ORIGINAL ARTICLE

The Prognostic Value of C-Reactive Protein (CRP) Levels in Patients with Acute Ischaemic Stroke

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Summary

Increasing evidence suggests that inflammation plays an important role in the development of both cardiovascular and cerebrovascular events. Recently C-reactive protein (CRP) levels have been reported to be a prognostic factor for cerebrovascular and cardiovascular events. The main objective of the study was to evaluate the prognostic value of CRP levels in a first ever ischaemic stroke at one month. All ischaemic stroke patients who were admitted to Hospital Universiti Kebangsaan Malaysia (HUKM) between May 2002 and July 2002 were eligible for the study. CRP levels were taken within 72 hours after an acute ischaemic stroke. The functional ability was assessed using the Barthel Index (BI) after one month of stroke. During the study period 84 patients were admitted to HUKM with the diagnosis of ischaemic stroke; 49 patients were enrolled and 35 were excluded. Twenty-nine patients (59.2%) had elevated CRP levels (median 1.64 ± 3.07 mg/dL, range 0.06 to 16.21 mg/dL). Elevated CRP levels were found to be a predictor of severe functional disability (BI<5) and were also associated with larger infarcts. In conclusion, elevated CRP levels are associated with poorer functional outcome and predict a larger infarct size.

Key Words: C-reactive protein, Acute ischaemic stroke

Introduction

Accumulating evidence suggests that inflammation plays an important role in the development of cardiovascular and cerebrovascular diseases[1,2]. Infections and inflammation may promote atherosclerosis and thrombosis by elevating serum level of C-reactive protein (CRP),[2] fibrinogen, leucocytes, clotting factors, and cytokines, and by altering the metabolism and functions of endothelial cells and macrophages[2,3]. Markers of inflammation, such as CRP, and pro-inflammatory cytokines are associated with stroke[4]. Elevated concentrations of CRP are predictive of cardiovascular disease in men and women[5]. CRP may also be a predictor of stroke risk. Baseline CRP concentrations were higher (1.38 versus 1.13 mg/L) among a subset of men who went on to have ischaemic stroke than among those without vascular events in the Physician's Health Study clinical trial[6]. In addition, those men in the highest quartile of CRP values had about two times the risk of ischaemic stroke compared with men in the lowest quartile. Data on 193 ischaemic stroke patients enrolled in the Villa Pini Stroke Data Bank suggest that CRP may be a marker of increased ischaemic stroke risk at one year[7]. Furthermore, among 228 consecutive ischaemic stroke admissions from an acute stroke unit serving a population of about 260000, CRP was shown to be an independent predictor of survival after ischaemic stroke[8]. These studies[4,5,6] support the role of CRP in the prediction of ischaemic stroke risk and outcome, as well as the possible role of inflammation before and after stroke.

Few other studies have shown that many patients with elevated CRP levels within 72 hours of stroke have an

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increased risk of death, with an excess of cardiovascular mortality[7,8]. One recent study showed that an increased CRP level was associated with a more severe short-term prognosis in patients with ischaemic stroke[8]. Several case control studies have also shown that in patients with ischaemic stroke, recent infections are a possible risk factor[9].

CRP levels are also known to be greater in smokers,[10,11] obese individuals with body mass index 130% of the ideal, individuals with abnormal fibrinolytic activity, and individuals with subclinical atherosclerosis[12,13]. These support the suggestion that CRP predicts an increased risk of atherothrombotic events in healthy individuals. Inflammation is not only appears to be a response to the underlying atherosclerotic disease, but also may be part of it. This is consistent with the beneficial effects of anti-inflammatory agents, such as aspirin, in reducing the risk of cardiovascular events[5].

Materials and Methods

An observational prospective open-ended study was carried out. All patients with a first ischaemic stroke admitted to the medical wards of HUKM, within 72 hours of stroke onset between May 2002 and July 2002, were eligible in the study. Informed consent was obtained from all patients or their immediate family members. All patients were screened according to a standard protocol consisting of a complete medical history, full neurological examination, standardized blood tests, at least one CT scan of the brain, standard 12-lead ECG and other investigations if needed as listed in the critical pathway for stroke patients available in our hospital.

A standardized data sheet was used to record the variables. The serum for CRP was taken within 72 hours of the stroke onset and was stored at -18°C. At the end of the study period, the CRP concentrations were measured by an independent person blinded to the clinical characteristics. The activities of daily living (ADL) were assessed using the Barthel Index (BI) before the occurrence of stroke and at one month after the stroke onset. Following discharge, patients were seen in the clinic one month after the stroke onset, and their functional ability was assessed. This was based on a weighted scale of ten different activities assessing mobility and self-care ability and was the gold standard of ADL measurement. For those who did not come at the appointed date, a telephone call was made to enquire the progress.

