Acute Phase Reactants as a Prognostic Factor in Acute Stroke

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Article info:
Received: 20 August 2011
First Revision: 28 August 2011
Accepted: 23 September 2011

Key Words:
Stroke,
Prognosis,
Acute Phase Reactant,
C Reactive Protein,
Transient Ischemic Attack.

ABSTRACT

Introduction: Elevated levels of CRP are present among patients at risk for further first-ever myocardial infarction and stroke. It has been shown that after ischemic stroke, increased levels of CRP are associated with unfavorable outcomes.

Methods: From 120 patients admitted to the emergency unit of our hospital with the diagnosis of stroke; CRP, D-dimer and ferritin level was measured and the patients were followed until discharge or death.

Results: CRP level was significantly different between the patients with TIA and stroke. D-Dimer level was also significantly different between the TIA & the admitted groups. Ferritin was not different between the prognosis groups. There was a correlation between CRP and D-Dimer ($r = 0.381$, $p = 0.001$), and also between CRP and ferritin ($r = 0.478$, $p = 0.000$).

Discussion: CRP is a useful adjuvant marker to determine the prognosis of patients with cerebro-vascular events admitted to the hospital, in both patients with stroke positive history and first-ever stroke.

1. Introduction

Despite a gradual decline in overall stroke death in many countries, stroke remains the third leading cause of death; stroke is also the leading cause of disability in adults. The human and financial costs of stroke are immense. Approximately 30% of survivors require assistance with activities of daily living, 20% require assistance with ambulation, and 16% require institutional care (Hunckey and Warlaw, 2000).

Routine empirical measurement of C-reactive protein (CRP) is a valuable aid in patient's management across a broad range of clinical practices. Sensitive CRP assay may become a new risk assessment marker for cardiovascular diseases, and guidelines for its application are under discussion (Pepys, 2001). Elevated levels of CRP are present among patients at risk for further first-ever myocardial infarction and stroke (Koenig, 2001).

It has been shown that after ischemic stroke, increased levels of CRP are associated with unfavorable outcomes (Sander, 2002). In another study, survival in patients with CRP levels >1.01 mg/dl was significantly worse (Muir et al., 1999). The aim of this study was to measure the CRP level as well as D-Dimer & Ferritin in patients with acute cerebro-vascular disease, who had been admitted to the hospital.

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By determining the CRP level we could better understand the prognosis of patients and could make better decisions about their hospitalization and implementation of more aggressive treatments.

2. Methods

From 120 patients admitted to the emergency unit of the Rasool-e-Akram hospital in Tehran in spring of 2008 with the diagnosis of cerebrovascular disease, eighty patients were included in the study. All patients were informed about the study and consents were obtained from them. The inclusion criteria were diagnosis of stroke, either ischemic or hemorrhagic (with first ever and previous stroke history), and TIA (transient ischemic attack). Exclusion criteria were related mainly to the conditions associated with increased levels of inflammation markers, including infection like pneumonia, sepsis or other inflammatory diseases like vasculitis (initial CRP level >10 mg/dl). CT scan of the brain was performed at enrollment within 24 hours after stroke onset to confirm the diagnosis of ischemic and hemorrhagic stroke. A full neurological examination, including screening with Modified Rankin Scale, was also carried out. All the patients were re-examined by the same neurologist, 24 hours after cerebrovascular attack.

Several laboratory parameters and cardiovascular risk factors such as smoking, hypertension, diabetes mellitus, and previous myocardial infarction were determined. Based on prognosis, patients were separated into three groups: 1) TIA: transient ischemic attack with symptoms lasting less than 24 hours, 2) admitted: patients who had ischemic or hemorrhagic stroke and need to be admitted, 3) death: patients who died after admission. We also categorized patients based on their CT scan into three groups: 1) patients with non-significant CT scan, 2) patients with ischemic lesions and 3) patients with hemorrhagic pattern.

A 902 Roche/Hitachi auto analyzer was used to determine the levels of CRP, D-Dimer, and Ferritin. In all patients, these were measured immediately after admission. Levels of CRP were determined with a commercially available, high-sensitivity, immunonephelometric, latex enhanced assay (Tina quant CRP Ultra sensitive, Roche diagnostic). D-Dimer and Ferritin were also determined by immunonephelometric method (Tina quant D-Dimer and Tina quant Ferritin, Roche diagnostic). Statistical analysis was performed with a SPSS v11 package.

