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LEVELS OF CRP IN ACUTE ISCHEMIC STROKE PATIENTS

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Abstract:

Aims: *The aim of the study was to evaluate CRP and risk factors for ischemic stroke.*

Methods: *This clinical study was conducted at the Department of Neurology, Services Hospital, Lahore for one-year duration from August 2019 to August 2020. The included stroke patients meeting inclusion and exclusion criteria.*

Results: *Out of 30 patients with ischemic stroke, 28 (93.3%) patients had a positive value of C-reactive protein. 37% of stroke patients smoked cigarettes. Mean levels of total cholesterol, triglycerides, and LDL levels were higher, and mean HDL levels were lower in stroke patients compared to controls. 17% of stroke patients had diabetes, and 80% of stroke patients had high blood pressure.*

Conclusion: *Elevated levels of C-reactive protein in the acute phase of ischemic stroke may be a prognostic marker.*

Key words: *CRP, acute ischemic stroke*

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INTRODUCTION:

Stroke is the most common neurological disorder in adulthood and remains the third leading cause of death after heart disease and cancer after age 40. Of the hundreds of thousands of stroke survivors each year, around 30 percent require assistance with daily activities, 20 percent require assistance with mobility, and 16 percent require institutional care [1-2]. Overall, its incidence ranges from 150 to 300 per 100,000 population, and its prevalence is 600/100,000 population. 85% of all strokes are caused by an ischemic infarction and 15% by hemorrhage. The highest observed stroke rate is 7/1000 in Pakistan, Russia, and the lowest is 2.4 / 1000 in India [3-4]. In Pakistan, the rate of stroke is 700,000 per year. Stroke, causing approximately 4 million deaths a year) and is the single most important single cause of severe disability in those living in their own home. There are many risk factors for a stroke. Some are non-modifiable such as age, gender, race, etc. and some are modifiable such as hypertension, diabetes, coronary heart disease (IHD), heart valve disease, smoking, dyslipidemia, asymptomatic carotid murmur / stenosis, aorta atherosclerotic arch, etc. C-reactive protein (CRP), one of the acute phase reagents, is an indicator of underlying systemic inflammation and a new plasma marker of atherosclerotic disease. Moreover, elevated plasma levels of C-reactive protein are not disease specific, but are sensitive markers produced in response to tissue damage, infectious agents, immune stimuli and inflammation. Increased levels of reactive protein (CRP) in the blood are associated with an increased risk of atherosclerosis, including stroke [5-6]. However, the role of CRP in the etiology and prognosis of ischemic stroke has not been clearly established. One hypothesis is that CRP plays a direct causal role in the pathogenesis of atherosclerosis by promoting expression of endothelial cell adhesion molecules, recruiting monocytes or activating complement, or mediating the uptake of low-density lipoprotein cholesterol by macrophages. Elevated blood levels of CRP in the acute phase of ischemic stroke mainly reflect the extent of ischemic brain injury and its complications. Higher values of C-reactive protein (CRP) are significantly associated with large infarct size and worst outcomes [7-8]. The use of plasma CRP levels can help identify a potentially large number of men and women at risk for cerebrovascular accidents. The aim of this study is to evaluate C-reactive protein in patients with acute ischemic stroke, to assess risk factors for ischemic stroke, and to observe elevated levels of C-reactive protein in patients with acute ischemic stroke.

MATERIALS AND METHODS:

It was a clinical trial conducted at the Department of Neurology, Services Hospital, Lahore for one-year duration from August 2019 to August 2020 on all stroke patients who presented to the outpatient department (OPD) and were also admitted to the neurology department meeting the inclusion and exclusion criteria. A patient over 30 years of age who had an acute ischemic stroke (4 weeks duration), clinically confirmed and by neuroimaging (CT / MRI of the brain) was defined as random and apparently healthy, and age and gender matching the case were controls. Under 30 years of age, neuroimaging confirmed hemorrhagic stroke, history of acute myocardial infarction, venous thrombosis and myeloproliferative diseases, history of rheumatology and connective tissue diseases, history of malignant tumors, recent surgery (within a month) and recent infection (within a month) were excluded from the study. After a detailed history and physical examination, a total of 73 patients were enrolled in the neuroimaging (CT / MRI) examination of the brain. Of these, 23 patients were excluded due to the presence of hemorrhage in neuroimaging. From the remaining 50 patients, 20 patients were excluded from the study group due to symptoms of infection, rheumatological diseases and previous acute myocardial infarction. Ultimately, a total of 30 patients who met the inclusion and exclusion criteria were included in the study group. Out of 30 patients, 25 were performed by computed tomography of the brain and in 5 of them by MRI. A detailed history was collected regarding age, high blood pressure, diabetes, smoking addiction, heart disease and oral contraceptive pills. They were also asked about a febrile infection or productive cough, diarrhea and dysuria. They were clinically assessed for the presence of sinusitis, diabetes, hypertension, tuberculosis, pneumonia, and bronchitis. In order to detect lymphadenopathy, cervical, supraclavicular, axillary and inguinal lymph nodes were searched for. They were also clinically assessed for the presence of any valvular and ischemic heart disease. All of them were tested for serum C-reactive protein, complete blood count, serum creatinine, random RBS blood sugar level, serum lipid profile, ECG and chest X-ray. Written consent was obtained from the patient or his relatives after the study procedure and study objectives had been clarified. A total of 30 people matched for age and sex and apparently healthy were selected as the control group. Control patients never suffered a stroke and were admitted to the neurology department for non-specific disorders and symptoms such as anxiety neurosis, muscle aches, burning extremities, tingling, numbness, headaches and somatoform disorders, and was not clinically identified. visible infection, inflammation, or