The WHO definition of stroke was used, namely, rapid onset of clinical signs of a focal or global disturbance of cerebral dysfunction, lasting for more than 24 hours or leading to death, with no apparent non-vascular cause, and thought to be due to either inadequate blood supply to a part of the brain as a result of low blood flow, thrombosis or embolism associated with diseases of the blood vessels, heart or blood or spontaneous haemorrhage into or over the brain substance. Recurrent stroke was defined as any new cerebrovascular event after the initial one, with an increased handicap at the time of the event, persisting >24 hours or evidence of a new lesion on the brain CT. A history of transient ischaemic attack was defined as a temporary, focal neurological deficit presumably related to ischaemia and lasting less than 24 hours. Glasgow coma scores (GCS) were obtained on the day of admission. The outcomes were recurrent events and functional disability at one month. Recurrent events were defined as any new stroke, transient ischaemic attack or cardiovascular event (myocardial infarction, angina, or heart failure). Functional status was reassessed at one month, using the BI. The inclusion criteria were all patients admitted to the medical wards of HUKM with a diagnosis of first ever stroke within 72 hours of stroke onset. The exclusion criteria were patients with a history of acute or recent clinical infection in the previous 2 weeks prior to admission, concurrent major renal, hepatic, and cancerous disease, surgery or major trauma in the previous month, history of an acute coronary event in the previous month, and all types of intracerebral haemorrhage.

Statistical analysis

Univariate analysis was performed on the demographic characteristics and the risk factors, admission parameters, type of stroke, CRP level, and outcomes. These were followed by multivariate analysis and logistic regression and the covariates were adjusted for each independent variable. The dependant variables were any recurrent stroke, TIA, death and functional status at the end of one month. Statistical analysis was done using the SPSS 11.0 package and a 'p' value of < 0.05 was deemed statistically significant.

Results

During the three-month study period, 84 patients with ischaemic stroke were identified, the majority of whom were female (50 patients or 59.5%). Of these only 49 patients were included in the study, while the other 35 patients were excluded for various reasons. Twenty

patients (23.8%) were excluded due to late presentation (>72 hours), nine (10.7%) due to recurrent stroke, three (3.6%) due to a history of cancers, two (2.4%) due to a history of myocardial infarction within the preceding three months and one (1.2%) due to concomitant cellulitis of the foot.

In the study sample, the mean age was 64.7 ± 10.91 years, and 34 of the patients (69.4%) were female. Twenty two patients (44.9%) fell within the age range of 60-69 years, fourteen (28.6%) more than seventy years, six (12.2%) in both the 50-59 years and 40 – 49 years age range, and one (2%) less than 40 years. The ethnic composition of the patients was as follows: 28 (57.1%) Chinese, nineteen (38.8%) Malay and two (4.1%) Indian. Demographic data and risk factors are shown in Table I. The majority of patients presented with lacunar infarcts (73.5%) followed by middle cerebral artery territory infarcts (20.4%), and posterior cerebral artery territory infarcts (6.1%). In this study, 14.3% of patients had two or more lesions on the brain CT and another 14.3% had normal brain CT findings. None of the patients had total anterior circulation syndrome or anterior cerebral artery territory infarcts during the study period.

On admission, the mean systolic blood pressure (SBP) was170.7 mmHg, diastolic blood pressure (DBP) 87.8 mmHg, and random blood glucose (RBS) 10.9 mmol/L. The median CRP level was 0.57 mg/dL, (range: 0.06 - 16.21 mg/dL). Twenty-nine samples (59.2%) were above the normal value (normal range < 0.5 mg/dL) (Figure 1). The CRP levels for the two patients who died were 16.21 mg/dL and 7.29 mg/dL. Two patients (4.1%) died within the first week of admission, and both of them had MCA territory infarcts. Eight patients (16.3%) were readmitted within the first month with recurrent events; four had recurrent stroke, three had cardiac events and one patient had a transient ischaemic attack. On follow-up at one month, none of the patients died at home and 13 patients (26.5%) were very severely disabled with BI<5.

