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Original Article

C-Reactive Protein in Thrombotic Stroke

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ABSTRACT

Background: *Stroke remains a major cause of human mortality and morbidity. Patients with stroke constitute 15- 20% of all admissions in medical college in spite of our increasing knowledge in the pathophysiology and epidemiology. Traditional risk factors like hypertension, diabetes obesity and smoking do not fully account for clinical occurrence of stroke in different population. Indeed atherosclerosis is accepted now as an inflammatory/infectious disease[1]. William. Osler in 1908 proposed that infection could be a causal factor in pathogenesis of atherosclerosis. Various microorganisms had been implicated as a potential link between the inflammation and pathogenesis of atherosclerosis, possible infections include Pylori, CMV, Herpes Simplex and Chlamydia pneumonia .Researches found that C-reactive protein is elevated several years before the first episode of stroke. Ridker etal[2,3] in 1994 showed 3 fold increase in stroke in CRP elevated patients in a study of 1086 subjects.CRP measurement provide a novel method to detect worrisome level of atherosclerosis in otherwise normal patients. Antimicrobial and antiviral therapy may someday be a part of arsenal of therapy to prevent stroke.[4] Limited studies are done in India correlating CRP with thrombotic stroke.*

Objective

1. *To study the C-Reactive protein rise in thrombotic stroke in subjects without traditional risk factors.*
2. *To identify existence of infection/inflammation in pathogenesis of stroke.*
3. *To study the correlation of serology Ig GH.pylori infection in CRP positive stroke.*

Materials and Methods: *200 subjects with first episode of stroke were taken for study. Subjects with CT proven thrombotic stroke without traditional risk factors were selected. These patients were evaluated for CRP levels (the study group). Age and sex matched normal control subjects were selected. All CRP positive stroke patient were screened for Ig-G H.Pylori.*

Results: *Out of 200 subjects with first episode of stroke 150 Subjects with CT proven thrombotic stroke were detected. Of the 150 subjects with CT proven ischemic stroke,80 pat ients were without traditional risk factors (the study group). In the semales constitute 60% and 22 were below age of 40(young stroke). CT findings showed majority of infarct were in basal ganglia and internal capsule. 64 out of 80 ischemic stroke patients had positive CRP (X^2= 22.88, p <0.001). 42 out of 64CRP positive patients were found seropositive for Ig-G H.Pylori.*

Conclusion: *C-Reactive protein was significantly elevated in patients with thrombotic stroke without traditional risk factors. Strong correlation between CRP positivity and seroprevalence of IgG H.Pylori.*

Keyword: *CRP, atherosclerosis, thrombotic stroke, H.pyloriinfection.*

Introduction

WHO defines stroke as rapidly developing clinical symptoms and /or signs of focal, at times global disturbance of cerebral function with symptoms lasting for more than 24 hrs. or leading to death with no apparent cause other than vascular origin .An incidence of 33 per 100,000 was in reported Rohtak study India. 1971-75 .Study by Dalal (1997) showed diabetes, hypertension, smoking obesity and low hemoglobin were most important risk factor for stroke in India, only 30-50%of stroke patients had traditional risk factors particularly Asians were high propensity for disease in young.

William Osler 1908 and Ophuls 1921 proposed infection could be a casual factor in pathogenesis of atherosclerosis .Researchers implicated various microorganism as potential link between inflammation and atherosclerosis .Atherosclerosis is now accepted as inflammatory disease - have since been reported between H Pylori, Chlamydia pneumonia, CMV, Herpes simplex and clinical marker of chronic dental infection and atherosclerosis based on seroepidemology studies

There are evidence of virus and bacteria in atheromatous plaque. Focal inflammation in arteries may be involved in genesis of thrombotic stroke Atheroscleros. is is now thought to be chronic inflammatory disease that develop in response to metabolic, infectious, physical or environmental injuries

