apparent stroke. Our findings confirm this difference in a cohort of Americans and suggest a larger difference between the two stroke types in Caucasians than in blacks. We were unable to account for this difference in HDL-cholesterol concentration on the basis of patient characteristics such as age or the incidence of HBP.

We believe that the importance of our study is our comparison of the risk factors of these two common ischemic stroke subtypes. Our selection process, although not providing absolute assurance of correct classification, was adequate to eliminate cases of intracranial hemorrhage and most cases of cardioembolic infarction. The clinical criteria we applied for defining lacunar infarction and our high rate of CT confirmation suggest that our lacunar stroke group contained primarily, if not exclusively, patients with lacunar lesions without coincident cortical infarction.

We also looked at the stroke patients in our series who received ultrasonography (combined B-mode and Doppler) of their extracranial carotid arteries. Of 19 patients with cortical stroke, 16 showed evidence of significant carotid disease compared with only four of 11 patients with lacunar stroke similarly studied. Our two groups thus represent populations distinguished in part by their likelihood of having large-vessel atherosclerosis.

Recent stroke data registries have recognized the importance of lacunar infarction disease and have separated this clinical stroke type from others, including large-artery thrombosis. It is not clear, however, how the risk factor profiles for these two distinct manifestations of cerebrovascular disease differ. Based on data from a population in south Alabama similar to ours, HBP is more common in patients with lacunar stroke, but the incidence is nearly as high among patients with large-artery stroke. Crouse et al. recently analyzed risk factors for extracranial carotid artery atherosclerosis identified by B-mode ultrasonography and confirmed the importance of both HBP and low HDL-cholesterol concentration as independent risk factors for the development of cervical carotid artery disease. HBP was equally common in our groups. These studies sug-

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Total cholesterol</th>
<th>Triglycerides</th>
<th>VLDL</th>
<th>LDL</th>
<th>HDL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cortical</td>
<td>48</td>
<td>204±8.8</td>
<td>221±24.3</td>
<td>26±3.0</td>
<td>139±7.3</td>
<td>39±2.1</td>
</tr>
<tr>
<td>Lacunar</td>
<td>36</td>
<td>218±12.4</td>
<td>188±2.8</td>
<td>25±3.5</td>
<td>147±11.5</td>
<td>47±3.7*</td>
</tr>
</tbody>
</table>

Data are mean±SEM mg/dl. VLDL, very low density lipoprotein cholesterol; LDL, low density lipoprotein cholesterol; HDL, high density lipoprotein cholesterol.

*p<0.05, different from cortical by analysis of variance.
gest that HBP is more often a common, rather than a
distinguishing, characteristic for patients with large-
and small-vessel disease. Whether the degree or
duration of HBP is an important factor is unknown
because these studies, as well as our own, did not
stratify HBP as to chronicity and/or severity.

To what extent do these two groups represent
distinct clinical "phenotypes" with critical differences
in risk profiles? This question is difficult to
answer from currently available data. Systematic
stroke data banks have not reported on the coin-
cidence of large-vessel disease and lacunar lesions,
suggesting that the presence of both types of lesions
in the same patient, by clinical and CT criteria at
least, may be uncommon.

Only recently have neuropathologic studies paid
special attention to lacunar disease. From the work
of Fisher23-24 and others,25 several causes of lacunar
lesions can be identified. Occlusion of penetrating
arteries can be caused by 1) lipohyalinosis and/or
fibrinoid necrosis, 2) microatheroma or "lipid mac-
rophage plaque,"24 3) middle cerebral artery (MCA)
stem or proximal division large-vessel atheroscle-
rosis, or 4) embolic occlusion of the proximal MCA.
Although the presence of a cardioembolic source, a
"giant lacune,"25 or distal MCA territory infarction
on CT may suggest one of the latter two mechanisms,
it is usually not possible to know clinically which
process is involved. The relative importance of these
different causes of lacunar disease, as well as the
coincidence of lacunar lesions with non-MCA large-
vessel cerebral atherosclerosis, is not known. Even in
a relatively well selected lacunar cohort, individuals
with different risk profiles may be present.

Lipohyalinosis, fibrinoid necrosis, and microather-
oma may represent various points along a contin-
uum of HBP damage to small vessels of the brain.25
If so, the primary relevant factor pertaining to
lacunar stroke is HBP.

