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PLASMA C-REACTIVE PROTEIN LEVELS AS A PROGNOSTIC MARKER IN FIRST EVER ACUTE ISCHEMIC STROKE

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ABSTRACT: BACKGROUND AND PURPOSE: Acute ischemic stroke may trigger an inflammatory response that leads to increased levels of C-reactive protein (CRP). High levels of CRP may be associated with poor outcome because they reflect either an inflammatory reaction or tissue damage. We related plasma CRP levels to first ever ischemic stroke and its role as a diagnostic aid. **METHODS:** Sixty patients fulfilling inclusion and exclusion criteria with first ever acute ischemic stroke were included in study**.** CT scan of brain was done after 24 hours of onset of symptoms to confirm the diagnosis. Plasma CRP level was determined after 12 hours and before 72 hours of onset of symptoms in all CT confirmed ischemic stroke patients. This clinical study was done from January 2008 to June 2009. CRP was randomly measured in 60 age and sex matched individuals admitted in other wards of the hospital matched in all possible criteria expect the disease under study as a control group. **RESULTS:** The CRP concentration in ischemic strokes was independent of infarction site, the value was more between 51-70 years of age group and almost equal in both genders. 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 x^2=73.65 which is statistically significant. Only 7 of the 60 control group had CRP >6 mg/l, which is insignificant. **CONCLUSION:** The CRP level is significantly higher in ischemic strokes and by its elevation between 12-72 hours of symptom onset is a bad prognostic indicator. The risk of poor outcome or death at 3 months increased with higher levels of CRP. Elevated CRP values is a risk factor in association with other risk factors like diabetes/hypertension.
KEYWORDS: C-reactive protein; Ischemic stroke, CT Scan brain.

INTRODUCTION: Stroke remains a major cause of human mortality and morbidity. Elevated serum levels of C-reactive protein (CRP) are found in up to three quarters of patients with ischemic stroke. Increase in CRP may reflect a systemic inflammatory response following ischemic stroke, the extent of tissue injury, or concurrent infections.

Furthermore traditional atherogenic risk factors such as hypertension, smoking, hyperlipidemia, and diabetes mellitus do not fully account for the clinical occurrence stroke in different populations.

Verification of the role of CRP as an early prognostic factor of functional outcome after ischemic stroke may be of clinical importance, because it is an easily-measured and readily available inflammatory marker. The aim of our study was therefore to determine the prognostic value of CRP measured in the very early phase of ischemic stroke for poor functional outcome and death in patients with acute ischemic stroke.

METHODS: The study was carried out in Basaveshwar Teaching & General Hospital, Gulbarga during the period from January 2008 to June 2009.

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The study was undertaken with the following Aims.
1. To observe Plasma CRP levels in acute ischemic stroke.
2. To evaluate the role of CRP as a prognostic aid in acute ischemic stroke.
3. To evaluate role of CRP as a risk factor in acute ischemic stroke.

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 patients were selected after excluding patients as listed in the exclusion criteria.

INCLUSION CRITERIA:
1. Age group 20-80years.
2. Patients with either type 2 diabetes mellitus or hypertension or both.
3. Ischemia proved by CT scan brain.

EXCLUSION CRITERIA: Patients with history of any heart disease, previous history of stroke or TIA, collagen vascular diseases, active tuberculosis, arteritis, hemorrhagic stroke, tumor, subarachnoid hemorrhage, head injury within past 3 months, meningitis, brain abscess or any chronic infection that affect CRP value.

STUDY PROTOCOL: Complete clinical history was taken from either the patient or his/ her relative. National Institute of Health (NIH) stroke scale was assessed in patients. Detailed neurological examination and all other systems were done. Routine blood investigations, urine routine, FBS, lipid profile, ECG, chest X-ray, 2D-ECHO were done. CRP estimation was done with latex CRP reagent by slide agglutination as per manufacturer's recommendations, which is a qualitative and semi-quantitative rapid latex slide text. The test was based on immunological reaction (agglutination reaction) between CRP particles had been coated with mono-specific antihuman CRP and sensitized to detect levels greater than 6 mg/L. All the patients in the study were followed up for 3 months.

STATISTICS: Data were presented as mean ± SD values were called significant (if $p<0.005$). The chi square test was used in most cases to compare frequency distribution.

RESULTS: There were 250 cases of first episode stroke in Basaveshwar Teaching and General Hospital during our study period

Of them 200 cases were CT proved ischemic stroke. 60 cases were studied after excluding the patients using the exclusion criteria. 60 age and sex matched controls were studied as the control group

Out of 60 patients in the study group where 61.6% were males and 38.4% were females. 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.