Avery characterized CRP as a protein increased in inflammation, infection and coined the term Acute Phase Reactants, it is synthesized in liver, Numerous prospective studies have confirmed CRP predicts thrombotic stroke independently, Patients with increase CRP have significant intima media thickness, as per Winbecketal (2002) Germany. CRP was statistically significant elevated in subjects with periodontal infection. As per Noack et al (2001)[4] Sept $p<0.036$ Elevated CRP were found to predict stroke as early as 6 to 8 yrs. in patients without traditional risk factors. No one knows the cause of the low grade inflammation in otherwise healthy patient. Hypothesis is infection partly contributed by virus, bacteria and chlamydia since atherosclerosis is inflammatory process circulating marker will reflect activity. In 1992 shot and colleagues detected c pneumonia in fatty steaks from arteries of 7 autopsies in South Africa. Krankenhaus et al showed 46% Chlamydia seropositivity measured by micro immunoflorence test. Wald etal showed 68% IgA Chlamydia seropositivity in a prospec-tive study involving 21,520 patients Ig G antibody H.Pylori was positive in 68 % in 292 patients in Finnish study. H.Pylori increases triglyceride level according to study, infection may contribute atherosclerosis through a number of local and systemic effects direct effect of arterial wall smooth muscle proliferation, endothelial injury, inflammatory mediators release, autoimmunity through cross reactivity of heat shock proteins, lipoprotein disturbance, monocyte activation, enhanced activity of pro coagulant.

Materials and Methods

Study was conducted in 200 first episode of stroke patient. 150 had CT proven thrombotic stroke of which 80 patients (study group) had no traditional risk factors. 40 age, sex and biochemical variables matched healthy persons (control group) from general population were included in study

Exclusion Criteria

1. Age>75 and<15
2. Hypertension, diabetes, dyslipidemia
3. Collagen vascular disease.
4. valvular heart, IHD cardiomyopathy
5. Smokers
6. History of TIA, patients on aspirin, obese patients, meningitis, brain abscess, head injury tumors, hemorrhagic strokes.

Study protocol

Clinical history taking, detailed general and neurological examination was conducted. Sriraj Stroke Score was calculated, socioeconomic status was assessed based on Kuppuswamy criteria, blood investigation, CT scan and CRP estimation was done within 1 hr. IgG H.Pylori was sent in case of CRP positive patient .

CRP was estimated using latex CRP reagent by slide agglutination as per manufactures recommendation with semi quantitative rapid latex slide test sensitized to detect level greater than 0.6mg/dl. Value of >6mg/dl was taken positive value.

Statistical analysis is done using SPSS version 21. Biochemical and physicals variables were expressed as mean ± SD. Students t- test and chi square test were used to compare categorical variables. A p value of <0.01 is considered significant.

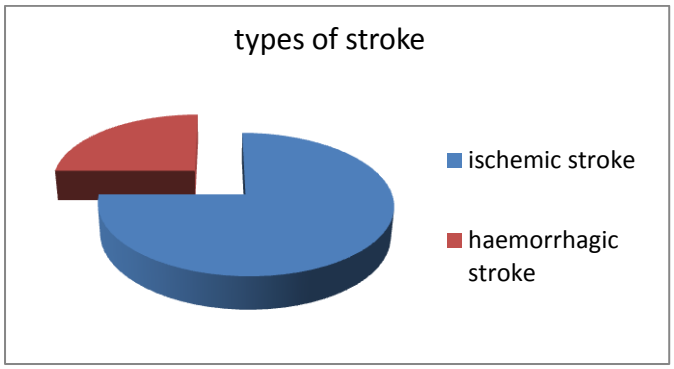
Results

Of the 200 total subjects studied 150 had ischemic stroke, confirmed by CT Scan. This constitued 75% of cerebrovascular accident cases.

