Prognostic Value of CRP in Acute Ischaemic Stroke

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Abstract

Introduction: Stroke is a worldwide health problem. It makes an important contribution to morbidity, mortality, and disability in developed and developing countries. Stroke is one of the leading causes of death after ischaemic heart disease and malignancy. C-reactive protein (CRP) is an annular (ring-shaped), pentameric protein found in blood plasma. Present work was conducted to address the role of CRP in acute stroke patient and its correlation with severity and outcome.

Material and methods: It was hospital based randomised case control observational study in which 50 patients of acute ischaemic stroke admitted in various medical wards of MB Govt Hospital and RNT Medical College, Udaipur were enrolled as cases and 50 healthy age and sex matched individuals were enrolled as controls. The study was carried-out between June 2019 and November 2019.

Results and observations: All these 50 patients of ischaemic stroke confirmed by CT and MRI were classified on the basis of severity according to NIHSS stroke classification in mild (1 - 4), moderate (5 - 15), severe (16 - 20) and very severe (21 - 42) type of stroke. CRP level of all these patients were sent at the time of admission and mean CRP levels were calculated and it was compared with both the groups and correlated with severity and outcome.

Conclusion: From the present study it can be concluded that higher the levels of CRP, the greater will be the severity of stroke and poorer will be the outcome.

Key words: CRP, C-reactive protein, stroke, NIHSS scores.

Introduction

Stroke is a worldwide health problem. It makes an important contribution to morbidity, mortality, and disability in developed as well as developing countries. Stroke is one of the leading causes of death after ischaemic heart disease and malignancy[1].

The World Health Organisation defines stroke as "rapidly developing clinical signs of focal or global disturbance of cerebral function with symptoms lasting more than 24 hours or leading to death with no apparent cause other than that of vascular origin"[2] which may be caused either due to interruption of blood supply to the brain or rupture of blood vessels of brain.

According to the WHO, worldwide 15 million people suffer from stroke every year. Out of this, there are around 5 million deaths and another 5 million are permanently disabled. High blood pressure contributes to more than 12.7 million strokes worldwide. In developed countries the incidence of stroke is declining due to efforts made in reducing the blood pressure and curtailing smoking. However, the overall rate of stroke remains high due to aging of the population. Around 70% of strokes and 87% of stroke-related deaths that occur globally are seen in middle and low income countries[3].

Stroke is one of the major killer disease worldwide and also in India, and its prevalence is increasing day by day. In 1998 - 1999, a study conducted in Kolkata showed that the crude prevalence rate of stroke was 147/1,00,000 population and annual incidence rate was 36/1,00,000 population .This was further increased to the level of 262 per 1,00,000 in rural areas and 424 per 1,00,000 in urban areas in the last decade[4].

On comparison of stroke rates in India and other countries, it was found that the rates are two to three times higher in India. The underlying reason for this increase is not yet completely understood. In India, rheumatic heart disease and cortical venous thrombosis are the two most important causes of stroke in the young. This may be partially responsible for increased stroke rates in India[5].

The clinical manifestations of stroke are highly variable because of the complex anatomy of the brain and its vasculature. There are so many factors which can affect the outcome of these patients and it includes age, sex, site, and size of the lesion, presence or absence of midline shift, GCS, TLC counts, temperature, blood glucose, blood pressure at the time of admission.

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C-reactive protein (CRP) is an annular (ring-shaped), pentameric protein found in blood plasma. It is secreted by liver[6] in response to inflammation. It is an acute-phase protein and it increases following interleukin-6 secretion by macrophages and T-cells[7]. It binds to lysophosphatidylcholine expressed on the surface of dead or dying cells or some bacteria so that it can activate the complement system via C1q[8].

It was first discovered by Tillett and Francis[9] in 1930 and was initially thought that it might be secreted by abnormal cells like cancer cells, inflammation, etc. But later it was proved that it is a native protein synthesized and secreted by liver cells[10].