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	No. of cases	Percentage
Mode of onset		
Sudden (within minutes)	49	82
Gradual (within hours)	11	18
Level of consciousness		
Alert	36	60.0
Drowsy	16	26.6
Comatose	8	13.4
Convulsions		
Present	10	16.6
Absent	50	83.4
Headache / vomiting		
Present	14	23.3
Absent	46	76.7
Facial weakness		
Present	20	33.3
Absent	40	66.7
Dysarthria		
Present	18	30
Absent	42	70
Table 1: Clinical Picture (N=60)		

As shown in table no 1, 82% of patients had sudden onset of symptoms. 60% were alert at the time of presentation. Convulsions were present in 16.6% and headache / vomiting in 23.3% of the cases. 33.3% had facial weakness while 30% of the patients had dysarthria at admission.

Cortical infarction constituted 73.4% of cases and rest 26.6% constituted subcortical infarction. Amongst the cases with cortical infarction, majority (33.3%) had infarction in the parietal lobe, followed by frontal and fronto-parietal areas which had 13.4% each. Rest were temporal and paritotemporal infarcts. Amongst the subcortical infarcts, basal ganglia and /or thalamus involved in majority of the cases.

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 2: NIH Stroke Scale (N-60)				

When categorization of stroke done according to NIH scale as shown in table no 2, 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.

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Risk Factor	Known Cases		Newly Detected		Total	Percentage
	Male	Female	Male	Female		
Diabetes	12	2	2	4	20	33.4
Hypertension	6	6	2	2	16	26.6
Diabetes + Hypertension	6	6	2	0	14	23.4
None (N=10)	--	--	--	--	10	16.6
Table 3: Risk Factor Chart (N = 60)						

As shown in table no 3, Diabetes and hypertension were the most important risk factor for acute ischemic stroke accounting for 56.4% patients and 50% of the cases respectively. Combination of diabetes and hypertension as risk factors of acute ischemic stroke was seen in 23.4% of the cases. 16.6% of the cases in the study had no risk factors of either diabetes or hypertension or both.

	No. of Cases	Percentage
Smokers only	16	26.6%
Smokers & Tobacco chewers	4	6.7%
Smokers + Tobacco Chewers + Alcoholics	4	6.7%
Alcoholics only	0	0
Alcoholics + Tobacco chewers	0	0
Smokers & Alcoholics	12	20%
None	24	40%
Table 4: Assessment of other Risk Factors		

As shown in table no 4, other risk factors were: 26.6% were smokers only, while 20% were both smokers and consumed alcohol, whilst 6.7% had all 3 risk factors of smoking, consuming alcohol and eating tobacco.

Biochemical parameters	Study group (N=60)	Control group (N=60)	p value
Means serum urea (mg/dl)	32.54+29.80	20.72+2.80	<0.01
Mean Serum creatinine (mg/dl)	1.04+0.36	0.77+0.20	<0.01
Mean fasting blood sugar (mg/dl)	144.4+58.2	85.58+7.2	<0.01
Table 5: Biochemical parameters in study and control group			

The mean serum urea, creatinine, fasting blood sugar were significantly raised in the study group with p value <0.01 shows that it was statistically highly significant.(table no 5)

Biochemical parameters (in Mg/dl)	Study group (N=60)	Control group (N=60)	P value
Means serum Cholesterol	190.8+35.3	159.6+21.8	<0.01
Mean Serum HDL	41.2+7.64	44.5+9.79	<0.05
Mean serum LDL	118.78+33.9	90.10+17.69	<0.01
Mean serum Triglycerides	192.5+78.4	141.36+41.3	<0.01
Table 6: Lipid profile in study and control group			

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Serum cholesterol, LDL, TG, was <0.01 and p value of HDL was <0.05 implying that the lipid profile was altered in the study group and was statistically highly significant. (Table no 6)

	No. of cases		Total
	Improved	**Expired**	
Diabetes	15	5	20
Hypertension	13	3	16
Diabetes + Hypertension	10	4	14
None (N=10)	8	2	10
Table 7: Prognosis chart showing patients who improved and who expired			

Of the 60 cases under study 76.6% improved, 23.4% expired. Of the 20 patients with only diabetes 5(25%) expired whereas of the 16 hypertensives, 3(18%) expired. Of the 14 patients who were both diabetic and hypertensive 4(28.5%) expired.

