AGE AND GENDER PREDILECTION OF PLASMA C-REACTIVE PROTEIN LEVELS ON MORTALITY IN FIRST EVER ACUTE ISCHEMIC STROKE

Medicine

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ABSTRACT

Background and Purpose: The measurement of markers of inflammation or thrombosis has been proposed as a method to improve the prediction of risk in patients with vascular disease. The role of C-reactive protein (CRP) as a novel plasma marker of atherothrombotic disease is currently under investigation. We related age and gender predilection of plasma CRP levels to first ever ischemic stroke and its role on mortality. **Methods:** Sixty patients with either hypertension or diabetes or both or none without thrombolysis with first ever acute ischemic stroke patients were examined. CT scan of brain was done after 24 hours of onset of symptoms to confirm the diagnosis. Plasma CRP level was determined after 12 - 72 hours range after the onset of symptoms in all CT confirmed ischemic stroke patients. This clinical study was done during June 2018 to January 2020. CRP was randomly measured in 60 age and sex matched individuals admitted in other wards of the hospital matched in all possible criteria except the disease under study as a control group. **Results:** The CRP concentration in ischemic strokes is independent of infarction site, the value was more between 51-70 years of age group and almost equal in both gender. 54 of the 60 ischemic strokes studied had CRP value >6 mg/l and only 6 patients had <6 mg/l ($p < 0.001$), chi square test value is $\chi^2 = 73.65$ which is statistically significant. Only 7 of the 60 control group had CRP >6 mg/l. **Conclusion:** In this study mean C-Reactive protein levels were significantly higher in patients with ischemic stroke when compared to controls. C-reactive protein level increases as age advances. C-reactive protein is a better prognostic marker with no gender predilection and not a mortality predictor.

KEYWORDS

C-Reactive Protein; Ischemic Stroke.

MATERIALS AND METHODS

This study "Age and Gender Predilection of Plasma C Reactive Protein levels on Mortality in first ever acute ischemic stroke" was carried out in Basaveshwar Teaching & General Hospital, Gulbarga during the period from June 2018 to January 2020.

The study was undertaken with the following aims:

- 1) To observe Plasma CRP levels in acute ischemic stroke.
- 2) To evaluate the role of age and gender predilection of CRP on mortality in first ever acute ischemic stroke.

Selection of Patients: This study was conducted in patients admitted with first ever attack of ischemic stroke to intensive care unit or acute medical ward in Department of Medicine, Basaveshwar Teaching & General Hospital, Gulbarga.

Period of Study: From June 2018 to January 2020.

Sample Size: 250 patients admitted with stroke (CT proved) were selected for the study, of this 200 patients had thrombotic stroke. Out of this 60 were selected after exclusion of patients having heart disease, infection, tuberculosis, malignancies anywhere in the body, previous history of stroke, TIA and other factors known to alter CRP value as the study group. 60 age and sex matched control subjects were selected from patients in other wards matched in every possible aspect except for the disease under study.

Study Group: Of 200 stroke patients, 60 were selected as the study group strictly adhering to the inclusion criteria.

Inclusion criteria:

- 1) Age group 20-80 years.
- 2) Patients with either or both type 2 diabetes mellitus and hypertension or none.
- 3) Ischemia proved by CT scan brain, in all cases of the study.

Exclusion Criteria:

- 1) Age < 20 years and > 80 years.
- 2) Patients with history of heart disease – any valvular heart disease, myocardial infarction.
- 3) Patients with previous history of stroke or TIA.
- 4) Patients with collagen vascular diseases, active tuberculosis, arteritis.
- 5) Patients with hemorrhagic stroke, tumor, subarachnoid

hemorrhage.

- 6) Patients with head injury within past 3 months.
- 7) CT negative stroke.
- 8) Patients with meningitis, brain abscess or any chronic infection that affect CRP value.

Study Protocol:

Clinical history was taken from either the patient or his/her relatives or attender, while taking history importance was given regarding presence or absence of vomiting, headache and convulsions. Past history of hypertension, diabetes, CAD, RHD, TIA, collagen diseases, meningitis, tuberculosis, endocrine disorders and congenital disorders were taken. Personal history regarding dietary habits, smoking, alcohol consumption and tobacco chewing were noted. NIH stroke scale was assessed in all patients to assess the neurological disability and its prognosis. Detailed neurological examination was done based on proforma. All other systems like cardiovascular system, gastrointestinal system, and respiratory system were examined in detail. Detailed investigations including blood hemoglobin, TLC, DC, urine routine, FBS, lipid profile, ECG, chest X-ray, 2D-ECHO were done, CT scan after 24 hours after onset of symptoms and C-reactive protein estimation was done anytime between 12-72 hours of symptom onset.