3. Results

Eighty patients were included in the study, 37 male and 43 female. The patient's mean age was 67.1 ± 13.1 years (mean ± SD). The group distribution has been depicted in chart I. Patient's characteristics on admission

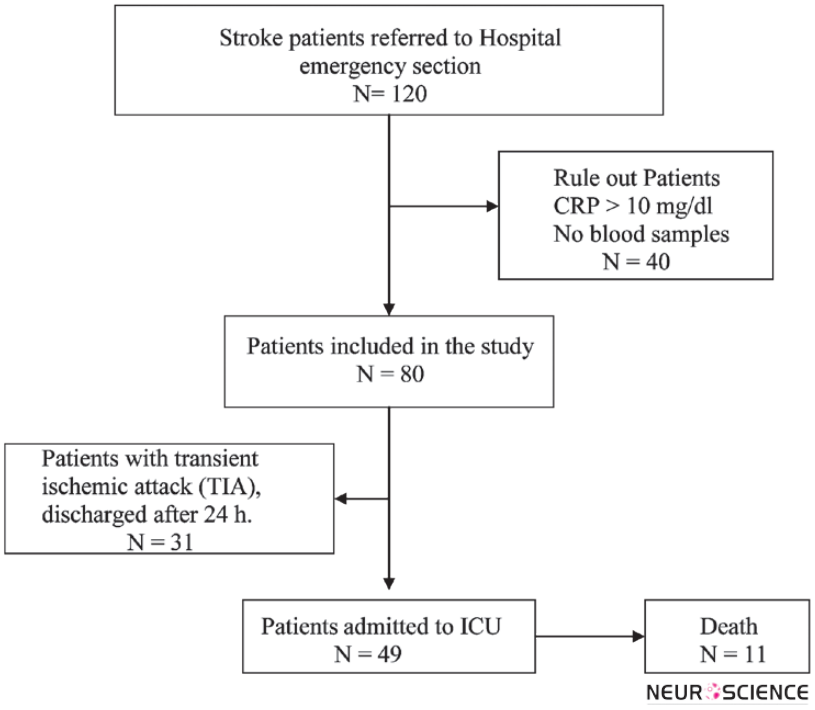

Figure 1. Flowchart of Patient Recruitment, Diagnosis and Follow up

Table 1. Characteristics of patients in the prognosis groups.

	TIA	Admitted	Death
Gender (M/F)	14/17	18/20	5/6
Aspirin	6	9	2
MI history	5	5	3
Stroke history	7	11	4
Diabetes mellitus	10	13	5
Hypertension	21	28	9
Smoking	5	6	4

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Table 2. CRP, D-Dimer, and ferritin in three prognosis groups (mean ± SD).

	TIA	Admitted	Death	P value TIA vs. admitted	P value TIA vs. Death	P value Admitted vs. Death
CRP	0.23 ± 0.21	1.64 ± 1.80	1.47 ± 1.97	0.000***	0.016*	0.73
D- Dimer	0.91 ± 1.05	3.64 ± 5.83	3.81 ± 5.77	0.024*	0.119	0.929
Ferritin	117.6 ± 137.3	158.9 ± 136.2	122.4 ± 83.1	0.519	0.999	0.632

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Table 3. Distribution of diagnosis groups between prognosis groups.

	TIA	Admitted	Death
Non-significant CT	16	15	0
Ischemic CT	2	29	7
Hemorrhagic CT	0	7	4

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are listed in table 1. Individual CRP, D-Dimer and ferritin values in the three groups are shown in table 2. CRP was significantly different between prognosis groups (table 2). D-Dimer was also significantly different between TIA & admitted groups (table 2). Ferritin was not different between prognosis groups. There was a correlation between CRP and D-Dimer ($r = 0.381$, $p = 0.001$), and also between CRP and ferritin ($r = 0.478$, $p < 0.001$).

We found that CRP is significantly different between prognosis groups in patients with previous stroke history ($p = 0.05$) as well as first ever stroke patients ($p = 0.012$).