Age in years	No. of deaths		Total	Percentage
	Male	**Percentage**		
21 – 30	0	0	0	0
31 – 40	1	0	1	7.1
41 – 50	1	0	1	7.1
51 – 60	2	0	2	4.3
61 – 70	2	4	6	42.9
71 – 80	4	0	4	28.6
Table 8: Age and sex distribution of Mortality cases				

The total number of deaths in our study as shown in table no 8, were 14, of which 10(71.4%) were males and 4(28.6%) were females. All female deaths occurred in the age group of 61 – 70. Whereas most deaths in males were in the age group of 71 – 80 constituting 28.6% of the cases. Total incidence of mortality (42.9%) was highest in age group of 61 – 70.

	C – reactive protein Levels			
	< 6mg /L	**Percentage**	**> 6mg/L**	**Percentage**
Study group (N=60)	6	10	54	90
Control (N=60)	53	88	7	12
Table 9: C-reactive protein level in CT proved ischemic stroke patients				

X2 = 73.65, p < 0.001

Table no 9 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/L 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/L.

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Age in Years	CRP Values		Total
	> 6mg/L	< 6mg/L	
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 10: CRP levels in relation to age (N = 60)			

Table no 10, 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)
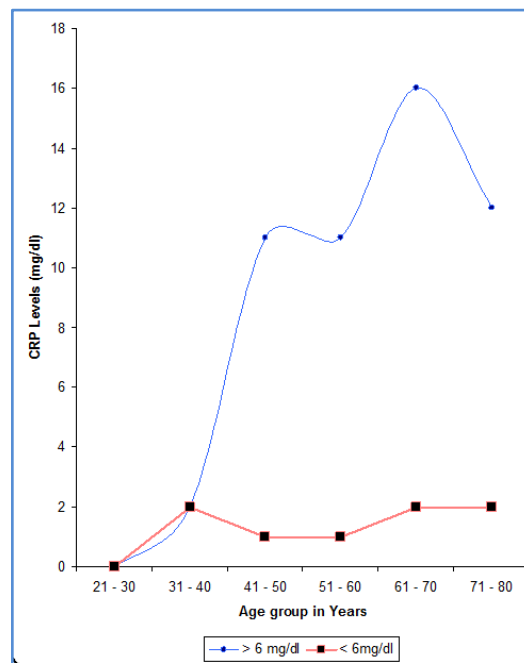

Fig. 1: CRP levels in relation with age

DISCUSSION: In our study young ischemic stroke less than 40 years of age constitutes 6.6% of all strokes. Kristensen B[1] et al and T. Song – Hai Lee[2] et al documented young ischemic strokes occurring in patients younger than 45 years old were < 5 percent of all cerebral infarctions.

Manson JE et al[3] 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 higher among the patients who had both diabetes and hypertension (28.5%) than compared to patients with either one of the risk factors.

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

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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 studies.[4] With respect to above observations, our study also observed significant high association between smoking and cerebral infarction.

Thomas S. Bowman et al.[5] documented that Total cholesterol, 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 inflammation[6] and a novel plasma marker of atherothrombotic disease.[7,8] 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 cells.[8]

In the present study, CRP was elevated in 54 (90%) patients out of 60 study group which is statistically significant.

Mario Di Napoli et al[9] studied, the rise of CRP in 72% of patients (P<0.0001) out of 473 first ever ischemic patients and suggested the CRP as an independent marker of underlying chronic inflammatory process in atherosclerosis. They also observed an increase in CRP within 3 hours after stroke compared with the pre stroke value.

In Irene Met al[10] study, CRP levels were measured in a random sample of 773 subjects of average 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 al[11] 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, among 54 ischemic stroke patients with high CRP levels 14 (25.9%) died in 3 months follow up. This was in concordance with a study done by hertog et al[12] on 516 patients, mortality was seen 23% of patients with high CRP levels at the end of 3 months. Who concluded that elevated CRP levels in the very early phase of acute ischemic stroke are independent prognostic factor.

CONCLUSION: The use of biomarkers as predictors of stroke lesion evolution and prognosis is becoming increasingly important, as they may be valuable tools in the search for an optimal management of stroke patients. The present study confirms results from previous studies that have advocated higher CRP as a powerful prognostic marker in patients with ischemic stroke when measured between 12-72hours. The risk of poor outcome or death at 3 months increased with higher levels of CRP. Elevated CRP values are a risk factor in association with other risk factors like diabetes/hypertension.

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LIMITATIONS OF THE STUDY:
1. Serial C - reactive protein could be a better prognostic predictor than isolated sample of CRP estimation, which was not done in this study.
2. To ascertain CRP as a risk factor for ischemic for further prospective studies a repeat CRP studies need to done.

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