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Original Research Paper

Serum C-reactive Protein Levels in Cerebrovascular Accidents

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ABSTRACT:
Background: C- reactive protein (CRP) is an annular acute-phase pentameric protein of 206 amino acids found in blood plasma with a molecular mass of 120,000 daltons and it increases within six hours of inflammation which can be measured in the serum. Stroke or cerebrovascular accident (CVA) is the sudden death of brain cells due to inadequate blood flow and one of the leading causes of mortality and morbidity worldwide. By correlating the relationship between stroke and CRP levels, the study aims to estimate serum CRP in patients suffering from CVA and compare these with apparently normal healthy individuals. Secondly, to find out any difference in serum CRP levels between hemorrhagic and ischemic stroke cases. **Materials & methods**: This is a cross-sectional study conducted in the Department of Biochemistry in collaboration with the Department of Medicine from November 2020 to October 2022. The study population consisted of 60 CVA patients and 60 age matched healthy individuals. **Results**: The study showed the highest prevalence of CVA cases in the age group of 51-60 years signifying the risk of stroke increases with age with a male to female ratio of 1.2:1. The level of serum CRP was found to be significantly higher in cases (6.56 ± 2.59) mg/L than the healthy controls (1.77 ± 0.88) mg/L indicating that the pathophysiology of CVA involves inflammatory pathways. And it showed significant increased CRP levels in case of ischaemic stroke (7.75±2.24) mg/L than that of haemorrhagic stroke (5.20±2.31) mg/L. **Conclusion**: The present study shows a significant increase in serum C-reactive protein in cerebrovascular accident patients and also it increases more in the ischaemic type than the haemorrhagic type. Further long-term perspective studies are needed to establish the role of CRP in stroke patients.

Keywords: C-reactive protein, cerebrovascular accident, inflammation, biomarker

INTRODUCTION:

Stroke or cerebrovascular accident is the sudden death of brain cells due to inadequate blood flow. WHO (ICD-11) clinically defines stroke as the acute focal neurological dysfunction caused by focal infarction at single or multiple sites of the brain or retina lasting more than 24 hours or lead to death in less than 24 hours.[1] Stroke is the 2nd leading cause of mortality worldwide consisting of approximately 6.5 million people annually with a prevalence of 101 million people.[2] There are various risk factors for stroke and few consists of high blood pressure, atrial fibrillation, high cholesterol levels, diabetes, cigarette smoking, heavy alcohol consumption, drug use, sedentary lifestyles, obesity, etc.[3-4] It is a medical emergency that could cause permanent neurological damage, complications and death.

There are two types of stroke: Ischemic stroke which are caused by interruption of blood supply accounting for 50-80% of all strokes and haemorrhagic stroke results from rupture of blood vessel or an abnormal vasculature. The clinical stroke symptoms include acute onset of unilateral paralysis, loss of vision, speech impairment, memory loss, impaired reasoning ability, coma or even death. Atherothrombosis is by far the most important cause of stroke.[5] It involves large and medium size vessels that can lead to ischemic heart, damage to the brain or infarction. But loss of consciousness, headache and vomiting usually are often associated with haemorrhagic stroke as there is presence of increase intracranial pressure from the leaking blood compressing the brain. C-reactive protein is an annular acute-phase pentameric protein made up of 206 amino acids found in blood plasma

with a molecular mass of 120,000 daltons. It is produced by the liver in the presence of acute inflammation and rises within 6 hours of the start of inflammation. It has a role in binding to phosphatidylcholine which is found on the surface of dead or dying cells and triggers the complement system via C1q. Several studies have found significant higher levels of CRP in ischemic stroke as compared to haemorrhagic stroke conveying its role in inflammatory process as a synergistic effect in the pathogenesis of ischemic stroke. CRP has two types: Standard CRP and high-sensitivity CRP (hs-CRP). Previously, standard CRP could detect only about 5mg/L and hs-CRP concentrations are elevated even in high-risk individuals of developing inflammatory diseases and coronary artery diseases. Hence, CRP can be used as a screening investigation for evaluating the severity of ischemic stroke.