In recent years, inflammation has emerged as an important factor in the genesis of atherosclerosis. There has been a lot of work regarding the role of CRP in cardio-vascular diseases like acute MI and they found a positive correlation of this inflammatory marker with these cardio-vascular disorders whereas there were very few works regarding the role of CRP with acute stroke patients. Hence, the present work was conducted to address the role of CRP in acute stroke patients and its correlation with severity and outcome.

Aims and objectives

1. Estimation of CRP in acute ischaemic stroke and comparison with healthy control patients.

2. To study the correlation between CRP level and severity in acute ischaemic stroke patients.

3. To study correlation between CRP level and short-term outcome at the end of first week.

Material and methods

Study site: Patients admitted in various medical wards of MB Govt Hospital and RNT Medical College, Udaipur.

Study design: Hospital-based randomised case control observational study.

Study period: All eligible 50 consecutive cases of ischaemic stroke admitted in various medical wards of MB Govt Hospital and RNT Medical College, Udaipur were studied from the period June 2019 to November 2019.

Study population: All the patients who presented within 72 hours of onset of symptoms and signs of acute ischaemic stroke and confirmed radiologically with CT or MRI and fulfilling inclusion and exclusion criterias were enrolled. Baseline data were collected within 24 hrs of admission.

Inclusion criteria

1. Acute ischaemic stroke patients of both the sexes having age more than 18 years were considered as cases.

2. 50 healthy age and sex matched individuals who were not suffering from any inflammatory, infectious, auto-immune, or malignant diseases were considered as controls.

Exclusion criteria

1. Patients who are having age less than 18 years.

2. Patients who presented with symptoms suggestive of stroke but with underlying aetiology, e.g., trauma, surgery, neoplasm, active infections.

3. Patients with stroke associated with haematological diseases, inflammatory diseases, severe hepatic illness, renal diseases, acute metabolic diseases, autoimmune diseases, intoxications with cocaine and amphetamines and acute coronary syndromes.

Study method

All these 50 patients with history of acute stroke admitted to the various medical wards of MB Govt Hospital and RNT Medical College, Udaipur were enrolled for the study after taking written consent. Detailed clinical profile of the patients were recorded on separate proforma regarding general information, i.e., age, sex, present and past history, history of systemic illness, and a thorough clinical examination including detailed neurological examination was done. All cases were evaluated clinically including diabetes mellitus, hypertension, ischaemic heart disease, previous history of stroke, alcohol intake, and smoking. All routine haematological investigations including haemoglobin, total and differential leucocyte counts, peripheral blood film examination, urine examination, blood sugar, urea, lipid profile, electrocardiogram, X-ray chest, and computerised tomogram and/or MRI were performed.

All these 50 patients of ischaemic stroke confirmed by CT and MRI were enrolled as cases and then they were classified on the basis of severity according to NIHSS stroke classification in mild (1 - 4), moderate (5 - 15), severe (16 - 20) and very severe (21 - 42) type of stroke.

The CRP levels of both these cases and controls were estimated. The CRP levels of these cases were sent at the time of their admission.

All these enrolled patients were followed-up and outcome was observed and interpreted at the end of 7 days in the form of death, deterioration, no change, improved, and complete recovery.

Mean level of CRP in the cases were compared with the controls and its correlation with the severity and outcome

of stroke was studied.

Statistical analysis

Summary statistics were done by proportions, mean, median, and standard deviation. The inferential statistics were done by, ANOVA and person correlation. All measurements were done using SPSS version 21.0. 'p' value < 0.05 were considered as statistically significant.

Observations and results

Table I: Age-wise distribution.

Age (years)	No. of cases (n = 50)
18 - 40	4 (8%)
41 - 60	14 (28%)
> 60	32 (64%)

Out of 50 cases, 32 (64%) belonged to > 60 years of age followed by 41 - 60 (28%) and 18 - 40 (8%) years age group.

Table II: Gender-wise distribution.

