C-Reactive Protein and Outcome After Ischemic Stroke

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Background and Purpose—Elevated concentrations of the acute-phase reactant C-reactive protein (CRP) predict ischemic cardiac events in both hospital- and population-based studies and may signify a role for inflammation in the destabilization of cardiovascular disease. We examined the relationship between CRP and outcome after acute ischemic stroke.

Methods—This was a subgroup analysis from a prospective observational study based in a University Hospital Acute Stroke Unit serving a population of ~260,000. Survival time and cause of death for up to 4 years after the index stroke were determined and related to CRP concentration within 72 hours of stroke and known prognostic variables by a Cox proportional hazards regression model.

Results—Ischemic stroke was diagnosed in 228 of 283 consecutive admissions. Median follow-up was 959 days. Geometric mean CRP concentration was 10.1 mg/L. Survival in those with CRP >10.1 mg/L was significantly worse than in those with CRP ≤10.1 mg/L (P=0.0009, log-rank test). Higher CRP concentration was an independent predictor of mortality (hazard ratio, 1.23 per additional natural log unit; 95% CI, 1.13 to 1.35; P=0.02), together with age and stroke severity on the National Institutes of Health Stroke Scale. Cardiovascular disease accounted for 76% of deaths in those with CRP >10.1 mg/L and 63% of deaths in those with CRP ≤10.1 mg/L.

Conclusions—CRP concentration is an independent predictor of survival after ischemic stroke. These findings are consistent with a role for inflammation in acute ischemic stroke, as well as with the hypothesis that elevated CRP may predict future cardiovascular mortality. (Stroke. 1999;30:981-985.)

Key Words: acute-phase reaction ■ cerebrovascular disorders ■ C-reactive protein ■ inflammation ■ prognosis

Elevated concentrations of acute-phase reactants, notably C-reactive protein (CRP), are predictive of future cardiovascular morbidity. Elevated CRP, together with fibrinogen and serum amyloid A protein, predict the risk of myocardial infarction (MI) in patients with both stable and unstable angina.1–3 Elevated CRP also predicts mortality in MI patients and is a more reliable predictor of outcome than peak creatine kinase concentration if thrombolytic drugs have been given.4 In a primary care population, CRP concentration correlates with cardiovascular risk indicators.5 In longitudinal studies of cardiovascular health, baseline CRP has been higher in subjects who develop ischemic heart disease, stroke, or peripheral vascular disease.6–9 Inflammation in atherosclerotic plaque is thought to be a significant contributory factor to the plaque rupture that precedes unstable vascular syndromes.1 These observations suggest that CRP may be a clinically useful risk marker for the development of unstable atherosclerotic disease, as well as a predictor of future cardiovascular morbidity and mortality.

We sought an association of CRP concentration with survival after acute stroke and explored whether there was an increased risk of cardiovascular death in patients with elevated CRP.

Subjects and Methods
Consecutive patients admitted to an acute stroke unit serving a catchment population of ~226,000 were studied during 1992–1993. Data were collected with respect to patient demography, medical history, and stroke risk factors. Strokes were classified according to the Oxfordshire Community Stroke Project system.10 An index of severity was obtained by scoring patients on the National Institutes of Health Stroke Scale (NIHSS).11 All patients were scored by a single observer within 24 hours of hospital admission.

Control blood samples were obtained from an age-matched control population without history of stroke, drawn from patients and relatives attending an ophthalmology outpatient department.

Blood was drawn in most patients within 24 hours of admission (maximum, 72 hours), and serum was stored at ~20°C for analysis as part of a study exploring the association of anticardiolipin antibodies in stroke. Samples were stored for a maximum of 18 months. After the end of the study period, CRP concentrations were measured with the use of nephelometry by an independent observer blind to the patients’ clinical characteristics. Treating physicians were blind to CRP results.