After performing logistic regression analysis, MCA infarct (OR 10.5; 95% CI 2.20 to 49.51), GCS < 9 (OR 12.0; 95% CI 1.11 to 129.41), and CRP level > 1.5 mg/dL, (OR 11.55; 95% CI 2.46 to 54.27) were found to be significant independent predictors for severe disability at one month with BI <5. On the other hand, age and sex were not found to be significant predictors of severe disability at one month, or bear significant relationship with the CRP levels. Type of stroke was noted to be associated with the value of CRP. A complete MCA infarct was associated with higher CRP levels while involvement of a division of the MCA had lower levels of CRP (OR 14.87; 95% CI 2.98-74.19). At one month, 16.3% of the patients had had a recurrent event, but after performing the multivariate and logistic regression analysis, there were no significant independent predictors for recurrent events. On performing the logistic regression analysis, CRP levels were found to be significant independent predictors for severe disability at one month. (Figure 2)

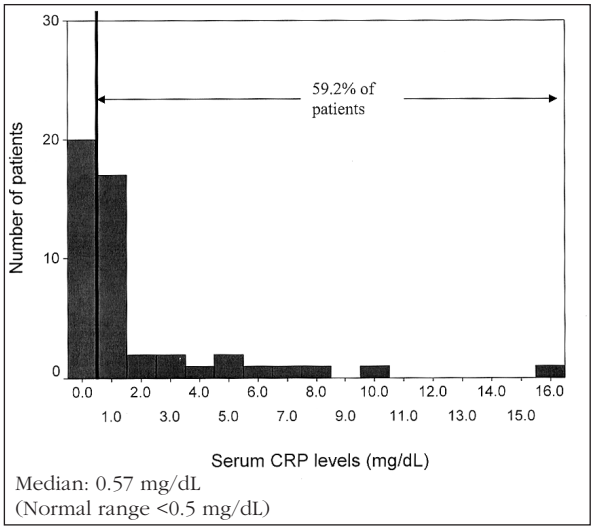

Fig. I: Serum CRP levels in the study population

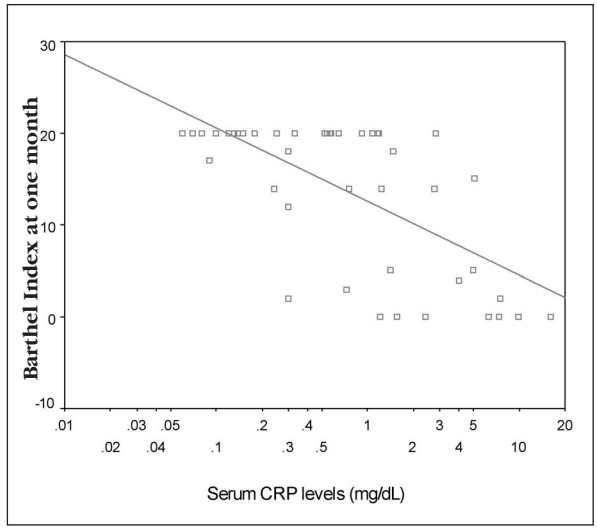

Fig. 2: Severity of functional disability in relation to C-reactive levels

Table I: Baseline characteristic of the study population

		Number	Percent (%)
Sex	Male	15	30.6
	Female	34	69.4
Age (years)	<40	1	2.1
	40-49	6	12.2
	50-59	6	12.2
	60-69	22	44.9
	>70	14	28.6
Race	Malay	19	38.8
	Chinese	28	57.1
	Indian	2	4.1
Diabetes mellitus		30	61.2
Hypertension		39	79.6
Atrial fibrillation		6	12.2
Ischaemic heart disease		7	14.3
Hyperlipidaemia		44	89.3
Type of stroke	MCA	10	20.4
	PCA	3	6.1
	Lacunar	36	73.5

Table II: Comparison of present study with other published studies

Variables	Muir et al N = 228	Di Napoli et al N = 193	Present study N = 49
CRP			
Method	Ultrasensitive	Standard	Standard
Elevated CRP (% of patients)	-	74	59.2
OR (for poor outcome)	-	25.6; 95% CI	11.55; 95% CI
		25.6; 95% CI	2.46 to 54.27
Mean age (years)	67 ± 13.0	74 ± 9.2	64.7 ± 10.9
Male (%)	54.4	51.3	30.6
Risk factors			
Hypertension	39.5	74.6	79.6
Diabetes	-	54.1	49.0
Ischaemic heart disease	41.7	39.9	14.3
Smoking	57.0	22.3	22.4
Atrial fibrillation	17.1	26.9	12.2
Hyperlipidaemia	-	42.0	89.9

Discussion

Stroke is the number one killer in those aged above 65 years in the hospitals of the Ministry of Health, Malaysia[14]. In the future, longevity will continue to improve, the proportion of senior citizens will reach 15-20% or more and the stroke incidence will continue to rise. This will be a burden to the government due to the high cost of treatment and rehabilitation of stroke patients. Therefore primary prevention is the key factor in any plan to reduce the incidence of stroke. High-risk groups must be identified and risk factors modified and treated.

