C-Reactive Protein Predicts Further Ischemic Events in First-Ever Transient Ischemic Attack or Stroke Patients With Intracranial Large-Artery Occlusive Disease

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Background and Purpose—The role of inflammation in intracranial large-artery occlusive disease is unclear. We sought to investigate the relationship between high-sensitivity C-reactive protein (CRP) levels and the risk of further ischemic events in first-ever transient ischemic attack (TIA) or stroke patients with intracranial large-artery occlusive disease.

Methods—Of a total of 127 consecutive first-ever TIA or ischemic stroke patients with intracranial stenoses detected by transcranial Doppler ultrasonography, 71 fulfilled all inclusion criteria, which included angiographic confirmation. Serum high-sensitivity CRP level was determined a minimum of 3 months after the qualifying event. Patients were followed up during 1 year after blood sampling.

Results—Thirteen patients (18.3%) with intracranial large-artery occlusive disease experienced an end point event: 9 cerebral ischemic events, 7 of which were attributable to intracranial large-artery occlusive disease, and 4 myocardial infarctions. Patients in the highest quintile of high-sensitivity CRP level had a significantly higher adjusted odds ratio for new events compared with those in the first quintile (odds ratio, 8.66; 95% CI, 1.39 to 53.84; P=0.01). A high-sensitivity CRP level above the receiver operating characteristic curve cutoff value of 1.41 mg/dL emerged as an independent predictor of new end point events (hazard ratio, 7.14; 95% CI, 1.77 to 28.73; P=0.005) and of further intracranial large-artery occlusive disease–related ischemic events (hazard ratio, 30.67; 95% CI, 3.6 to 255.5; P=0.0015), after adjustment for age, sex, and risk factors. Kaplan-Meier curves showed that a significantly lower proportion of patients with a high-sensitivity CRP >1.41 mg/dL remained free of a new ischemic event (P<0.0001).

Conclusions—High-sensitivity CRP serum level predicts further intracranial large-artery occlusive disease–related and any major ischemic events in patients with first-ever TIA or stroke with intracranial large-artery occlusive disease. These findings are consistent with the hypothesis that inflammation may be involved in the progression and complication of intracranial large-artery occlusive disease. (Stroke. 2003;34:0000-0000.)

Key Words: atherosclerosis ■ C-reactive protein ■ outcome ■ stenosis ■ stroke

Intracranial large-artery occlusive disease represents an important cause of stroke worldwide,1,2 and patients affected by this condition are at high risk of suffering recurrent ischemic events and vascular death.3–5 However, there is uncertainty regarding the most effective preventive therapy for this disease, and scientific evidence to determine the selection of patients at higher risk is limited.6

C-reactive protein (CRP), a sensitive indicator of systemic inflammation, has been shown to be a powerful predictor of future first-ever7–9 and recurrent10–13 coronary and cerebral ischemic events, a novel marker of atherothrombotic disease that may reflect the amount of inflammatory activity within the atherosclerotic plaque,14 and a direct mediator of atherogenesis.15–17 Although inflammation is considered to play a major role in all stages of atherothrombosis at extracranial arterial territories,18 its relative contribution to the initiation, progression, and eventual destabilization of atherosclerotic lesions in intracranial large arteries remains largely unknown. We conducted a prospective study to evaluate the relationship between CRP level determined several months after first-ever transient ischemic attack (TIA) or stroke in patients with intracranial large-artery occlusive disease and the risk of further ischemic events.

Subjects and Methods

Patient Selection

Our study group consisted of first-ever TIA or ischemic stroke patients with intracranial stenoses detected by transcranial Doppler...
ultrasonography (TCD) and confirmed by MR angiography (MRA) or CT angiography (CTA). Between September 1999 and November 2001, intracranial stenoses were detected by TCD in a total of 127 consecutive first-ever TIA or ischemic stroke patients admitted to our Stroke Unit. Examinations during admission included the following: medical history; physical examination; routine blood biochemistry and blood count, ECG, chest x-ray; thyroid function; immunological study; transthoracic echocardiography and Holter ECG when indicated; cranial MRI or CT scan, including angiographic sequences; and cervical carotid ultrasound. Twenty patients underwent transesophageal echocardiography. Fifty-five patients were excluded for the following reasons: absence of angiographic confirmation (n=4); volume of implantable cardioverter defibrillator; embolic cardiopathy (n=17); neoplasm (n=7); inflammatory conditions (n=5); use of immunosuppressants (n=3); nonatherosclerotic causes of intracranial stenosis, such as Sneddon syndrome, moyamoya disease, vasculitis (n=8); placement of stents (n=2); stroke-related death or severe disability (n=8); and denial of informed consent (n=1). At the inclusion visit, performed a minimum of 3 months after the qualifying event, informed consent and blood samples were obtained from 72 patients. One of them moved to a distant city and was lost to follow-up. The remaining 71 intracranial large-artery occlusive disease patients were followed up during 12 months after blood sampling. This study was approved by the local ethics committee.