Materials and methods:

This is a cross- sectional study conducted in the Department of Biochemistry in collaboration with the Department of Medicine from November 2020 to October 2022. Sixty patients of acute stroke (>18 years) within 48 hours of onset admitted in ward were selected irrespective of sex and socioeconomic status. Patients with a known case of atrial fibrillation, valvular heart disease and on anticoagulant treatment, patients with duration of symptoms >48 hours, having past history of vascular diseases and malignancies and those having active infections, sub-acute thyroiditis & chronic inflammatory bowel diseases were excluded. The study was approved by the Research Ethics Board, Institutional Ethics Committee (IEC).

Methods of Data Collection:

Detailed socio-demographic and clinical symptoms were recorded for each patients including age, gender, residence, patient history, investigations including serum CRP. Blood was collected from patients with stroke within 48 hours of onset.

Sample Collection and Laboratory Measurements:

A written consent form was taken from all the subjects. Overnight fasting venous blood of five ml was collected in plain vial and allowed to clot at room temperature. The clot was retracted, and serum separated by centrifugation at 2000 rpm for 10 minutes. Serum C-Reactive protein was determined by ELISA method using CALBIOTECH CRP ELISA kit which is a quantitative determination test.

Statistical Analysis:

All statistical analysis were performed using using IBM: SPSS statistics version 21. Results were reported as mean±SD (standard deviation) for quantitative variables and number of cases along with percentage for categorical variable, students t test was used to test the significance. p-value <0.05 were considered statistically significant.

RESULTS:

In this study, there were 60 CVA cases and all the study participants were above 30 years with highest prevalence in the age group of 51-60 years (35%) followed by 61-70 years (25%). There were 33 (55%) males and 27 (45%) females among the cases signifying the risk of stroke increases with age with a male to female ratio of 1.2:1.

As shown in table 2, the majority of CVA cases had SBP in the range of 161-170 mmHg with 55%, out of which 18 were males and 15 were females respectively. Fig 1. Showed a higher cases of ischemic stroke with a percentage of 53.33% (35 cases) than the haemorrhagic stroke i.e.46.67 % (28 cases). Table 3 shows the significant increase of mean±SD of serum CRP levels in case of ischemic stroke (7.75±2.24) mg/L and haemorrhagic stroke (5.20±2.31) mg/L when compared with the controls (1.77±0.88) mg/L with p-value <0.001.

Table 4 shows that maximum CVA cases (53) were in the range of serum CRP levels more than 3 mg/L followed by 7 cases in the range of 1-3 mg/L. In order to study the correlation among the parameters listed above, Pearson's correlation coefficient "r" was advocated. The analysis is based on the CVA case group only.

Table 5 and 6 highlights that the mean±SD (mg%) of Total Cholesterol (TC), Triglyceride (TG), Low density lipoprotein (LDL), Very Low Density Lipoprotein (VLDL) were highest when the level of CRP was >3 mg/L except for High Density Lipoprotein (HDL) and there is a strong positive correlations of serum CRP levels with TC, TG, LDL, VLDL but negative correlation with HDL cholesterol which are highly significant (correlation matrix).

DISCUSSION:

Cerebrovascular accident (CVA) or stroke has a complex pathophysiology involving both the inflammatory and oxidative pathways. Moreover, only clinical symptoms and scans have been diagnosing till date with no blood markers for stroke. As it is an emergency case, earlier diagnosis is preferred, which otherwise may lead to permanent complications and even death.