Gender	No. of cases (n = 50)
Male	33 (66%)
Female	17 (34%)

In the present study, 33 (66%) were males and 17 (34%) were females.

Table III: Comparison between NIHSS score CRP.

NIHSS Score	1 - 4	5 - 15	16 - 20	21 - 42
No. of cases (50)	0	17	0	33
Increased CRP (38)	0	6 (6.68 ± 2.60)	0	32 (7.76 ± 2.82)

The above table shows the comparison between CRP levels in acute ischaemic stroke and the severity of stroke as assessed by NIHS scores.

Table IV: Comparison CRP levels between cases and controls.

Age group	Mean CRP levels controls	Mean CRP levels cases	P value
18 - 40	2.85 ± 1.72	3.4 ± 1.45	0.00128
41 - 60	2.66 ± 1.66	5.77 ± 2.86	
> 60	–	6.87 ± 3.54	

The CRP levels of cases and controls were studied. The above observations were made which showed that the levels of CRP were elevated significantly in cases as compared to that of controls.

Table V: Outcome in relation to CRP.

CRP	No. of Cases	Outcome				
		Deaths	Deteriorated	No change	Improved	Complete recovery
0 - 3 Mean CRP: 2.16	12 (24%)	1 (8.3%)	0	0	7 (58.33%)	4 (33.33%)
> 3 Mean CRP: 7.72	38 (76%)	17 (44.7%)	11 (28.9%)	4 (10.52%)	6 (15.78%)	0

The outcome was divided into death, deteriorated, no change, improved, and recovery. The outcome was noted within 7 days of admission in the hospital. The cut-off for normal CRP was 3 mg/l above which all the observations made were considered as abnormal.

Discussion

Acute ischaemic stroke is a major cause of disability and deaths in our country. With the advent of promising therapies for acute ischaemic stroke, there is higher expectation for rapid recovery and good outcome. Inspite of these new therapies, prognosis is still not very good which may be because of the fact that its outcome may be influenced by many factors like extent of brain injury, severity and duration of insult, as well genetic predisposition, temperature, blood glucose, and various other unknown factors. Globally, stroke is the third commonest cause of moratlity[11] and the fourth leading cause of disease burden[12].

C-reactive protein is an acute phase reactant which increases during any acute inflammation. Increased CRP levels have also been described in smokers, sedentary and obese persons, malignancy, type 2 diabetes, gestational diabetes, and metabolic syndrome persons[13].

In the present study, 50 patients were included who suffered from acute ischaemic stroke and confirmed by clinical and radiological examinations. The concentrations of CRP were measured in all patients.

In our study, 64% (32 patients) of the patients belonged to the age group of above 60 yrs with 28% (14 patients) belonging to the age group between 41 to 60 yrs. Only 8% (4 patients) of the total population belonged to less than 40 yrs. This indicates that the most common age of presentation of stroke is old age that is above the age of 60. Hayes *et al*[14] 2011 found that the risk of stroke doubles with each decade after 45 yrs and over 70% of all strokes occur above the age of 65. Similar findings were noted by Kissela *et al* 2012 and Roy-O'Reilly *et al* 2018.

Regarding the influence of sex, we found that 66% (33 patients) of the total cases were male and 34% (17 patients)

of the total cases belonged to the female community. Among the females affected, all of them belonged to post-menopausal age. Thus maximum number of affected patients were males. This finding is inaccordance with the study conducted by Haast et al[15] who found that pre-menopausal women are protected from stroke and other cardiovascular events due to the presence of oestrogen. However, after menopause they are affected by stroke at a similar incidence as compared to the male community. Wang et al 2019 also noted the similar findings.

