Postacute C-Reactive Protein Levels Are Elevated in Cervical Artery Dissection

Just Genius, MD; Tuan Dong-Si, MD; Armin P. Grau, MD; Christoph Lichy, MD

Background and Purpose—C-reactive protein (CRP) is associated with atherogenesis and stroke in mostly elderly subjects. We tested whether elevated CRP may also be linked to spontaneous cervical artery dissection (CAD) and cryptogenic stroke.

Methods—We investigated high-sensitivity CRP levels in 62 patients <60 years of age experiencing cerebral ischemia resulting from large artery atherosclerosis (LAA; n=21), CAD (n=21), or cryptogenic etiology (n=20) >9 months ago, and in 54 sex- and age-matched population controls. Receiver operating characteristic curve was used to identify the best CRP cutoff level for dichotomization.

Results—CRP was elevated above control levels (0.54 [0.33 to 0.84] median, interquartile range mg/L) in patients with LAA (2.59 [0.56 to 3.99] mg/L; P<0.001) and with CAD (2.37 [0.57 to 4.78] mg/L; P=0.0013) but not in patients with cryptogenic etiology (0.74 [0.14 to 7.86] mg/L). CRP levels above the cutoff level of 0.71 mg/L were independently associated with former CAD (P=0.005) but not with former LAA after adjustment for age, gender, and conventional risk factors.

Conclusion—Our results strongly suggest that CRP is associated with CAD, independent from conventional risk factors, and that inflammatory mechanisms may play a role in its pathogenesis. This finding should be confirmed by larger studies. (Stroke. 2005;36:e42-e44.)

Key Words: atherosclerosis ■ dissection ■ inflammation ■ stroke ■ young adults

Several prospective studies in elderly populations with a high burden of atherosclerosis established the importance of high-sensitivity C-reactive protein (CRP) measurement as a marker of increased risk of coronary1,2 and cerebral ischemic events.3 Initially considered a sole marker of vascular inflammation, accumulating data now suggest that CRP may actively contribute to atherogenesis by proinflammatory effects.4 By stimulation of adhesion receptor expression and monocyte recruitment in the vessel wall, CRP may contribute to endothelial dysfunction and to development and destabilization of plaques. The role of CRP in less common etiologies such as spontaneous cervical artery dissection (CAD) has not yet been addressed. CAD importantly contributes to stroke incidence in younger patients and may spontaneously occur in complete absence of classical risk factors. The pathogenesis of spontaneous CAD is insufficiently understood; however, there is evidence that acute infections may trigger CAD.5,6 Therefore, a proinflammatory diathesis may be a predisposition for CAD.

Because CAD is a rare condition and a prospective approach to clarify a role of CRP is not suitable, we decided to perform a retrospective study investigating the chronic-stage CRP levels in patients with former CAD and with cerebral ischemia caused by other etiologies.

Subjects and Methods
We enrolled 62 consecutive patients with history of ischemic stroke (n=39) or transient ischemic attack (TIA; n=20) who routinely presented for follow-up. Inclusion criteria were age <60 years and CI attributable to either large artery atherosclerosis (LAA; n=21), nontraumatic CAD (n=21), or cryptogenic embolism (n=20). CI had occurred 9 to 24 months before study entry. Diagnosis of LAA was based on >50% carotid or vertebral stenoses with typical ultrasonographic features. CAD was diagnosed if fat-suppressed T1-weighted MRI revealed a mural hematoma. All patients with CAD had at least 1 follow-up MRI scan that showed stable occlusion or reopening of the affected vessel. The diagnosis of cryptogenic stroke was restricted to cases without any evidence of vascular disease, thrombophilia, or a cardiac source of embolism. As a control group, we enrolled 54 age-matched volunteers without known vascular disease randomly selected from the population registries of the same geographic region. After informed consent, all subjects received a standardized examination and a questionnaire addressing classical risk factors and medication, including statins, which are known to interfere with CRP levels. Also, symptoms of recent infection and of infection 1 week before the ischemic event were evaluated systematically. Exclusion criteria in participants were...
chronic inflammatory and malignant diseases and signs of recent infection. The study was approved by the local ethics committee.

Serum samples were taken from resting patients and immediately stored at –70°C. CRP was determined in duplicate with a highly sensitive ELISA (Eurimmun).

Mann–Whitney U and t tests were used to compare 2 groups, as appropriate, Kruskal–Wallis test for analyses across all groups, and Spearman’s rank correlation coefficient for correlation analyses. Stepwise binary logistic regression served to adjust for all variables that significantly correlated with the outcome variable. Receiver operating characteristic (ROC) curve was used to define the CRP cutoff value, with a maximum sensitivity and specificity to discriminate between patients and controls.