**Baseline Vascular Risk Factors and Clinical Variables**

Cigarette smoking was defined as present if the patient reported at least 10 cigarettes per day during the past 5 years. Hypertension was defined as a systolic blood pressure ≥140 mm Hg or a diastolic blood pressure ≥90 mm Hg or current use of antihypertensive medications. Hypercholesterolemia was defined as a total cholesterol ≥220 mg/dL or the current use of cholesterol-lowering agents. Diabetes mellitus was defined by history of fasting glucose ≥140 mg/dL or use of hypoglycemic medication. History of diagnosed coronary artery disease and intermittent claudication was also recorded.

Qualifying strokes and TIAs were considered potentially attributable to intracranial large-artery occlusive disease if the ischemic lesion was located within the territory supplied by a stenosed artery or if the symptoms could be explained by cerebral ischemia within a region perfused by a diseased vessel, in the absence of any other potential causes. Stroke severity was assessed with the maximum National Institutes of Health Stroke Scale (NIHSS) score obtained during admission. The use of the following drugs at inclusion visit was registered: acenocoumarol, aspirin, clopidogrel, triflusal, statins, and angiotensin-converting enzyme inhibitors.

**Ultrasound Protocol**

TCD recordings were performed with the use of a Multi-Dop-X/TCD (DWL Elektronische Systeme GmbH) device, with a hand-held transducer, in a range-gated, pulsed-wave mode at a frequency of 2 MHz. We used a standard method of insonation without compression testing. According to validated criteria, intracranial stenoses were diagnosed if the mean blood flow velocity at a circumscribed insonation depth was >80 cm/s, with side-to-side differences >30 cm/s and signs of disturbed flow. TCD examinations were performed on admission and repeated at the inclusion visit.

Baseline cervical internal carotid artery (ICA) atherosclerosis was categorized as follows: absent, mild, if 1 or both ICAs had a mild <50% stenosis; moderate, when any of the ICAs presented a moderate <70% stenosis; and severe, if any ICA had a severe stenosis or there was a history of carotid surgery or angioplasty.

**MRA and CTA**

MRA was performed with a 1.5-T whole-body imager system with 24-mT/m gradient strength, 300-ms rise time, and an echo-planar–capable receiver equipped with a gradient overdrive (Magnetom Vision Plus, Siemens Medical Systems). We used a 3-dimensional time-of-flight sequence with magnetization transfer suppression and tilted optimized nonsaturating excitation, using 1.5-mm-thick sections, 200-mm field of view, 200×512 matrix, and acquisition time that ranged from 7 to 11 minutes. Maximal intensity projections (MIP) reconstructions were performed at the time of imaging. Data were reconstructed around the head-to-foot axis and right-to-left axis. If necessary, target MIP reconstructions were performed.

CTA was performed on a Multislice MX8000 Philips spiral CT scanner with 4 rows of detectors. Ninety milliliters of iodinated contrast medium (320 mg/mL) was administered intravenously at a rate of 3 mL/s with a 13-second prescan delay. Scanning began at the cranial base and continued cranially for 80 mm. Total acquisition time average was 22 seconds. Raw data were transferred to a workstation, and MIP reconstructions were obtained.

The number of angiographically confirmed stenoses in every patient was used to assess the extent of intracranial large-artery occlusive disease.

**Blood Sampling and High-Sensitivity CRP Level Determination**

Blood samples were drawn a median of 8 months after the qualifying event. Acute infections, surgery, trauma, ischemic events during the previous 3 months, and incident neoplasm or inflammatory conditions were ruled out by careful medical history and physical examination previous to sampling. After centrifugation at 3500 rpm and 4°C for 15 minutes, serum was blind coded and stored at −80°C until used. High-sensitivity CRP levels were obtained with a Behring Nephelometer Analyzer and expressed in milligrams per deciliter. All determinations were done by duplicate. The mean intra-assay coefficients of variation were <10% for all cases.

**Clinical End Points**

Clinical interviews were performed every 6 months during 1 year after blood sampling. End point events included the following: certainly diagnosed ischemic stroke or TIA attributable to intracranial stenoses; intracranial large-artery occlusive disease–unrelated stroke or TIA; and coronary ischemic events and sudden death.

