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A STUDY ON SERUM FIBRINOGEN LEVEL AND ITS PROGNOSTIC SIGNIFICANCE IN PATIENTS WITH ACUTE ISCHEMIC STROKE

A T Appuraj[A] , T Ravindran[B]

[A] - *Assistant professor, Department of General Medicine, Karpagam Faculty of Medical Sciences & Research, Coimbatore.*

[B] - *Associate professor, Department of General Medicine, Kilpauk Medical College and Hospital, Chennai.*

Medicine

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Corresponding Address

Dr. A T APPURAJ
Email id: drappu25@gmail.com.
Phone number: 9790061591
Address: Assistant professor, Department of General Medicine, Karpagam faculty of medical sciences, Othakkalmandapam, Coimbatore-32.

Abstract:

Objective: The present study was aimed to evaluate the prognostic significance of serum fibrinogen with stroke severity by correlation with clinical outcome stroke scales.

Methods and material: A prospective hospital based case control (cross sectional) study was conducted in 100 subjects among which 50 were controls & 50 were newly diagnosed acute ischemic stroke patients based on CT Brain plain. Age and sex matched persons not having focal neurologic deficit and after verifying exclusion criteria via questionnaire were taken as controls. The plasma fibrinogen level was measured quantitatively by Clauss method.

Statistical analysis : Mean values of all parameters in subgroups were calculated by independent sample-t- test. To compare the distributions of dichotomous data viz., gender, age, smokers, presence of hypertension or diabetes and fibrinogen levels, Chi-square test was used. Association between acute ischemic stroke and fibrinogen level was assessed by logistic regression model. ANOVA test was used to assess the association between stroke scales and fibrinogen level. All statistical analyses were performed using SPSS (software package used for statistical analysis) package. A p-value of less than 0.05 was considered to be statistically significant.

Results: Acute ischemic stroke was very severe in patients with higher fibrinogen levels. Also, the outcome at the end of one month was poor in patients with higher fibrinogen levels during stroke onset. There was a significant difference between mean fibrinogen level among cases and controls.

Conclusion: Serum fibrinogen level was higher in patients with acute ischemic stroke compared to controls. Among the patients with acute ischemic stroke, the higher serum fibrinogen level correlates with: Clinical severity assessed by National Institute of Health Stroke Scale and Poor prognosis and stroke outcome at end of one month after stroke onset, assessed by Modified Rankin's Scale.

Keywords: acute ischemic stroke, serum fibrinogen level,severity and outcome.

Introduction

Fibrinogen plays a key role in blood clotting. Its association with increased incidence of stroke is related to its ability to promote thrombosis or clot formation by causing platelets to clump inside blood vessels.[1] It also interacts with monocytes/ macrophages which are thought to play a important role in atherogenesis. This interaction also triggers the procoagulant activities. Normal serum Fibrinogen level is 233 to 496 mg/dl. Fibrinogen bridges adjacent platelets together to form platelet aggregates and results in arterial thrombosis leading to ischemic stroke.[1,2]

It is an independent risk factor for recurrences of stroke apart from age, smoking, hypertension, diabetes and other risk factors. It is also a predictor of future recurrences of stroke and adverse cardiovascular events. Hence, fibrinogen levels are to be measured in patients with stroke at the earliest and to be treated.[3,4]

Fibrinogen also plays a vital role in a number of physio-pathological processes in the body like inflammation, atherogenesis and thrombogenesis. This is due to infiltration of the vessel wall by fibrinogen, increase in blood viscosity and its, haemorrheological effects, increased platelet aggregation and thrombus formation. The binding of fibrinogen to ICAM-1 on the endothelial cells mediate the adhesion of platelets. Fibrinogen and its metabolites cause endothelial damage and dysfunction by a variety of mechanisms. This phenomenon may be compounded by the decrease in arterial intimal fibrinolytic activity and plasminogen concentration observed in cardiovascular disease.[5,6] Fibrinogen is involved in the process of platelet aggregation. It crosslinks the platelets by binding the glycoprotein IIb-IIIa receptor on their surface. This has become more relevant with the advent of glycoprotein IIb-IIIa receptor inhibitors, which block this final common pathway of platelet binding. Hence, Measurement of plasma fibrinogen levels could potentially be more useful than those of other acute phase reactants such as C-reactive protein, as fibrinogen is probably more specific to vascular disease.[7] The primary objective of this study dissertation is to test the hypothesis that increased fibrinogen in ischemic stroke is associated with poor prognosis. Besides, the dissertation also identifies the association of fibrinogen with other multiple variables like age, sex, body weight, smoking, cholesterol, hypertension and diabetes.[8-10]

Materials & Methods

The study was conducted after having obtained Ethical clearance from Human Ethical Committee at Kilpauk Medical College and hospital, Chennai. Biochemical analysis was done in department of biochemistry, Kilpauk Medical College and hospital, Chennai. Informed consent in the prescribed form was obtained from all patients included in the study after explanation of the probable benefits in local language.