In our study, the severity of stroke was classified according to NIHSS stroke classification in mild (1 - 4), moderate (5 - 15), severe (16 - 20) and very severe (21 - 42) type of stroke. Among the 17 patients with score between 5 - 15 (moderate stroke) 6 patients had raised CRP. The mean CRP was 6.68 ± 2.60 in this group. In the 33 patients with score between 21 - 42 (very severe stroke), 32 patients had raised CRP. The mean CRP was 7.76 ± 2.82. The p value was calculated between both groups. It was 0.00014 when the mean CRP levels of NIHS score in the 21 - 42 group was compared with that of group with scores 5 - 15. Thus we can reasonably conclude that higher levels of CRP are seen in patients with poorer NIHSS scores. The findings published by Geng et al in 2016 also show the same that higher the levels of CRP, the greater will be the NIHSS scores and poorer will be the outcome.

The CRP levels of controls and cases were studied. In the age group of 18 - 40, the mean CRP level in controls was 2.85 ± 1.72, while in cases it was 3.4 ± 1.45. In the age group of 41 - 60, the mean CRP was 2.66 ± 1.66 while that in cases it was 5.77 ± 2.86. Above the age group of 60, the CRP levels in controls were zero as no subjects in this age group were studied while that in cases was 6.87 ± 3.54. The p values were calculated in each group. It was found to be 0.00012 for CRP levels of cases as compared to controls. This is consistent with the findings published by Napoli et al 2001 and Yu et al 2014.

Regarding the correlation with CRP with outcome of the stroke, the following observations were made. The outcome was divided into death, deteriorated, no change, improved, and recovery. The outcome was noted within 7 days of admission in the hospital. The cut-off for normal CRP was 3 mg/l above which all the observations made were considered as abnormal. Of the total number of patients with normal CRP (24%), i.e., 0 - 3 mg/l there was 1 (8.3%) death. 7 (58.33%) patients improved and 4 (33.33%) patients underwent complete recovery. The number of patients with raised CRP (more than 3 mg/l) was 38 (76%) cases. Of these 38 patients, there were 17 (44.7%) deaths, 11 (28.9%) patients condition deteriorated and 4 (10.52%) patients had no significant improvement in their condition. An improvement in condition was noted only in 6 (15.78%)

patients while complete recovery was not seen in any. The poor outcome was considered as those cases that died or deteriorated. The mean CRP levels were 2.16 in the group with normal CRP and 7.72.43 in the group with raised CRP. The p value was calculated between both groups. The p value was 0.0002. The result is significant at p value < 0.05.

In the study conducted by Hertog et al[16] in 2009 it was found that acute ischaemic stroke may give rise to an inflammatory response that leads to raised levels of C-reactive protein (CRP). High levels of CRP may be associated with poor outcome. The study evaluated the prognostic value of CRP within 12 h of onset of ischaemic stroke. Levels of CRP were routinely measured within 12 h of symptom onset in 561 patients with acute ischaemic stroke. CRP values were divided as < 7 or ≥ 7 mg/l. They studied the relation between CRP values and poor outcome (modified Rankin scale score > 2) or death at 3 months. A multiple logistic regression model was applied to adjust for age, sex, NIHSS score, current cigarette smoking, diabetes mellitus, hypertension, statin use, and stroke subtype. It was found that patients with CRP levels ≥ 7 mg/l had a significantly increased risk of poor outcome or death at 3 months. In addition, the risk of poor outcome or death at 3 months increased with higher levels of CRP. CRP within 12 h of ischaemic stroke is an independent prognostic factor of poor outcome at 3 months.

Conclusion

Stroke is one of the most common and devastating disorders and is the second leading cause of death worldwide. Incidences of stroke are increasing day by day in both developed and developing countries including India.

The clinical manifestation of stroke is highly variable. There are a lot of factors which can affect the outcome in these patients, e.g., TLC levels, extent of lesion, blood sugar levels, etc. Although the role of all these factors have been extensively investigated, very few studies have been published so far regarding the role of CRP in stroke.

From the present study we can conclude that the CRP levels are usually significantly high in cases of acute ischaemic stroke as compared to that of normal healthy population and the levels of CRP at the time of admission of stroke will predict the outcome and severity of stroke.

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