**Statistical Analysis**

Analyses were performed with the SPSS statistical package, version 9.0. Statistical significance for intergroup differences was assessed by the χ² test for categorical variables and the Student t and Mann-Whitney U tests for continuous variables. High-sensitivity CRP concentration was not normally distributed (Kolmogorov-Smirnov test). Using multivariate logistic regression analysis, we computed age-, sex-, and vascular risk factor–adjusted odds ratios (ORs) for new ischemic events associated with increasing quintiles of the population distribution of high-sensitivity CRP, with the lowest quintile as the reference. Univariate analyses were performed to detect variables associated with the occurrence of any major vascular event and of an intracranial large-artery occlusive disease–related cerebral ischemic event. Receiver operating characteristic (ROC) curves were configured to establish cutoff points of high-sensitivity CRP levels that optimally predicted the occurrence of end point events. Cox proportional hazards multivariate analyses were used to identify predictors of further intracranial large-artery occlusive disease–related cerebral ischemic and any major vascular events, in which age, sex, vascular risk factors, and variables showing P<0.1 on univariate testing were included. Results were expressed as adjusted hazard ratios (HRs) and corresponding 95% CIs. Finally, cumulative event-free rates for the time to an ischemic event were estimated by the Kaplan-Meier product limit method, and the groups with high-sensitivity CRP cutoff points were compared by the log-rank test. A probability value <0.05 was considered significant.

**Results**

**Baseline Variables**

Thirty women and 41 men were studied. Table 1 shows baseline characteristics of the study population. Mean age of...
patients was 67.4 ± 10.3 years. Fifty-four patients (76.1%) were hypertensive, and 39 (55%) were diabetic. The qualifying ischemic event was a stroke in 54 cases (76.1%) and a TIA in the remaining 17 (23.9%). Forty-one (76%) of the patients was 67.4

| TABLE 1. Baseline Characteristics of the Study Group |
|-----------------|-----------------|-----------------|-----------------|
| Age             | 67.4 ± 10.3     | Sex (F), y       | 30 (42.3)       |
| Current smoking | 26 (36.7)       | Hypertension/ACE inhibitor, n (%) | 54 (76.1)/27 (38) |
| Diabetes, n (%) | 39 (55)         | Hypercholesterolemia/statins, n (%) | 54 (76.1)/33 (46.5) |
| Total/HDL cholesterol, mg/dL | 183.9±61.3/45.4±14.9 | >2 risk factors, n (%) | 33 (46.5) |
| Coronary disease, n (%) | 9 (12.7) | Intermittent claudication, n (%) | 11 (15.5) |
| Qualifying event stroke/TIA | 54 (76.1)/17 (23.9) | Antiaggregation, n (%) | 45 (63.4) |
| ICA: normal/mild/mod/severe (%) | 51 (72)/10 (14)/2 (3)/8 (11) | Multiple stenoses, n (%) | 45 (63.4) |
| Hs-CRP, mg/dL, median (Q1–Q3) | 0.36 (0.14–1.07) |

ICA indicates cervical internal carotid artery; Hs-CRP, high-sensitivity C-reactive protein; Q1–Q3, interquartile range.

CRP Predicts New Major Vascular Events
Thirteen end point events occurred (annual risk, 18.3%). They were distributed in 7 intracranial large-artery occlusive disease–related ischemic events, 2 lacunar infarctions, and 4 myocardial infarctions, 3 of which affected patients without a known history of coronary disease. Age-, sex-, and vascular risk factor–adjusted ORs for new events by high-sensitivity CRP quintiles are shown in Table 2. Patients in the highest quintile had a significantly higher risk of suffering new events compared with those in the first quintile (OR, 8.66; 95% CI, 1.39 to 53.84; \( P = 0.01 \)). In univariate analysis, shown in Table 3, high-sensitivity CRP concentration (\( P = 0.009 \)) was significantly associated with a higher recurrence rate, whereas presence of \( >2 \) risk factors (\( P = 0.06 \)), total/HDL cholesterol (\( P = 0.09 \)) and antiaggregation (\( P = 0.07 \)) showed a trend toward significance.

CRP Predicts Further Cerebral Ischemic Events Attributable to Intracranial Large-Artery Occlusive Disease
Seven intracranial large-artery occlusive disease–related cerebral ischemic events (4 strokes and 3 TIs) were recorded. Ischemic events were attributable to previously symptomatic stenoses in 3 of the 7 cases, to confirmed but initially asymptomatic stenoses in 2 cases, and to newly developed MRA-confirmed stenoses in the remaining 2 patients. The responsible stenoses were located in the MCA in 5 cases and in the intracranial ICA in 2. In univariate analysis, shown in Table 3, high-sensitivity CRP concentration (\( P = 0.0004 \)) was significantly associated with a higher recurrence rate. Presence of a single stenosis showed a trend toward significance (\( P = 0.09 \)). A ROC curve provided a cutoff point of high-sensitivity CRP level of 1.41 mg/dL (61.5% sensitivity, 89.7% specificity), which was used to include the variable into the multivariate model. After adjustment for age, sex, and vascular risk factors, a Cox regression model identified elevated high-sensitivity CRP level as an independent predictor of further major vascular events (HR, 7.14; 95% CI, 1.77 to 28.73; \( P = 0.005 \)). Kaplan-Meier curves in Figure 1 show that a significantly lower proportion of patients with a high-sensitivity CRP > 1.41 mg/dL remained free of a new ischemic event (\( P < 0.0001 \)).