Study design and participants

This was a Prospective cross sectional study. The study was conducted in 100 subjects among which 50 were controls & 50 were newly diagnosed acute ischemic stroke patients based on CT Brain plain.

Patients admitted with history of acute onset of stroke in medical wards in the Department of Medicine, Kilpauk Medical College Hospital were enrolled in after excluding the exclusion criteria. Age and sex matched persons not having focal neurologic deficit and after verifying exclusion criteria via questionnaire were taken as controls.

Blood collection &laboratory methods:

After overnight fasting, blood samples were taken in the morning. Blood sugar, cholesterol and fibrinogen were measured. The plasma fibrinogen level was measured quantitatively by Clauss method. Venous blood is collected in an evacuated siliconized tube containing 1 volume 0.11 mol/lt of sodium citrate (3.8%) and 9 volumes of whole blood which is centrifuged for 15 minutes at RCF of 2000 g. the buffer provided in the kit is used to prepare 1: 10 dilution of patient's plasma sample. 0.2 ml of diluted (50µl) citrated plasma is incubated for one minute, then 25 µl of thrombin reagent is added at room temperature and clotting time is then determined at 37˚ C using a coagulation instrument. The Fibrinogen concentration is then determined by matching the clotting time from the standard provided and prepared in the kit.

Statistical analysis

Mean values of all parameters in subgroups were calculated by independent sample-t- test. To compare the distributions of dichotomous data viz., gender, age, smokers, presence of hypertension or diabetes and fibrinogen levels, Chi-square test was used. Association between acute ischemic stroke and fibrinogen level was assessed by logistic regression model. ANOVA test was used to assess the association between stroke scales and fibrinogen level. All statistical analyses were performed using SPSS (software package used for statistical analysis) package. A p-value of less than 0.05 was considered to be statistically significant.

Results

The study group comprises of 50 patients with acute ischemic

stroke. Among the study group, 44% (22) were hypertensive, 30% (15) were diabetics, 46% (23) were smokers, 28% (14) were alcoholics, 50% (25) were obese, 60% (30) were having hypercholesterolemia. The two groups were statistically matched regarding baseline characteristics. In this study, the mean fibrinogen level among cases was 612.20 with a standard deviation of 186.069 and standard error of mean 26.314. Likewise, the mean fibrinogen level among control group was 296.80 with standard deviation of 134.854 and standard error of mean 19.071, with a p value of 0.001 (< 0.05) which was statistically significant.

TABLE 1:
Mean Fibrinogen level among Cases and Controls

	Number	Mean Fibrinogen	S.D.	STD. Error	p Value
Cases	50	612.2	186.069	26.314	0.001
Controls	50	296.8	134.854	19.071	

The mean fibrinogen level in the study group increases as age advances, which was higher than that of control group, with a p- value of 0.001 which was statistically significant. The mean fibrinogen level among males and females in study group was higher than control group which was statistically significant ($p<0.05$). In the study group, the mean fibrinogen level of hypertensive, diabetic, smokers, alcoholic, obese and hypercholesterolic patients were higher than that of seen in control groups, which was statistically significant.(Table 2).

Likewise, the mean fibrinogen level of normotensive, non diabetic, non smokers, non alcoholics, non obese and normal cholesterol patients in study group were higher than that of control group which was also statistically significant ($p<0.05$).(Table 2).

TABLE 2:
Comparison of mean serum fibrinogen level among cases and controls with baseline characters like sex, blood pressure, diabetes, smoking, alcohol use, body weight and cholesterol level with p value < 0.001 which is statistically significant.