CT Scanning:

In all cases, only plain CT was done. The CT scan is done after 24 hours of stroke.

Figure 1

Figure 1 Ct Scan Brain Showing Large infarct (7 x 4 cm) in the left Parietal Cortex

Figure 2

Figure 2 CT Scan Brain Showing Infarct in the Left Temporoparietal Region

OBSERVATIONS

There were 250 cases of first episode stroke in Basaveshwar Teaching and General Hospital during the period of June 2018 to January 2020.

Of those 200 cases were CT proved ischemic stroke. Of those 60 cases were studied after excluding the patients using the exclusion criteria.

60 age and sex matched controls were studied as the control group.

Table-1: Type of Stroke CT Evaluated (N = 250)

Type of stroke	No. of cases	Percentage
Ischemic stroke	200	80%
Hemorrhagic	50	20%
Total	250	100%

The above table shows that 80% of cases were ischemic strokes while only 20% constituted hemorrhagic stroke which included intracerebral and sub Arachnoid hemorrhage.

Table – 2 : Sex Distribution in Study Group (N = 60)

Sex	Total	Percentage
Males	37	61.6%
Females	23	38.4%

Table 2 shows sex distribution of the study group where 61.6% were males and 38.4% were females.

Table 3 Age and sex distribution in study group(N=60)

Age in years	No. of patients				Total	Percentage
	Male	Percentage	Female	Percentage		
21 – 30	0	0	0	0	0	0
31 – 40	4	10.8	0	0	4	6.6
41 – 50	6	16.2	6	28.1	12	20.0
51 – 60	8	21.6	4	17.4	12	20.0
61 – 70	10	27.0	8	37.8	18	30.0
71 – 80	9	24.4	5	21.7	14	23.4

Table 3 shows maximum thrombotic stroke patients were in the age group of 61 – 70 constituting 30% of the study population. Young stroke (age <40 years) were found only in 6.6% (Ratio of 1:15) of cases all of whom were males. Women < 50 years accounted only for 6 cases i.e. 10% of the total cases.

Table 4 : Age and Sex Distribution of Control Group (N = 60)

Age in years	No. of patients				Total	Percentage
	Male	Percentage	Female	Percentage		
21 – 30	0	0	0	0	0	0
31 – 40	4	10.8	0	0	4	6.6
41 – 50	6	16.2	6	28.1	12	20.0
51 – 60	8	21.6	4	17.4	12	20.0
61 – 70	10	27.0	8	37.8	18	30.0
71 – 80	9	24.4	5	21.7	14	23.4

Table 4 shows that similar age and sex matched controls were taken for the study as CRP increases with age.

Table 5: Localization of Lesions on CT Scan (N=60)

	No. of cases	Percentage
Cortical		

Frontal	8	13.4
Parietal	20	33.3
Temporal	2	3.3
Parietotemporal	6	10.0
Frontoparietal	8	13.4
Sub cortical		
Basal ganglia, Thalamus	12	20.0
Internalcapsule	4	6.6

Cortical infarction constituted 73.4% of cases in which maximum cases (33.3%) had infarction in the parietal lobe, followed by frontal and fronto-parietal areas which had 13.4% each. Sub cortical infarction constituted 26.6% with basal ganglia and / or thalamus involved in 20% cases.

Table 6 : NIH Stroke Scale (N-60)

NIH Scale	No. of patients		Total	Percentage
	Male	Female		
Minor Stroke (1-4)	8	2	10	16.6
Moderate Stroke (5-15)	18	15	33	55
Moderate - Severe Stroke (16-20)	10	4	14	23.4
Severe Stroke (> 20)	1	2	3	5

Table 6 shows Minor stroke accounted for 16.6% cases, while most patients (both male and female) 55% had moderate stroke, only 5% cases had severe stroke, whilst 23.4% had moderate to severe stroke.