CRP Predicts Further Major Vascular Events

| TABLE 2. Multivariable-Adjusted Odds Ratios for a New Ischemic Event, by Hs-CRP Quintile |
|---------------------------------|-----------------|-----------------|
| CRP Quintile | Odds Ratio | 95% CI | \( P \) |
| 1 (0.02–0.12) | 1.00 | ... | ... |
| 2 (0.12–0.25) | 0.54 | 0.04–6.76 | 0.63 |
| 3 (0.26–0.47) | 0.5 | 0.04–6.21 | 0.59 |
| 4 (0.57–1.39) | 0.46 | 0.03–5.74 | 0.54 |
| 5 (1.41–8.54) | 8.66 | 1.39–53.84 | 0.01 |

Odds ratios adjusted for age, sex, and vascular risk factors. In parentheses, CRP-quintile limits in mg/dL.
When the adjusted multivariate Cox regression model was applied (HR, 30.67; 95% CI, 3.6 to 255.5; P = 0.0015), Kaplan-Meier curves are shown in Figure 2.

### Discussion

The present study demonstrates that elevated high-sensitivity CRP concentration identifies intracranial large-artery occlusive disease patients at a higher risk of suffering new ischemic events after their first-ever stroke or TIA. This finding is in agreement with a growing body of evidence that supports the hypothesis that inflammation may determine an increased risk of recurrent ischemic events. Moreover, CRP concentration during admission may in part constitute a response to cerebral ischemia or stroke secondary complications. Therefore, our high-sensitivity CRP determination several months after stroke may better reflect the dynamics of the subjacent atherosclerotic disease.

Unstable atherosclerotic plaques with a rich inflammatory component have been found infrequently in intracranial large vessels, and it has been suggested that the atherosclerotic process in intracranial arteries may have differential characteristics. However, in our series elevated CRP levels predicted the occurrence of new cerebral ischemic events potentially caused by intracranial large-artery occlusive disease, paralleling the findings reported in coronary patients. Furthermore, intracranial stenoses are known to be dynamic lesions whose progression may determine an increased risk of recurrent ischemic events. Since CRP level may be a marker of the inflammatory activity of the underlying atherosclerotic disease, our observation supports an important role for inflammation in the progression and destabilization of intracranial large-artery occlusive disease.

We found that elevated baseline high-sensitivity CRP levels predicted the occurrence of new ischemic events after first-ever stroke in a highly selected group of patients with intracranial large-artery occlusive disease. Previous stroke studies in unselected patients demonstrated that CRP concentration determined during admission and at discharge was a predictor of stroke outcome and the risk of recurrent events. However, to our knowledge, the impact of CRP levels on the natural history of intracranial large-artery occlusive disease had not been addressed. Moreover, CRP concentration during admission may in part constitute a response to cerebral ischemia or stroke secondary complications. Therefore, our high-sensitivity CRP determination several months after stroke may better reflect the dynamics of the subjacent atherosclerotic disease.
response and an increased propensity to plaque progression and complication. In addition, the relative frequency of incident coronary ischemic events in patients with raised CRP levels emphasizes the conception of atherosclerosis as an inflammatory systemic disease and reinforces the need to treat atherosclerotic patients globally. Finally, further research is required to understand the causes of persistent inflammation in these high-risk intracranial large-artery occlusive disease patients.

This study has limitations. First, a greater cohort would be desirable to improve the power of the study, which is 85% for the prediction of any ischemic event and 80% for the prediction of new intracranial large-artery occlusive disease–related events. Second, we relied on clinical data to rule out infection and other inflammatory diseases before sampling, but we cannot exclude that some patients had unrecognized conditions responsible for the elevated high-sensitivity CRP levels observed. In this context, a second high-sensitivity CRP determination would have been appropriate. Third, although an extensive workup was done to exclude nonatherosclerotic intracranial stenoses, neither TCD nor MRA nor CTA provides information regarding the histopathological nature of the lesions responsible for vessel narrowing, and we may have included patients with stenoses caused by different underlying vascular pathologies. This fact may explain in part the differences in the prognostic value of the extent of intracranial large-artery occlusive disease between previous studies and ours.

In conclusion, increased high-sensitivity CRP levels strongly predict the risk for new intracranial large-artery occlusive disease–related and other ischemic events in first-ever TIA or stroke patients with intracranial stenoses. Elevated high-sensitivity CRP concentration may identify high-risk intracranial large-artery occlusive disease patients, in whom strict vigilance regarding vascular risk factors and therapy combining antithrombotic and anti-inflammatory strategies may be indicated.

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