Table 1. Types of stroke

Types of stroke	No. of case	Percentage
Ischemic stroke	150	75%
Hemorrhagic stroke	50	25%

Fig 1: Types of stroke

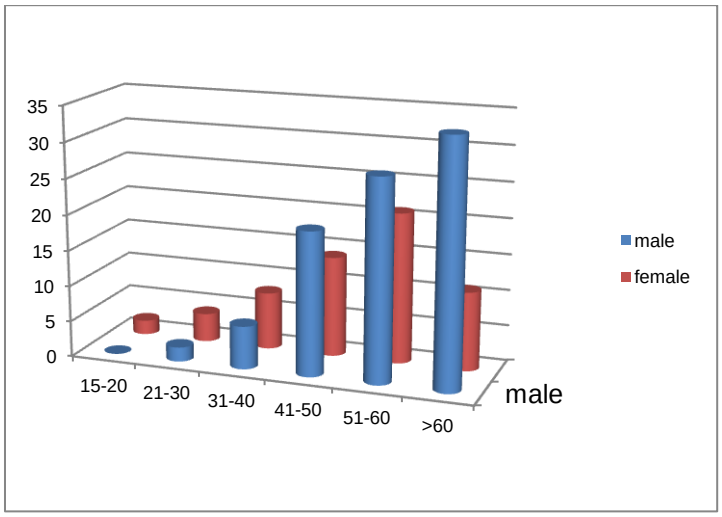


Age and sex wise distribution of 150 thrombotic stroke patients were done. 51-60 age group had maximum frequency in females and >60 in males. Male predominance noted in disease frequency.

Table 3 Age and sex wise distribution (thrombotic stroke patient)

age group	male	female
15-20	0	2
21-30	2	4
31-40	6	8
41-50	20	14
51-60	28	21
>60	34	11

Fig 2: Age and sex wise distribution



Out of 150 only 80 were free of traditional risk factors, they were taken as study group. Physical and biochemical variables like Mean systolic BP, Mean diastolic BP, Mean Body Mass Index, Mean FBS, Mean serum creatinine, Mean serum cholesterol, Mean serum High Density Lipoprotein, Mean serum Low Density Lipoprotein, Mean serum Triglycerides were compared between control and study group. A p value of >0.05 were noted in all the values; showing insignificant difference between control and study group. Thus an age and sex biochemical variables matched comparable control group of 40 subjects from general population. was confirmed

Table 2: Comparison of the study variables between control and study group.

Variables	Study group(n=80)	Control(n=40)
Mean systolic BP	124.2±4.06	125.0±5.99
Mean diastolic BP	80.9±4.43	80.22±6.09
Mean FBS	84.29±8.43	83.33±8.29
Mean serum creatinine	0.75±0.15	0.74±0.12
Mean serum cholesterol	162.97±25.75	159.7±23,8
Mean HDL	47.97±6.02	44.3±7.8
Mean LDL	89.1±16.83	84.8±27.8
Mean Triglyceride	127.9±35.46	153.1±67.25
Mean BMI	21.24±1.03	21.01±1.27

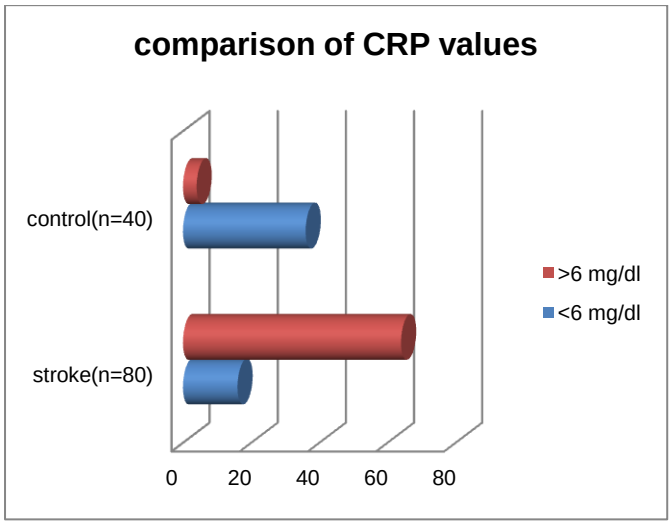
Comparison of CRP values in stroke and control groups were done CRP. >6 mg/dl was noted in 80% of patients.CRP positivity is noted in majority of ischemic stroke with a $p<0.001$.($X^2 = 22.88$, $p <0.001$).

Table 4: Comparison of CRP values in stroke and control groups.

study groups	CRP Values	
	<6 mg/dl	>6 mg/dl
stroke(n=80)	16	64
control(n=40)	36	4

(X^2 = 22.88, p <0.001).