The differences in HDL-cholesterol concentra-
tion found in our study and that of Murai et al14
suggest a factor related to HDL-cholesterol that is
not shared by the stroke groups. We believe it
plausible that this factor may in part determine
which patients with HBP develop large-vessel ath-
erosclerosis and which have manifestations primar-
ily limited to the penetrating arteries. The differ-
ences in HDL-cholesterol concentration in our study
cannot be accounted for by other illness, age,
smoking (which lowers HDL-cholesterol concentra-
tion), or medications. Although HBP, clinically
apparent IHD, and smoking are predictive of stroke,
presence of these risk factors did not discriminate
between cortical and lacunar stroke in our cohort.

IHD, however, remains a potential confounding
variable. Detection of asymptomatic coronary artery
disease requires special investigations that were not
part of our study. Although clinically apparent IHD
did not account for the differences in HDL-
cholesterol concentration in our study, we cannot
eliminate the possibility that our groups may have
differed in the presence or severity of undetected
coronary artery atherosclerosis.

We also considered the potential effects of the
timing of blood sampling on our results. The major-
ity of our patients were studied 2-30 days after their
stroke (mean±SD 9±9 days for the cortical and
11±11 days for the lacunar stroke groups). Stressful
events such as myocardial infarction and surgery
are associated with a decrease in total cholesterol
concentration over several weeks after the event.26
Two studies have examined the acute effects of
stroke on plasma lipid concentration. Hollanders et
al27 reported a steady decline in total cholesterol
concentration over the first 4 weeks after cerebral
infarction, but HDL-cholesterol content was not
measured. The more recent study of Mendez et al28
assessed cholesterol and lipoprotein concentrations
1, 7, and 90 days after cerebral infarction and TIA.
Significant decreases in total and LDL-cholesterol,
but not HDL-cholesterol, contents were observed
on Day 7 in the patients with cerebral infarction; the
authors suggest that sampling soon after infarction
may underestimate premorbid levels of cholesterol
and LDL-cholesterol and suggest that the finding of
low HDL-cholesterol concentration in their and
other studies, some of which waited 8-12 weeks
after ictus before sampling, are not explained by the
timing of biochemical measurements. In addition,
other studies11,19,20 have used the presence of pre-
disposing carotid atherosclerosis prior to a major
ischemic event and have also found low HDL-
cholesterol concentrations in patients with signifi-
cant carotid artery disease.

Could the type of stroke have a differential effect?
The data of Mendez et al28 argue against this. The
authors found that TIA patients, whose stress pres-
sumably was less than that of patients who experi-
enced infarction, also had minor variations in HDL-
cholesterol content prior to a major ischemic event and
have also found low HDL-cholesterol concentra-
tions in patients with significant carotid artery disease.

The observed differences in HDL-cholesterol con-
tent are not explained by a racial imbalance between
our groups. When only the white patients are con-
sidered, the difference between the cortical (33
mg%) and lacunar stroke groups (46 mg%) remained
significant (p<0.0002) despite a reduction in sample
sizes. We also used multiple logistic regression to
analyze the effect of stroke type and race, the two
significant variables by univariate analysis, on HDL-
cholesterol content. Although both stroke type and
race significantly affect HDL-cholesterol level, the
interaction between these variables was not signif-
cant (p=0.114).

Our analysis indicates that while the HDL-
cholesterol concentration difference was primarily
the result of a strikingly low mean for white patients
with cortical stroke, evidence from this sample is
not sufficient to conclude that HDL-cholesterol
values are uniquely low for white, as opposed to
black, patients with cortical stroke. The trend suggests, however, that racial differences in HDL-cholesterol level by stroke type might emerge from a similar study of a larger cohort.

The race difference we observed is consistent with previous studies. Blacks are known to have higher HDL-cholesterol concentrations than whites. The difference between groups was not seen among blacks whose mean HDL-cholesterol values (48 mg/dl) were identical. Why this difference was not seen in blacks requires further investigation.

We conclude that patients with cortical infarction have lower HDL-cholesterol concentrations than patients with lacunar stroke. This difference suggests that a factor related to lipid metabolism may in part determine risk for these different expressions of cerebrovascular disease.

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References


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