Categorizing the patients based on diagnosis into the following three groups: non-significant (n = 18, %22.5), ischemic (n = 51, %63.8), and hemorrhagic (n = 11, %13.8), we found a significant difference in CRP level between them (non-significant & ischemic patients: $p = 0.001$; non-significant & hemorrhagic patients: $p = 0.04$). Table 3 shows the distribution of CT scan diagnosis groups between prognosis groups. There is a good correlation between the diagnosis groups and the prognosis groups ($r = 0.563$, $p<0.001$).

4. Discussion

In this study the CRP concentrations increased (≥ 5 mg/l) in about %65 of patients within 24h after ischemic stroke. We found that CRP measurement on admission for acute-cerebro-vascular events predicts the further development of the event. There was a significant dif-

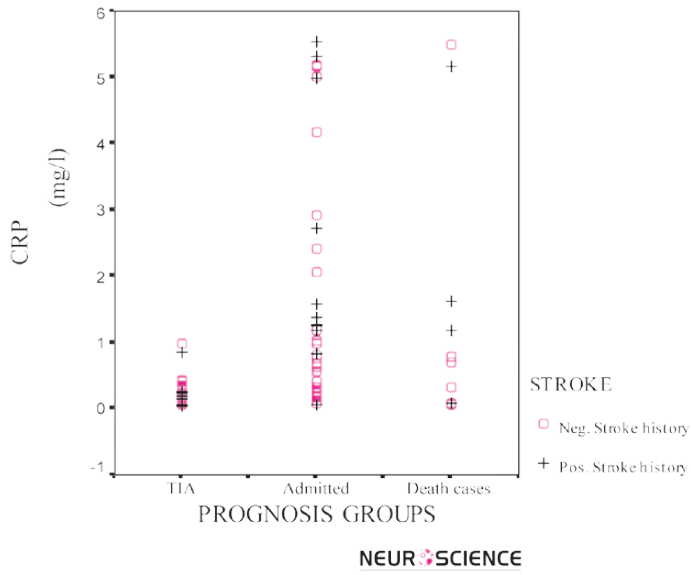

Figure 2. Distribution of CRP between prognosis groups (Transient Ischemic Attack (TIA), admitted, and death cases) categorized based on stroke history. Only 2 of TIA prognosis group (6.7%) had CRP ≥ 5 mg/l. But, 25 cases of the admitted group (66%) and 7 of the death group (64%) had CRP ≥ 5 mg/l.

ference between TIA and admitted or death patients. CRP level was less than 5 mg/l in about 93% of TIA group. In a previous work, researchers had not found any prediction value for the patient's groups (Canova et al., 1999). In our study we did not found any difference in CRP between admitted and death groups. But we found a significant correlation between CRP, D-Dimer, and Ferritin, which corresponds with previous works (Di Napoli et al. 2002). Categorizing patients based on diagnosis showed that there is a good correlation between the prognosis and the diagnosis groups. There was a correlation between CRP and prognosis groups ($r = 0.358$, $p = 0.001$), but there was no correlation between CRP and the diagnosis groups. This pattern was also repeated for D-Dimer ($r = 0.262$, $p = 0.31$). It may be concluded that CRP and D-Dimer can predict the outcome independent of the CT scan's results.

High CRP in healthy individuals indicates increased risk of coronary and cereberovascular events (Ridker et al., 1997), and a worse prognosis in myocardial infarction (Pietila et al., 1996), and ischemic stroke. This indicates that CRP should be considered as a marker of cardiovascular risk (Pepys, 2001). In patients with acute myocardial infarction or ischemic stroke the extent of necrosis is the main but not the only determinant of prognosis (Di Napoli et al, .2001). Response to the necrotic insult are probably multiple and may need independent additional determinants of prognosis (Canova et al., 1999).

in order to be in accordance with other authors who studied on first ever stroke patients (Di Napoli et al. 2000), we also divided patients into two major groups, with previous stroke history and first ever stroke, correlation between CRP, D-Dimer and Ferritin was stronger in patients with previous stroke history (Di Napoli et al., 2002). So we can conclude that CRP is a useful adjuvant marker to determine the prognosis of patients with cerebro-vascular events admitted to the hospital, in both patients with stroke positive history and first-ever stroke patients. Unfortunately it is impossible to measure the CRP level before stroke and we could not determine its value as a diagnostic factor. More studies are needed to determine any difference between different sources of stroke.

Acknowledgment

The authors thank Dr. S. M. Blourchi, manager of Daneshafzar Eng. Co., and Miss. Pakdel for providing the CRP kit.

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