Survival was determined by record linkage to the Scottish Deaths Register,12 a technique validated in an epidemiological study of...
hypertension and also used for end point monitoring in a large clinical trial. This system does not record admissions to private hospitals or admissions to institutions outside Scotland. The date and certified cause of death, classified by the International Classification of Diseases, Ninth Revision, are recorded.

The concentration of CRP follows a log-normal distribution, and all data were log-transformed for analysis. Kaplan-Meier survival curves for groups with CRP levels above and below the log-transformed mean were compared by the log-rank test. A univariate analysis of cardiovascular risk factors and recognized prognostic indicators in stroke was performed by a univariate Cox proportional hazards regression model: the model included age, NIHSS score, admission blood glucose concentration, serum total cholesterol concentration, and history of smoking, MI, angina, atrial fibrillation, prior stroke, hypertension, and cardiac failure. Significant univariate factors were then entered into a multivariate Cox model with backward stepping to remove nonsignificant factors sequentially until all remaining variables were significant. Both the primary and secondary certified causes of death were compared. If pneumonia or infection was recorded as either primary or secondary cause of death, this was recorded as the principal mode of death. Stroke was coded as the principal cause of death only if no alternative acute event was recorded in up to 4 categories on the death certificate. Death certificates cannot distinguish hemorrhagic from ischemic stroke reliably. We used χ² tests to compare differences in proportions, unpaired t tests for continuous normally distributed variables (age, serum cholesterol), and Mann-Whitney tests for nonnormally distributed variables (NIHSS scores).

Results
Of 283 patients entering the study, 27 had nonstroke diagnoses (5 brain tumor, 8 seizures, 3 multiple sclerosis, 4 nonorganic weakness, and 7 others). In 3 cases, inadequate data were recorded for a definitive diagnosis. An additional 25 patients had primary intracerebral hemorrhage on imaging and were excluded from the final analysis, which consisted of 228 patients with ischemic stroke. The distribution of CRP concentrations is shown in Figure 1. In 189 controls, mean±SD CRP concentration was 4.2±1.9 mg/L. Patients were divided into 2 groups on the basis of a CRP concentration above or below (or equal to) the mean of the log-transformed value (10.1 mg/L; 95% CI for mean, 8.59 to 11.9). Overall, the mean age of patients was 67±13 years (range, 30 to 96 years). Follow-up was for a median of 959 days (interquartile range, 394 to 1070 days) after admission. Demography and risk factor profiles are shown in Table 1 for the 2 groups, and stroke characteristics are shown in Table 2. There were a number of significant differences between the groups. Those with CRP above the mean were older (P=0.01), had more severe strokes as judged by the NIHSS.
and lower total cholesterol concentrations ($P<0.001$) and higher proportion of patients with CRP above the mean had definite infarcts identified on CT scan (84% versus 66%; $P=0.005$, Fisher’s exact test). No significant difference between mean log CRP concentration was found among Oxfordshire Community Stroke Project classes ($P=0.31$, 1-way ANOVA).

Mean CRP concentration in the low-CRP group was 4.2 mg/L and in the high-CRP group was 33.9 mg/L. If patients subsequently dying of pneumonia were excluded, mean values were 4.2 and 32.1 mg/L, respectively.

In the low-CRP group, 35 of 132 patients died compared with 46 of 96 in the high-CRP group in the study period; this equated to a significant survival difference in survival between above and below mean log CRP groups (Figure 2; $P=0.00009$, log-rank test), with increased mortality in those with higher CRP concentrations. Although the majority of the difference was accounted for by early mortality, the Kaplan-Meier curves continued to diverge for up to 6 months after stroke. Univariate predictors of survival were age, NIHSS score, CRP concentration, cholesterol concentration, and histories of previous MI, stroke, and cigarette smoking. In a multivariate Cox proportional hazards regression model, 3 factors were significant. These were CRP concentration (hazard ratio, 1.23 [95% CI, 1.13 to 1.35] per additional natural log unit; $P=0.02$), age (hazard ratio, 1.40 [1.27 to 1.54] per decade; $P<0.001$), and NIHSS score (hazard ratio, 1.24 [1.17 to 1.32] per 4 points; $P<0.001$). The effect of different quartiles of CRP concentration on survival demonstrated worse outcome at each successively higher quartile; numbers do not permit definitive interpretation, and the graph is consistent with both a “dose-response” effect or possibly a threshold effect around the median (Figure 3).