symptoms of a neurological deficit. All data obtained was recorded in a structured form of case files. Serum C-reactive protein was determined by the Nephelometric System using a commercial kit (DADE BEHRING BN 100, USA) at the Department of Microbiology and Immunology, Bangabandhu Sheikh Mujib Medical University. Taking aseptic precautions, 5 ml of random venous blood were collected into a test tube. It was held for 5-10 minutes until it clotted. It was then centrifuged at 5,000-10,000 rpm for 10 minutes. The serum was thus separated. 200 µl of serum was withdrawn into the sample cup. The reagent was then transferred to a predefined reagent container. The Behring Nephelometer 100 automatically took reaction buffer, diluent and distilled water. The quantitative measurement of C-reactive protein was estimated from the serum after an automated analyzer program directed at the computer. The level of C-reactive protein was expressed in mg / l. The random blood sugar level was also determined by the kit method and the fast lipid profile was also assessed by the kit method. Total WBC count, differential WBC count, Hb%, and ESR were performed at the clinical pathology unit. At the Clinical Pathology Unit, a routine and microscopic examination was performed routinely to rule out urinary tract infections. The P / A chest X-ray was taken at the Department of Radiology and Imaging. Neuroimaging (brain computed tomography / brain magnetic resonance imaging) was performed at the radiology and imaging department, as well as at some private diagnostic centers. Electrocardiogram [EKG] - Standard 12-lead ECG was performed at the Department of Cardiology. Blood pressure was measured with a mercury sphygmomanometer. It was measured from the middle of the left arm in the supine position. Data analysis was performed with computer software; The statistical package for social sciences (SPSS) was used to analyze the collected data. Relevant analysis was performed, such as unpaired student "t" test, Chi-square test, Z test, etc. The minimum significance level was $p < 0.05$.

RESULTS:

This was a follow-up study conducted to evaluate serum C-reactive protein in patients with acute ischemic stroke. A total of 30 patients clinically diagnosed with ischemic stroke were assessed and confirmed by neuroimaging. Age and gender of a similar number of healthy people were also taken into account as a control. Most (63%) of the respondents were between 51 and 80 years old.

Table-I

Age distribution of the study subjects

Age (years)	Case (n=30) No. (%)	Control (n=30) No. (%)	P value
<40	7 (23.3)	3 (10.0)	
41 50	4 (13.3)	11 (36.7)	
51 60	6 (20.0)	10 (33.3)	>0.05^{ns}
61 70	10 (33.3)	5 (16.7)	
71 80	3 (10.0)	1 (3.3)	
Range	35 80	32 71	
Mean±SD	56.30±13.70	53.43±9.94	>0.10^{ns}

The study showed that 21 (70%) patients are male and 9 (30%) female patients. Among the controls, 25 (83.3%) were men and 5 (16.7%) were women. It was found that 28 (93.3%) patients were positive for C-reactive protein and only 2 (6.7%) patients were negative for C-reactive protein. In the control group, all of them had a negative value of C-reactive protein.