The aim of the study was to elucidate the relationship between serum CRP levels and prognosis after cerebral ischaemia. All patients were selected to avoid possible confounding factors capable of increasing the markers of inflammation. Patients with a history of recent clinical infection, concurrent major renal or hepatic diseases, and cancers, or recent myocardial infarction, surgery or major trauma in the previous month were excluded. A high proportion of patients (23.8%) presented late (>72 hours) to hospital. This finding has important implications on the management of acute stroke particularly with regards to thrombolytic therapy.

The mean age of patients in the study was 64.7 ± 10.9 years. This observation is comparable to a few other studies, for example Muir et al, [7] (mean age: 67.1 ± 13 years) and Hartmann et al,[15] (mean age: 66 ± 12.4 years). However, Di Napoli et al,[8] Natalia et al,[16] and Vemmos et al,[17] reported higher mean ages. Using the univariate analysis, older patients (age>70 years) were found to have a higher mortality (p = 0.05). However, using the multivariable analysis, there was no significant difference in mortality at one month between younger and older patients. There was also no significant difference in the occurrence of recurrent events and functional status between younger and older patients. As the number of patients who died (2 patients) and above 70 years (12.2%) was small, no definite conclusion should be drawn from the results.

Hyperlipidaemia (89.8%) was the commonest risk factor present in the study population, followed by hypertension (79.6%), diabetes mellitus (49.0%), cigarettes smoking (22.4%), ischaemic heart disease (14.3%), and atrial fibrillation (12.2%). This frequency of risk factors was not entirely comparable with other studies[18,19,20] whereby hypertension was the commonest risk factor. Although the present study was not designed to evaluate risk factors, there is now evidence that hyperlipidaemia is a risk factor for ischaemic stroke. Nevertheless these studies were done on patients with concomitant ischaemic heart disease. In properly designed studies, statins have been shown to reduce stroke occurrence by about 29%[21-24]. Apart from reducing cholesterol levels, statins have also been shown to reduce the serum CRP levels. A trial using pravastatin demonstrated that the median CRP levels were reduced by 16.9%[25].

In the present study, 73.5% of the patients presented with a lacunar syndrome (18.4% of whom had no lesions and 14.3% two or more lesions on the initial brain CT), 20.4% MCA infarct, and 6.1% PCA infarct. Those with MCA infarcts had a higher mortality rate (OR 10.5; 95% CI 2.20 to 49.51) compared to those with non-MCA infarcts, and they also had poorer functional abilities (OR 11.57; 95% CI 2.46 to 54.27). These results are similar to those of Muir et al, and [7] Di Napoli et al[8].

Elevated serum CRP levels may reflect the extent of ischaemic area. Necrosis triggers a rise in circulating CRP. Therefore the extent of necrosis may determine the CRP response. However, Di Napoli et al [8] in their study also found that 26% of stroke patients had normal CRP levels, compared to 48.2% in the present study. Hence, ischaemic stroke does not necessarily induce an acute phase response in all patients but patients with persistently elevated CRP levels appear to have a worse outcome. This supports the hypothesis that post-ischaemic inflammation may contribute to continuing ischaemic brain injury. The CRP levels in MCA infarcts do not appear to be predictive of the functional disabilities at one month because all patients with MCA infarcts were moderately or severely disabled (BI: 0 -5) despite having a wide range of serum CRP levels (from 0.72 to 16.21 mg/dL). However, for non-MCA infarcts, the higher CRP levels appear to predict a worse outcome. The small number of patients and the short study period limit the conclusion that can be drawn from this study. Brain CT was only performed on admission and it was not repeated after one week to determine the actual infarct size. This may under- or overestimate the influence of infarct size on stroke outcome. The other limitation of the present study was the wide variation in the timing of blood taking (for the CRP levels). This variability is likely to affect the study results because serum CRP levels are known to change during the few days following an ischaemic event[26].

Conclusion

Elevated CRP levels are associated with poorer outcome from ischaemic stroke and predict a larger infarct size. A poor GCS on admission and large infarcts were also predictors of poorer functional outcome. Predictors of stroke mortality could not be analysed in this study because of the unexpectedly low one-month mortality rate.

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