The present study shows that the mean±SD of age in years for controls and CVA cases as 55.52±11.75 years and 58.35±11.54 years respectively. The difference in the age between control and CVA cases are not statistically significant indicating both groups are of comparable age as observed in table 2. The mean age of CVA cases is similar with findings of study done by Naik M et al[6] and Shrestha A et al[7] who found the

mean age of CVA cases around 58.5 years, which is almost similar with the present study. Age groups of 51-60 years comprised of 40% of total stroke patients in this study showing the maximum incidence in this group . It correlates with the findings of Eapen RP et al[8] and Wadhawani J et al[9] who also found the highest incidence of CVA cases in the same age group as above. Hence, the risk of stroke is higher with increase in age.

Table 1 shows that the prevalence of CVA is higher among males with 33 (55%) cases than females with 27 (45%) cases, the male to female ratio in the study group is 1.2:1 and this variation in sex-wise distribution is statistically insignificant. This finding is comparable with reports of Shrestha A et al[7] where male: female ratio is 1.4:1 in stroke patients. These findings may be due to differences in risk factors such as smoking and alcohol drinking which are more prevalent among men in India compared to women.[10]

As depicted in table 2, out of 60 CVA cases majority of the patients 37(61.66%) showed systolic blood pressure (SBP) between 161-170 mmHg indicating that majority of the patients have blood pressure on higher range. The study shows higher percentage of ischemic stroke 35 (53.33%) than the haemorrhagic stroke 28(46.67%) (Fig.1). This is supported by the stroke statistics findings that most strokes (85%) are ischemic strokes.[11] Elevated CRP level was associated with higher incidence of ischemic stroke but not with hemorrhagic stroke was also reported by a study by Sharma DJ et al.[12]

The present study established that serum CRP levels were significantly higher in in patients with ischemic stroke (7.75±2.24 mg/L) and haemorrhagic stroke (5.20±2.31 mg/L) in comparison with the controls (1.77±0.88 mg/L) with $p<0.001$ as depicted in table 3. This finding is in accordance with the findings of Kocer A et al.[13]

When patients are distributed according to serum CRP levels (table 4), it is evident that maximum number of patients (53 cases) are seen above 3 mg/L, followed by 7 cases between 1-3 mg/L and no cases are seen below 3 mg/L indicating that majority of CVA cases have serum CRP at higher range. Finally, when the serum CRP levels are compared in both types of stroke, patients of ischemic stroke patients had significantly higher levels than the haemorrhagic stroke than the controls (7.75±2.24 mg/L vs 5.20±2.31 mg/L vs 1.77±0.88 mg/L, $p<0.001$) as shown in table 3.

This is in accordance with study conducted by Shoaeb MA et al[14] who shows significantly higher serum CRP levels in ischemic stroke than hemorrhagic. Another study by Roudbary SA et al[15] also shows that CRP level is significantly higher in ischemic than that of haemorrhagic stroke. This could be explained by the crucial role played by the inflammatory process in the pathogenesis of ischemic stroke while theoretically no role in the hemorrhagic stroke. High CRP levels are associated with long-term poor functional outcomes in patients with ischemic stroke. Acute local inflammation and changes in inflammatory cytokines levels develop in patients with ischemic brain injury due to arterial occlusion.[16]

Further studies are needed to explicate the role of CRP in stroke patients. Other limitation of this study includes small sample size and also a single centre-based study.

In this study, as shown in table 6, a significant positive correlation is seen between serum CRP levels and TC ($r = 0.646$, $p<0.001$), TG ($r= 0.538$, $p<0.001$), LDL ($r=0.636$, $p<0.001$), VLDL ($r=0.538$, $p<0.001$) and a negative correlation with HDL cholesterol ($r= -0.617$, $p<0.001$). These findings are in accordance with the findings of Ahuja J and Basu A[17] and thus shows that increased serum CRP is associated with the risk factor of stroke.

CONCLUSION:

The level of CRP is seen to be raised in CVA cases and is significantly more than the controls. When the two types of stroke are compared, ischemic stroke had significant higher levels of CRP as compared to haemorrhagic stroke indicating its role in inflammatory process as a synergistic effect in the pathogenesis of ischemic stroke and thus it can be used as a screening investigation for evaluating the severity of ischemic stroke. Further studies with adequate sample size with long term prospective are needed to establish the role of serum CRP in cerebrovascular or stroke patients.