Table II

Study of risk factors among the study subjects

Parameters	Case (n=30) No. (%)	Control (n=30) No. (%)	P value	Odds ratio	95% CI
Smoking habit			>0.50^{ns}	1.351	0.460-3.968
Yes	11 (36.7)	9 (30.0)			
No	19 (63.3)	21 (70.0)			
Hypertension			<0.001***	20.000	5.384-74.298
Yes	24 (80.0)	5 (16.7)			
No	6 (20.0)	25 (83.3)			
Diabetes			<0.05*	2.200	1.647-2.939
Yes	5 (16.7)	0			
No	25 (83.3)	30 (100.0)			
Cardiac disease			>0.10^{ns}	2.034	1.569-2.637
Yes	1 (3.3)	0			
No	29 (96.7)	30 (100.0)			
Oral contraceptives (female only)	(n=9)		>0.10^{ns} (n=5)	1.833	1.069-3.144
Yes	3 (33.3)	0			
No	6 (66.7)	5 (100.0)			

The study shows the prevalence of risk factors among cases and controls. (Table-II) A current smoker who quit smoking for less than 6 months was considered a smoker. For group 11 (36.6%) smokers were compared with 9 (30%) in the control group (p-value> 0.50). Hypertension was significantly (p <0.001) distributed between the group of patients (80.0%) and the control group (16.7%). Diabetes mellitus occurred in 5 patients (16.7%), and none of the controls had DM. Three out of 9 patients (33.3%) had previously used oral contraceptive pills. One patient (3.3%) had a history of heart disease in the form of IHD. The mean systolic blood pressure was 152.67 (SD ± 21.65) mmHg and 127.50 s (SD ± 8.17) mmHg between patients and controls, respectively (Table III). Similarly, the mean diastolic blood pressure was 90.17 (SD ± 13.93) mmHg and 78.83 (SD ± 8.38) mmHg between patients and controls, respectively. In this table of systolic and diastolic blood pressures were significantly higher in the group of patients (p <0.001).

Table III

General examination findings

Parameters	Case (n=30)	Control (n=30)	t value	df	P value
Pulse rate (b/min)					
Mean±SD	81.33±10.26	76.13±5.14	2.482	58	<0.05*
Range	68 120	68 88			
SBP (mmHg)					
Mean±SD	152.67±21.65	127.50±8.17	5.958	58	<0.001***
Range	100 190	120 150			
DBP (mmHg)					
Mean±SD	90.17±13.93	78.83±8.38	3.820	58	<0.001***
Range	40 110	70 100			

The total white blood cell count was higher in the group of patients with neutrophilic leukocytosis ($p < 0.001$). ESR was slightly higher in the patient group, 12.40 (SD ± 4.88) vs. 9.77 (SD ± 2.65) ($p < 0.05$). Serum creatinine was within the normal range (Table IV).

Table IV

Investigation results

Parameters	Case (n=30)	Control (n=30)	t value	df	P value
Hb (g/dl)					
Range	9.80-16.00	10.00- 15.00			
Mean±SD	11.58±1.69	11.94±1.30	0.917	58	>0.10^{ns}
Total count (cmm)					
Range	8000-14500	7000-11000			
Mean±SD	11363.33	9650.00 ±1596.65	4.953 ±1020.40	58	<0.001***
Differential count (%)					
Neutrophil					
Range	55-84	58-80			
Mean±SD	75.33±6.02	68.13±4.86	5.097	58	<0.001***
Lymphocyte					
Range	12-35	15-32			
Mean±SD	18.63±4.98	23.63±3.90	4.330	58	<0.001***
Monocyte					
Range	1- 6	2-6			
Mean±SD	3.57±1.63	4.43±1.22	2.326	58	<0.05*
Eosinophil					
Range	1-4	2-6			
Mean±SD	2.80±0.92	3.80±0.85	4.368	58	<0.001***
ESR (mm/1st hr)					
Range	2-20	6-18			
Mean±SD	12.40±4.88	9.77±2.65	2.597	58	<0.05*
Serum creatinine (mmol/L)					
Range	78- 130	70-110			
Mean±SD	107.70±8 96	84.60±7.50	10.825	58	<0.001***

Table V

Effect of risk factors on C-reactive protein

Parameters	Present No. (%)	Absent No. (%)	P value	Odds ratio	95% CI
Smoking habit			>0.10^{ns}		
n	11 (36.7)	19 (63.3)			
CRP +ve	11 (100.0)	17 (89.5)		1.118	0.958-1.304
CRP ve	0	2 (10.5)			
History of hypertension			>0.10^{ns}		
n	24 (80.0)	6 (20.0)			
CRP +ve	23 (95.8)	5 (83.3)		1.150	0.796-1.661
CRP ve	1 (4.2)	1 (16.7)		0.250	0.018-3.446
History of diabetes			>0.50^{ns}		
n	5 (16.7)	25 (83.3)			
CRP +ve	5 (100.0)	23 (92.0)		1.087	0.968-1.220
CRP ve	0	2 (8.0)			
History of cardiac disease			>0.50^{ns}		
n	1 (3.3)	29 (96.7)			
CRP +ve	1 (100.0)	27 (93.1)		1.074	0.973 -1.186
CRP ve	0	2 (6.9)			
History of OCP (female only)			>0.10^{ns}		
n	3 (33.3)	6 (66.7)			
CRP +ve	3 (100.0)	5(83.3)		1.200	0.839- 1.716
CRP ve	0	1 (16.7)			

The mean value of C-reactive protein was 42.06 mg / l (SD ± 21.26) vs. 4.30 (SD ± 0.72) between the study and control groups. ($p < 0.001$) There was no significant effect of risk factors on the level of C-reactive protein (Table V) and no significant relationship with ESR.