Certified causes of death are shown in Table 3. In both groups, cardiovascular events were the most common certified cause of death. A higher proportion of patients with log CRP concentrations above the mean died of cardiovascular causes (76% of deaths versus 63% in the group below the mean), although this was not statistically significant ($P=0.23$, Fisher’s exact test; odds ratio for vascular versus nonvascular death with CRP above mean, 1.88; 95% CI, 0.72 to 4.93). Pneumonia or other infection was recorded as the primary or secondary cause of death in only a minority of patients. The median survival time for those dying of MI was 40 days (interquartile range, 11 to 437 days) in the high-CRP group and 824 days (interquartile range, 323 to 857 days) in the low-CRP group. Median survival for patients certified as dying of stroke was 32.5 days in the low-CRP group and 47 days in the high-CRP group.

**Discussion**

A single measurement of CRP within 72 hours of symptom onset in ischemic stroke patients was an independent predictor of survival in this study. The excess mortality resulted from cardiovascular disease, with stroke and MI being the most common certified causes of death. While this observation is in agreement with several hypotheses, as discussed below, there are important limitations to the study that should caution against overinterpretation.

First, the study was not prospectively designed to assess the effect of CRP on outcome, and a detailed history of infection before or after the index stroke was not recorded. Second, only a single blood level was checked, and the timing of sampling in relation to stroke onset was not recorded. Previous studies have found the peak CRP level (which occurs at 48 hours or later in MI patients) to be the most valuable outcome predictor, while we could not be certain that timing was equivalent in our 2 groups. Third, and most importantly, the certified cause of death may not be accurate with regard to the immediate mode of death. The long median survival time for those dying of MI was 40 days (interquartile range, 11 to 437 days) in the high-CRP group and 824 days (interquartile range, 323 to 857 days) in the low-CRP group. Median survival for patients certified as dying of stroke was 32.5 days in the low-CRP group and 47 days in the high-CRP group.

**TABLE 3. Certified Cause of Death Throughout Study Period and Within 30 Days of Incident Stroke**

<table>
<thead>
<tr>
<th>Cause of Death</th>
<th>CRP $\leq$10.1 mg/L</th>
<th>CRP $&gt;10.1$ mg/L</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$\leq30$ d</td>
<td>All</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>Malignancy</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Acute MI</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Stroke</td>
<td>7</td>
<td>14</td>
</tr>
<tr>
<td>Other cardiovascular event</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Other</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Total</td>
<td>9</td>
<td>35</td>
</tr>
</tbody>
</table>
survival time of patients coded as dying of stroke suggests that causes other than direct effects of brain injury are more likely to have been the true immediate cause of death.\textsuperscript{3,5}

Despite these limitations, elevated CRP concentration predicted poor survival independently of stroke severity and age, and survival curves continued to diverge over a 6-month period.

Why should CRP concentration be predictive of outcome? Three explanations are possible: (1) CRP concentration may reflect the degree of stroke severity, correlating with the degree of inflammation directly consequent to cerebral infarction; (2) CRP concentration may indicate underlying unstable atherosclerotic disease; and (3) CRP may be raised as a consequence of secondary complications of stroke at the time of sampling.