Results

For demographic data and risk factor prevalence, see Table 1. CRP levels were elevated above control levels (0.54 [0.33 to 0.84] mg/L) in patients with LAA (2.59 [0.56 to 3.99] mg/L; P < 0.001) and CAD (2.37 [0.57 to 4.78] mg/L; P = 0.001) but not in patients with cryptogenic embolism (0.74 [0.14 to 7.86] mg/L; Figure). CRP levels were not different between patients with stroke (2.65 [0.42 to 4.34] mg/L) and patients with TIA (1.97 [0.35 to 2.77] mg/L; P = 0.24). ROC analysis yielded a cutoff value of 0.71 mg/L (sensitivity of 67.7% and specificity of 72.2%). Based on this cutoff level, all 3 etiologic groups were associated with high CRP levels. However, after adjustment for confounding variables, only the association with CAD remained statistically significant (Table 2).

Discussion

Our study shows elevated CRP levels in the postacute phase after CI resulting from LAA and CAD but not cryptogenic mechanisms. Such CRP measurements are likely to reflect an individual’s CRP levels before the clinical event because in longitudinal measurements, CRP levels have been shown to persist in the same quartile of the general distribution. It is unlikely that our result reflects a late response to tissue injury because there was no difference between stroke and TIA in our study and the inflammatory response usually does not persist for more than ~3 months after stroke. Further, in the subgroup of CAD, all patients had stable findings on follow-up magnetic resonance angiography previously. Vascular risk factors correlate with elevated CRP. This may explain why the association between LAA and CRP was rendered nonsignificant after adjustment for vascular risk factors. The classical risk factors do not importantly contribute to CAD, and accordingly, the association between CAD and CRP remained significant in the multivariate model.

The pathogenesis of CAD is incompletely understood. Studies have shown that acute infection frequently precedes CAD, suggesting that inflammation plays a role in CAD pathogenesis. Elevation of CRP in patients with previous CAD could point to a role of chronic infection or to a genetically determined susceptibility to inflammatory stimuli. The strongest limitation of the present study is the low number of subjects in subgroups. However, our findings encourage investigation of CRP in larger populations with CAD, which should also aim to find a possible correlation with recurrency. A European multicenter study consecutively

| TABLE 1. Clinical Characteristics of Study Groups |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Controls (n=54) | LAA (n=21) | P | CAD (n=21) | P | Cryptogenic (n=20) | P |
| Age (±SD)* | 39.4±7.7 | 44.2±7.6 | 0.095 | 40.5±8.2 | 0.6 | 42.1±7.0 | 0.25 |
| Male sex | 55% | 86% | 0.017 | 52% | 0.9 | 60% | 0.8 |
| Hypertension | 6% | 67% | <0.001 | 24% | 0.04 | 35% | 0.001 |
| Diabetes mellitus | 0% | 5% | 0.24 | 0% | na | 10% | 0.05 |
| Smoking | 35% | 43% | 0.26 | 0% | 0.001 | 35% | 0.6 |
| Hyperlipidemia | 9% | 29% | 0.05 | 24% | 0.13 | 31% | 0.04 |
| Statin therapy | 4% | 24% | 0.004 | 19% | 0.05 | 15% | 0.03 |
| Symptoms of infection 1 week before ischemia | na | 5% | na | 24% | na | 0% | na |
| CRP level (mg/L) | 0.54 | 2.59 | 0.0008 | 2.37 | 0.0012 | 0.74 | 0.85 |
| (interquartile range) (0.33–0.84) (0.56–3.99) | 0.39† | (0.57–4.78) | 0.005† | (0.14–7.86) | 0.54† |

*Age at event for patients and age at inclusion for controls. †Binary logistic regression, adjusted.
involving CAD patients is under way and hopefully will help to elucidate this important issue further.

References

### Table 2. CI Risk in Relation to CRP in Etiological Subgroups

<table>
<thead>
<tr>
<th></th>
<th>CRP&lt;0.71 mg/L, no. (%)</th>
<th>CRP&gt;0.71 mg/L, no. (%)</th>
<th>OR (95% CI)* Unadjusted P</th>
<th>OR (95% CI)* Adjusted P†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls</td>
<td>39 (72)</td>
<td>15 (28)</td>
<td>6.5 (2.1–19.8) 0.001</td>
<td>2.2 (0.35–13.5) 0.4</td>
</tr>
<tr>
<td>LAA</td>
<td>6 (29)</td>
<td>15 (71)</td>
<td>8.3 (2.5–26.7) 0.0002</td>
<td>7.9 (1.8–34) 0.004</td>
</tr>
<tr>
<td>CAD</td>
<td>5 (24)</td>
<td>16 (76)</td>
<td>3.1 (1.1–9.2) 0.053</td>
<td>1.7 (0.3–10.2) 0.55</td>
</tr>
<tr>
<td>Crypto genic</td>
<td>9 (45)</td>
<td>11 (55)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Odds ratio (OR) for prevalence of CRP > ROC cutoff level compared with controls.
†Binary logistic regression including dichotomized CRP, adjusted for risk factors proven relevant in chi² comparison.
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