Total cholesterol, triglycerides, and LDL were higher, and HDL was lower. For the total cholesterol group, triglycerides, LDL, and HDL between CRP + ve and CRP -ve were not significant. In the control group, they all have CRP –ve. Comparison of the lipid profile between CRP -ve and control CRP -ve also showed no significant difference.

Nine patients (30%) had an enlarged heart on chest X-ray, the rest in the PA projection is normal (p-value <0.001). An ECG was performed in all cases. Fourteen patients (46.7%) had non-specific ST-T segment changes, and 1 (3.3%) patient had ECG atrial fibrillation.

DISCUSSION:

The present study showed that the mean age of the patients was 56.37 (SD ± 13.73). This finding is in line with the results of a previous study by Muhammad, 2006 at the neurology department. Similar prior studies had comparable age-related statistics, for example (Bell et al., 1990) studied 51 stroke patients with most (50-69) years; Another study from 2001 looked at a sample with a mean age of 58 (SD ± 12) years. Seventy (70) percent of the subjects were male[7-8]. The male to female ratio was 2.33: 1. A 1995 study found that men were 1.5 times

more affected by stroke than women. This difference found in the study may be due to the attitude of our society that women are less likely to go to hospitals for treatment. This study found elevated serum C-reactive protein levels in 28 (93.3%) of 30 patients. The mean value of C-reactive protein was 42.06 (SD ± 21.26), while in the control group it was 4.30 (SD ± 0.72). These results are in line with the results of several studies. Possible explanations are: 1. CRP levels may reflect the severity of a stroke, correlating with the degree of inflammation immediately following the infarction. 2. CRP levels may indicate unstable atherosclerotic disease. 3. CRP may increase as a result of secondary complications of stroke at the time of sampling. We found that 2 stroke patients were negative for C-reactive protein. Grau, 1997 found that approximately 25% of patients with a first-ever ischemic stroke had normal CRP levels after stroke [9-10]. This may be due to the variability in the degree of the inflammatory response to ischemic stroke (Gabay et al., 1999). In 1999, they demonstrated high CRP values in their studies, compared with much lower predictive levels of cardiovascular morbidity in epidemiological studies, which may suggest a strong acute phase response rather than a low-grade chronic inflammatory response. The inflammatory process represented by an elevated CRP may also result from the plaque itself. The study found that 37% of stroke patients were smokers. A study showed that 59.84% of smokers among stroke patients. This difference may be due to the different number of cases and the anti-smoking campaign[11-12]. The contribution of cigarette smoking to the increased risk of stroke is controversial. Although it may have an indirect effect. One 1998 study found an orderly relationship between increasing exposure to cigarette smoke and the incidence of cerebral infarction. The potential role of viral infections in atherosclerosis has attracted much attention in ischemic heart disease, but has not yet been recognized as being relevant to carotid artery disease. Inflammation of inflammatory cells, especially macrophages, is associated with rupture of the carotid plaque in a manner analogous to coronary artery disease, and in patients with carotid atherosclerosis, the concentration of both circulating and locally synthesized pro-inflammatory cytokines is increased. Therefore, in most patients, CRP may be a useful marker of atherosclerotic instability. In the case of coronary artery disease, two recent studies seem to indicate that statin therapy and lowering CRP levels may reduce the progression of atherosclerosiss [13-14]. In cerebrovascular diseases, the influence of some categories of drugs on the atherosclerotic process modifying the acute phase of inflammation has been studied. It has been suggested that statins and angiotensin converting enzyme inhibitors may be more effective at high CRP levels, and the efficacy of antiplatelet therapy such as aspirin or clopidogrel in secondary prevention may be related to levels of inflammatory markers [15].

CONCLUSIONS:

Stroke is actually one of the major health problems worldwide due to its high prevalence, morbidity, mortality, and residual disability. It is extremely important to select and address patients at high risk of negative outcomes through the most intensive pharmacological and rehabilitation approach. Our study confirms that the level of C-reactive protein is elevated in the acute phase of ischemic stroke and may be a prognostic marker. Further prospective studies are needed to demonstrate this hypothesis.

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