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# Variability of the systemic acute phase response after ischemic stroke

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**Abstract**

Despite apparent relationships between ischemic stroke and the acute phase response (APR), considerable variation in the APR exists between individuals. We therefore performed post-hoc analysis of individual APR profiles in 31 patients with ischemic stroke in relation to volume of brain infarction. Patients with ischemic stroke had serial blood samples taken within 12 h, and up to 12 months of symptom onset, for analysis of plasma C-reactive protein (CRP) and interleukin-6 (IL-6). Computed tomography (CT) brain infarct volume was measured at 5 to 7 days (median 23.9 $cm^3$).

An increase in plasma CRP after the admission sample was evident in 94% of patients by day 5 to 7 (median increase 558% of admission value). CRP response, assessed as area under the curve between admission and day 5 to 7, correlated strongly ($r=0.62$, $p<0.001$) with CT infarct volume. Those with greater infarct volumes had more evidence of infection, either prior to or during the first week after stroke. The pattern of response was similar for IL-6, although only 77% showed an increase in plasma IL-6 after the admission sample (median increase 148% of admission value).

These data suggest that, although infection and other factors may contribute to systemic inflammation, the extent of acute brain injury after ischemic stroke is a major factor influencing the magnitude and variability of the APR.


*Keywords:* Stroke, acute; Acute phase response; Inflammation; C-reactive protein; Interleukin-6

## 1. Introduction

Considerable interest has focused on the role of inflammation in cerebrovascular disease. Concentrations of peripheral inflammatory markers, particularly C-reactive protein (CRP), correlate strongly with cerebral infarct volume and independently predict mortality and recurrent vascular events in patients with acute ischemic stroke [1].

Despite apparent relationships between stroke and the acute phase response (APR), some reports have noted that not all patients have elevated concentrations of CRP within 24 h of stroke [2] and that peripheral inflammatory profiles in response to ischemic stroke exhibit considerable variation between individuals [3–5]. The latter report in this journal compared the temporal profile of CRP in stroke patients with CRP in healthy controls, matched for age and sex, and controls matched for age, sex and vascular risk factors [5]. A finding of particular interest was that, although CRP concentrations were higher on days 1, 14 and 90 after stroke compared to healthy controls, median CRP concentrations in the stroke patients did not change over time and were not significantly different to controls with vascular risk factors. The authors commented on differences in CRP profiles

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Table 1
Patient characteristics and stroke severity

| | |
|---|---|
| Mean age (SD) (years) | 69.0 (13.1) |
| Number male | 24 (65%) |
| NIHSS score presentation | 13 (3, 24) |
| NIHSS score 5 to 7 day survivors ($n$=34) | 11 (1,39) |
| CT Infarct volume ($cm^3$) ($n$=31) | 23.9 (0, 294.8) |

NIHSS score and infarct volume are presented as median (minimum, maximum).

between stroke patients and reported that only 16% exhibited a pattern typical of an APR.

In contrast to these data, we reported previously a significant early elevation in median plasma CRP concentration, within 12 h of ischemic stroke onset, at 24 h and at 5 to 7 days compared to controls matched for age, sex and degree of atherosclerosis [6]. This increase persisted at 3, but not 12 months, and was also apparent for other inflammatory markers, including white blood cell (WBC) count and plasma interleukin-6 (IL-6). We have also shown that the peak inflammatory response in the first week after ischemic stroke was associated with brain infarct volume [7]. However, we were certainly aware of variation in APR between individuals, and therefore decided to re-examine our data in the light of the above report [5]. The aim of the present report is to present post-hoc analyses of individual APR profiles that we believe help to explain the apparent discrepancies between reports and characterise the inflammatory response in greater detail.

## 2. Methods

The study was approved by the Local Research Ethics Committee. Patients over 18 years of age, within 12 h of onset of symptoms of acute stroke, were screened prospectively. Written consent or assent was obtained in all cases recruited. Venous blood was drawn at study entry, 24 h after recruitment, and also at 5 to 7 days, 3 months and 12 months at 09:00. Plasma CRP and IL-6 were assayed using high-sensitivity enzyme-linked immunosorbent assays described elsewhere [6]. Computed tomography (CT) brain scans were performed within 24 h to exclude primary intracerebral haemorrhage or stroke mimic and repeated at 5 to 7 days for volumetric analysis using a semi-automated technique [8]. Stroke severity was assessed using the National Institutes of Health Stroke Scale (NIHSS) score [9] at presentation and 5 to 7 days. Infections or other events likely to influence plasma inflammatory markers in the 6 weeks prior to each

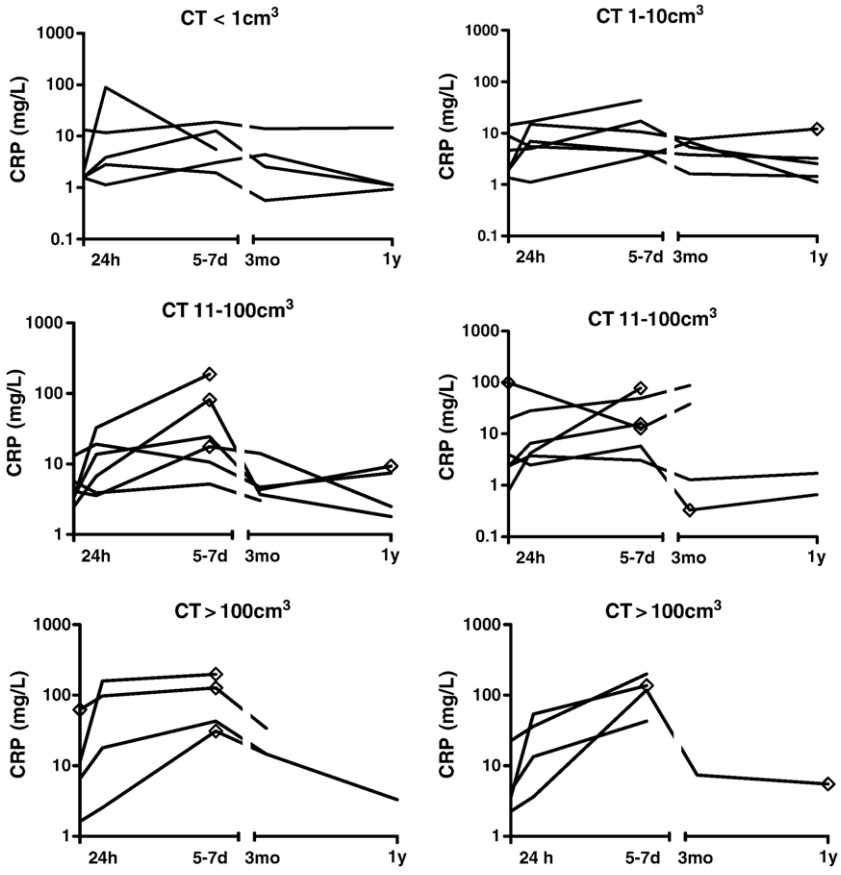


Fig. 1. Individual plasma CRP profiles for stroke patients after admission. The CRP profiles are plotted for individual patients on the basis of infarct volumes of <1 $cm^3$ ($n$=5), 1–10 $cm^3$ ($n$=6), 11–100 $cm^3$ ($n$=12, two graphs for clarity) or >100 $cm^3$ ($n$=8, two graphs for clarity). Evidence of infection is recorded as a diamond symbol (◇) from the first point after detection.