TABLES AND FIGURES:

Table 1. Sex and mean age distribution in control and CVA cases

Group	Male	Mean±SD (in years)	Female	Mean±SD (in years)	Total	Mean±SD (in years)
CVA	33	57.24±10.56	27	59.70±12.72	60	58.35±11.54
Control	34	55.18±11.10	26	55.96±11.63	60	55.52±11.75

Table 2. Distribution of systolic blood pressure among CVA cases

Systolic BP (mmHg)	Male	Female	Total	Percentage (%)
<140	2	4	6	10
141-150	1	3	4	6.67
151-160	9	3	12	20
161-170	18	15	33	55
170-180	3	2	5	8.33

Fig 1. Distribution of different types of CVA cases

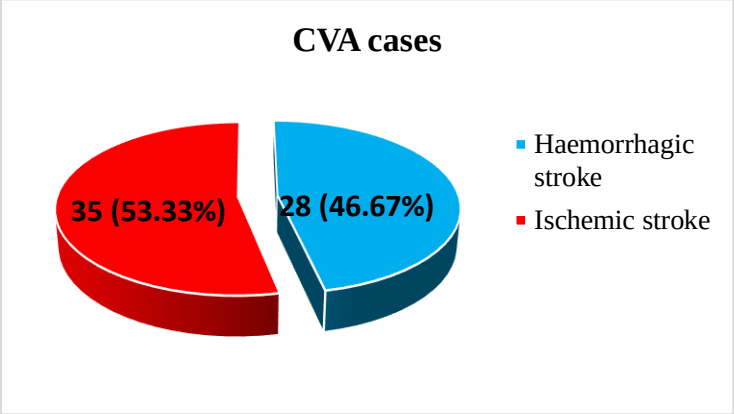

Table 3. Serum CRP in CVA cases and controls (values are expressed in mean±SD)

Parameter	Controls (n=60)	Haemorrhagic stroke (n=28)	Ischemic stroke (n=32)	p-value
Serum CRP (mg/L)	1.77±0.88	5.20±2.31	7.75±2.24	<0.001

Table 4. Distribution of CVA cases at different CRP levels

CRP levels (mg/L)	Male	Female	Total	Percentage (%)
<1	0 (0)	0 (0)	0	0
1-3	2 (3.33)	5 (8.33)	7	11.67
>3	31 (51.67)	22 (36.67)	53	83.33

Table 5. Mean±SD (mg%) of TC, TG, LDL, VLDL and HDL at different levels of C-Reactive protein (CRP)

CRP (mg/L)	TC (Mean±SD in mg/dl)	TG (Mean±SD in mg/dl)	LDL (Mean±SD in mg/dl)	VLDL (Mean±SD in mg/dl)	HDL (Mean±SD in mg/dl)
<1	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00
1-3	201.57±30.68	181.14±44.96	113.34±26.53	36.22±8.99	52±6.83
>3	239.71±50.04	221.86±56.36	160.60±49.79	44.37±11.27	34.73±7.74

Table 6. Correlations matrix of Total cholesterol (TC), Triglyceride (TG), Low Density Lipoprotein (LDL), Very Low Density Lipoprotein (VLDL), High Density Lipoprotein (HDL), serum C-reactive protein (CRP)

	TC	TG	LDL	VLDL	HDL	CRP
TC	1	0.482	0.996	0.483	-0.436	0.646
TG	0.482	1	0.295	1.000	-0.222	0.538
LDL	1	0.295	1	0.295	-0.572	0.636
VLDL	0.483	1.000	0.295	1	-0.222	0.538
HDL	-0.436	-0.222	-0.572	-0.222	1	-0.617
CRP	0.646	0.538	0.636	0.538	-0.617	1

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