Table 7 : Mortality chart showing sex distribution

Risk Factor	Known Cases		Newly Detected		Total	Percentage
	Male	Female	Male	Female		
Diabetes	2	1	1	1	5	35.7
Hypertension	2	1	0	0	3	21.4
Diabetes + Hypertension	2	0	2	0	4	28.6
None (N=10)	0	0	0	0	2	14.3

Table 7 shows Total number of deaths in the study were 14 (10 males, 4 females). **Diabetic** deaths constituted for 35.7% of the cases of them 3 were males and 2 females. **Hypertensive** group saw 21.4% (3) deaths in total and mortality was seen only in known cases of which 2 were males and one female.

Table 8: C-reactive protein level in CT proved ischaemic stroke patients

	C – reactive protein Levels			
	< 6mg / dl	Percentage	> 6mg/dl	Percentage
Study group (N=60)	6	10	54	90
Control (N=60)	53	88	7	12

Table 8 shows CRP values of CT evaluated ischemic stroke patients after admission, > 12 hours < 72 hours after the symptoms onset 54 of the 60 thrombotic stroke patients had CRP > 6 mg/dl only 6 patients had CRP < 6mg/dl (P < 0.001). Chi- square test value was 73.65, which is statistically very significant. Only 7 patients in the control group had CRP > 6mg/dl.

$$X^2 = 73.65, p < 0.001$$

Table 9 : CRP levels in relation to age (N=60)

Age in Years	CRP Values		Total
	> 6mg/dl	< 6mg/dl	
21 – 30	0	0	0
31 – 40	2	2	4
41 – 50	11	1	12
51 – 60	11	1	12
61 – 70	16	2	18
71 – 80	12	2	14

Table 9 shows the relation of CRP values with age, i.e. CRP level is more between the age group of 61 – 70 and is less in young adults (< 40 years of age).

Figure 1 : CRP Levels in Relation to Age (N=60)

DISCUSSION

Strokes kill »5 million people each year. Cerebrovascular disease is the second cause of death world wide^{1,2}.

Kristensen B³ et al documented young ischemic strokes occurring in patients younger than 45 years old was rare and less than 5 percent of all cerebral infarctions. A recent stroke registry study by T.Song – Hai Lee⁴ et al revealed that the incidence of young stroke was 6.8% of all strokes. In our study young ischemic stroke less than 40 years of age constitutes 6.6% of all strokes and highest incidence in males was noticed after the age of 61-70 years i.e.27% and in females also the incidence was highest in the age group of 61-70 years i.e.37.8%.

The greater prevalence of stroke in men is well known, but recent issues emphasize the importance of stroke in women⁵. Over the entire life time, » 16% of women but only 8% of men will die of stroke⁶. Knowledge of sex differences might be of interest in improving preventive strategies and the in-hospital management of stroke patients. Jaume Roquer et al⁷ documented mean age for stroke was higher in women than in men. In contrast to above studies, we documented the increased incidence of acute thrombotic stroke in both males and females after the age of 60 years with slight predominance in males. We also documented the incidence of thrombotic stroke after 60 years of age in males and females were 73% and 76.9% respectively.

Smoking is widely accepted as one of the risk factors for cerebral infarction in western populations. Smoking is thought to affect lacunar infarction mainly through reversible factors, such as increased platelet aggregation and arterial vasoconstriction induced by sympathetic activity rather than through atherogenic factors and this relationship has not been observed in most Japanese epidemiological studies⁸. Contrary to the above study, the above relation of smoking with acute ischemic stroke is not observed in our population.

Manson JE et al⁹ in their study had proved that stroke in diabetics is more likely to be fatal, when compared to any other novel risk factors. In terms with that of the above study, we also observed that mortality was highest among the diabetic group when compared to hypertensive group or diabetic and hypertensive group.

Thomas S. Bowman et al¹⁰ documented that TC, HDL and Triglyceride level were not independent risk factors for ischemic stroke and TC: HDL ratio did not have a linear association with the risk of ischemic stroke. In contrast to the above study we did notice the much

significance rise in TC, LDL and TG and decrease in HDL in relation to ischemic stroke when compared to controls in our study.