Fig 3: Comparison of CRP values in stroke and control groups.

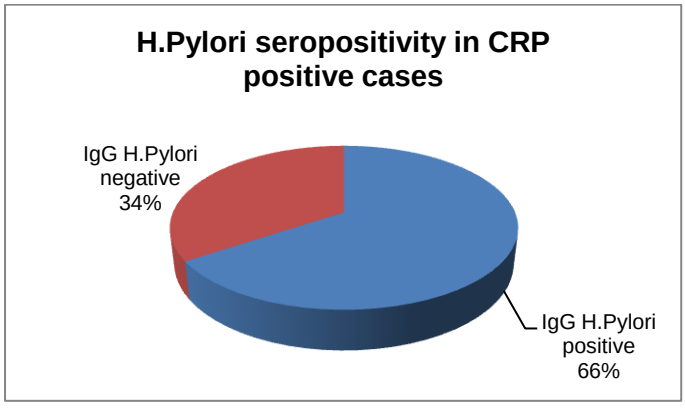


IgG H.Pylori seropositivity was noted in 66% of CRP positive cases. Strong relation between subclinical H.Pylori infection and significant atherosclerosis was noted.

Table 5 comparison of IgG H.Pylori seropositivity in stroke patients.

IgG H.Pylori	Number of CRP positive cases
positive	42
negative	22

Fig 4: comparison of IgG H.Pylori seropositivity in stroke patients



Discussion

Study was conducted on 200 patients with first episode of stroke. 150 had ischemic stroke (80%) and 50 hemorrhagic (20%); comparable with study of Dalaletalin 1989. Maximum incidence was noted in age group of>60 (males) and 51-60(females). Similar to study by Abraham etal (1970) and Razdanetal (1994) mean age of males 61.4±1 and female 56.4±1 was observed. 22 patients were below the age of 40, giving a 27% comparable to Dalal et al 30% and Banal etal15-32 %. Male:female ratio was 1.5:1 in Rohtak study; 1.6:1 in Venkataraman et al (l995); a comparable ratio of 1.5:1 was obtained in this study. CT evaluation showed supra tentorial stroke 51.33% of which cortical 24.6%,subcortical 46%and multiple site 4% .Analysis of clinical symptoms showed a sudden onset in 87% of cases,a gradual in 13%. Headache or vomiting was seen in 25%, similar to Pougvarin et al (1991); convulsion only in 8.7%. Atheromatous markers were present in 43 patients. Anterior circulation stroke in 68% and posterior in 25% similar to Dennis et al 1991.

SSS scoring sensitivity and specificity for ischemic stroke 61% and74%, positive predict value 84% similar to Hawkin G C 1995 and Dhar etal 2001 showed sensitivity of 87%. Mean BMI was 21.24±1.03 kg/m^2, mean weight 60.17±3.08 kg, mean FBS 84.2 ±8.43,urea 20.1±1.19, total cholesterol 162.97±25.7, LDL 89.1 ±1.86, HDL 47.9±6.02, triglyceride 127.9±35.5,mean systolic BP 129.5±22.8 mm of Hg, diastolic BP 80.7±11.4 mm of Hg.

CRP value >6 mg/l was present in 64 0f 80 stroke patient x^2= 27.8, comparable with study ofRidkeretal[2]. Out of 64 CRP positive patients 42 had seropositive Ig G H.Pylori comparable with study by Patel (1995), Mandell M A (1995)[5,6,7]and Ridker (1997)[2,3]. Predictive power of CRP positivity as a marker of future risk of stroke was highly evident in this study.

Conclusion

C Reactive protein was significantly elevated in thrombotic stroke. Elevation was not correlated with BMI, hypertension, diabetes, obesity and other traditional risk factors. H Pylori serology was significantly positive in thrombotic stroke patient without traditional risk factors. CRP might provide novel method to predict future risk of stroke in general population. Atherosclerosis is now thought to bea chronic inflammatory disease that develops in response to metabolic, infectious, physical or environmental injuries.

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