In experimental acute stroke, the release of inflammatory mediators (eg, interleukin 1, interleukin 6 [IL-6], tumor necrosis factor-\(\alpha\)) in direct response to brain injury occurs within 2 hours of onset of focal ischemia,\textsuperscript{16} and anti-inflammatory therapies are neuroprotective.\textsuperscript{17,18} Beamer and colleagues\textsuperscript{19} found significantly elevated IL-6 in patients after stroke in whom intercurrent infection had been excluded. Elevated IL-6 and CRP concentrations were present in patients with large established infarcts on CT but not in those with lacunar stroke. In our study, patients with elevated CRP had higher NIHSS scores and were more likely to have CT evidence of cortical infarction on scans performed predominantly within 12 hours of admission. These findings support the observations of Beamer et al and are consistent with elevated CRP reflecting the extent of brain infarction. However, since a detailed search for concurrent infection was not undertaken in our study, it is impossible to exclude the possibility that an acute infection at the time of sampling was responsible for both the poor clinical state and the elevated CRP.

The high CRP values in this study compared with the much lower levels predictive of cardiovascular morbidity in epidemiological studies (eg, 1.51 mg/L\textsuperscript{6}) would suggest a vigorous acute-phase response in many of our patients rather than a chronic low-grade inflammatory response. However, higher concentrations have been reported in women who later developed cardiovascular disease in a longitudinal study (median of 6.45 mg/L at baseline).\textsuperscript{8} Standard laboratory methods report CRP concentrations only when elevated into the range normally associated with acute infection or inflammation; the discrepancies in absolute concentrations between epidemiological studies suggest that assay methods may be inadequately standardized at these relatively low levels of CRP.

The inflammatory process represented by CRP elevation could also result from underlying atherosclerotic plaque itself. The potential role of viral infection in atherogenesis has received attention in ischemic heart disease but has yet to be found relevant to carotid artery disease. Inflammation cell infiltration, especially by macrophages, has been associated with carotid plaque rupture\textsuperscript{20} in a manner analogous to coronary artery disease, and concentrations of both circulating and locally synthesized proinflammatory cytokines\textsuperscript{21,22} are elevated in patients with carotid atherosclerosis. We did not determine the precise mechanism of stroke in this population, and it is likely that carotid atherosclerosis represents at most 25% of strokes studied. However, cardioembolism is the other principal mechanism of stroke and in the majority of our patients occurs with a background of ischemic heart disease. In the majority of patients, CRP may therefore be a useful marker of atherosclerotic instability.

Systemic infection is significantly more common in stroke patients than in controls in the weeks preceding hospitalization.\textsuperscript{23} Acute-phase proteins, notably IL-6 and fibrinogen, are potent prothrombotic stimuli and could therefore predispose to acute thrombus formation on preexisting atherosclerotic plaque. CRP concentration correlates with titers of antibodies to Chlamydia pneumoniae and Helicobacter pylori in a general population and with cardiovascular disease prevalence.\textsuperscript{5} The higher incidence of subsequent fatal MI and the short median time to this event in patients with elevated CRP are consistent with this possibility.

Despite fitting attractive hypotheses, the observations of this study may simply reflect correlation of CRP concentration with either the extent of cerebral infarction caused by the incident stroke or the presence of secondary complications of stroke at the time of sampling; infection, underlying malignancy, or deep vein thrombosis may all cause elevation of CRP and other inflammatory mediators. However, CRP concentration predicted future mortality independently of stroke severity judged by the NIHSS score, and excess vascular mortality persisted well beyond the subacute period after stroke in those with elevated CRP. These observations would mitigate against these factors providing a complete explanation. To ascertain the significance of our observations, more detailed appraisal of the incidence of infectious complications and mode of death is required. If increased CRP shortly after stroke is confirmed as an index of subsequent cardiovascular risk, these patients could be targeted for more aggressive conventional treatment or novel therapies intended to stabilize atherosclerotic plaque.

Acknowledgments

This study was supported by the McFeat Bequest of the University of Glasgow. The authors wish to thank Elizabeth Colquhoun for invaluable assistance with collection and organization of samples, Iain Sim for assistance with data retrieval, and Chris Povey of the Scottish Deaths Register, Edinburgh, for survival data.

References


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Stroke. 1999;30:981-985
doi: 10.1161/01.STR.30.5.981

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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