CRP, one of the acute phase reactants, is an indicator of underlying systemic inflammation¹⁰ and a novel plasma marker of atherothrombotic disease^{11,12,13}. It is likely that CRP has many pathophysiological roles in the inflammatory process, including binding of phosphocholine and recognition of foreign pathogens and phospholipid constituents of damaged cells¹⁰. Kerstin Winbeck et al¹⁴ study documents, raised CRP in 127 patients without thrombolysis with a first ischemic stroke no more than 12 hours after symptom onset. In contrast, a CRP increase between 12 and 24 hours after symptom onset predicts an unfavorable outcome and is not a best parameter to predict outcome which is estimated before 12 hours of onset of symptoms. In the present study, CRP was measured only after CT image confirmation of infarction which was done after 24 hours of onset of symptoms. So CRP level was estimated after CT confirmation and before 72 hours of onset of symptoms. In the present study, CRP was elevated in 54 patients out of 60 study group which is statistically significant.

Mario Di Napoli et al¹⁵ studied, the risk of CRP in 72% of patients (P<0.0001) out of 473 first ever ischemic patients and suggested the CRP as a independent marker of underlying chronic inflammatory process in atherosclerosis.

Montaner et al¹⁶ described a peak level of interleukin-6 after 24 hours of symptom onset.

Recently, Di Napoli¹⁷ observed an increase of CRP within 3 hours after stroke compared with the prestroke value. Mahapatra SC et al¹⁸ observed CRP value 76 mg/L in 64 patients out of 80 total thrombotic stroke patients (P<0.001). The study was undertaken to assess the role of inflammation in pathogenesis of ischemic stroke.

Rathore HS et al¹⁹ performed a study to measure and compare CRP levels in the cortical and lacunar infarct and to find out their diagnostic importance at an early stage of stroke. CRP was estimated in 25 cases of lacunar and 25 cases of cortical infarct. The CRP was considered positive if its value was more than 6 mg/L, observed rise of CRP in 12% cases of lacunar infarct and 88% cases of cortical infarct. In the present study the CRP rise was 82.4% in cortical and 26.6 in subcortical. It was clearly observed in our study that CRP was raised in all subtypes of cerebral infarct without much difference.

In Irene M et al²⁰ study, CRP levels were measured in a random sample of 773 subjects » 55 years of age and follow-up was done for the next 6.5 years. They documented the progression of subclinical atherosclerosis and CRP predicts myocardial infarction and stroke.

In our control study involved age and sex matched healthy individuals; the rise of CRP level was noted in 12% of cases. The prediction of myocardial infarction and stroke couldn't be done since it needs longer follow-up.

In L. Masoti et al²¹ study they retrospectively measured CRP values in 196 elderly patients for relationship between CRP and short term prognosis and concluded that elevation of CRP could represent a negative prognosis in elderly patients with ischaemic stroke, in particular, for short term prognosis. In the present study, there were 14 deaths, 10 were males and 4 were females and in all of them CRP >6mg/dl which is in terms with that of the above study reiterating that elevated CRP levels were a bad prognostic indicator.

SUMMARY

Stroke incidence increases with advancing age and is more in males when compared to females. Incidence of stroke is more common in diabetics then when compared to hypertensives or patients with both hypertension and diabetes. Fatal stroke was highest among the diabetic group. Non-fatal stroke was common among the hypertensive group. Mortality was highest among moderate stroke group on NIH stroke scale. C-reactive protein is an independent risk predictor for ischemic stroke. **C-reactive protein level increases as age advances and has no significant gender predilection, so age and gender predilection of CRP plays no effect on mortality in first ever ischemic stroke patients.** C-Reactive protein level has no significant relation to site and size of infarct. C-Reactive level cannot differentiate the subtypes (cortical and sub cortical) of cerebral infarct at the time of early

diagnosis. C-Reactive protein is a sensitive parameter to predict future myocardial infarction and stroke. In control group about 88% individuals had no significant rise of CRP.

CONCLUSION

In this study mean C-Reactive protein levels were significantly higher in patients with ischemic stroke when compared to controls. **C-reactive protein level increases as age advances and has no significant gender predilection so age and gender predilection of CRP plays no effect on mortality in first ever ischemic stroke patients.** It is also observed that by elevated C - Reactive Protein in ischemic stroke can be diagnosed positively but subtypes (cortical, subcortical) of cerebral infarction cannot be differentiated at the time of early diagnosis. C - Reactive Protein levels being raised within 72 hours of an acute ischemic stroke is poor prognostic indicator. C - Reactive Protein levels were raised in all cases who expired.

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