S.NO	CHARACTERS	MEAN FIBRINOGEN						p Value
		CASES			CONTROLS			
		MEAN	S.D.	S.E.	MEAN	S.D.	S.E.	
1	Sex							
	Male	590.32	197.37	35.449	350.65	139.76	25.102	0.001
	Female	647.89	164.78	37.802	208.95	61.72	14.161	0.001
2	Blood pressure							
	Hypertensive	561.36	198.67	42.356	315.45	157.23	33.522	0.001
	Normotensive	652.14	168.44	31.833	282.14	115.19	21.769	0.001
3	Diabetes							
	Present	542.67	209.91	54.2	272.67	133.5	34.468	0.001
	Absent	642	169.42	28.638	307.14	136.03	22.993	0.001
4	Smoking							
	Present	594.78	202.84	42.295	332.17	148.05	30.87	0.001
	Absent	627.04	173.02	33.298	266.67	116.95	22.507	0.001
5	Alcohol use							
	Present	577.14	188.08	50.268	328.57	133.06	35.562	0.001
	Absent	625.83	186.14	31.023	284.44	135.36	22.56	0.001
6	Body weight							
	Obese	733.6	57.146	11.429	312	131.846	26.369	0.001
	non obese	490.8	191.614	38.323	281.6	138.795	27.759	0.001
7	Cholesterol							
	High	662	164.283	43.763	304.67	128.378	23.439	0.001
	Normal	537.5	195.714	43.763	285	146.629	32.787	0.001

The mean fibrinogen level is higher in patients with higher NIHSS score i.e., very severe neurologic impairment and lowest in patients with mild impairment, NIHSS score <5. The mean fibrinogen level in mild impairment cases was 312, moderately severe cases was 560, severe cases was 710 and very severe cases was 771.18. Hence, it was clear that the fibrinogen levels were higher in patients with acute ischemic stroke with very severe impairment.(Table 3).

Table 3:
Mean fibrinogen level among cases with mild, moderate, severe and very severe impairment assessed based on NIHSS score at the onset of stroke. NIHSS – National Institute Of Health Stroke Scale.

NIHSS Score	No. Of Cases	Mean Fibrinogen Cases		
		Mean	S.D.	S.E.
Mild(<5)	10	312	110.635	34.986
Moderate(6-15)	13	560	93.452	25.919
Severe (16-25)	10	710	11.547	3.651
Very Severe (>25)	17	771.18	33.89	8.22

After one month of acute ischemic stroke onset, the morbidity and mortality were assessed using Modified Rankin's Scale (MRS). It was found that the outcome was worse in cases with higher fibrinogen levels. There were 3 dead with a MRS score of 6 and mean fibrinogen level of 823.33. The mean fibrinogen level in patients with no symptoms at one month after stroke onset was 258.57 (MRS score 0). The mean fibrinogen level in patients with MRS score of 1 was 441.43 and they had no significant disability despite symptoms. The mean fibrinogen level in patients with slight disability (MRS score2) was 557.50. The mean fibrinogen level for MRS score of 3, 4 and 5 were 683.64, 734.44 and 764.44 respectively.(Table 4).

Table 4:
Mean fibrinogen level among cases with morbidity outcome with (scores 0 to 6) assessment done at one month follow up using MRS score. MRS – Modified Rankin Scale.

Mrs Score At 1 Month	No. Of Cases	Mean Fibrinogen Cases		
		Mean	S.D.	S.E.
0	7	258.57	83.95	31.73
1	7	441.43	32.367	12.234
2	4	557.5	5	2.5
3	11	683.64	33.548	10.115
4	9	734.44	22.423	7.474
5	9	764.44	25.55	8.517
6	3	823.33	37.859	21.858

Discussion

Stroke is defined by WHO as 'rapidly developing clinical signs of focal (or global) disturbance of cerebral function, with symptoms lasting 24 h or longer, or leading to death, with no apparent cause other than of vascular origin'.[11] This includes both cerebral infarction or intracerebral and subarachnoid hemorrhage. A time window of 24 h distinguishes stroke from transient ischaemic attack (TIA), which is defined as a neurological deficit lasting less than 24 h. The term cerebrovascular disease compasses all vascular disease affecting the brain including stroke, vascular dementia, and asymptomatic cerebrovascular disease.[11,12]

The onset of ischemic cascade induces the initiation of inflammation, excitotoxicity, nitric oxide production, free radical damage and apoptosis, which all play a role in tissue injury. The molecular consequences due to brain ischemia include changes in cell signalling and its transduction, metabolism, gene regulation or expression.[13,14] There will be release cytokines, like interleukin-1(IL-1) and tumor necrosis factor-α (TNF-α) after onset of ischemia which leads to leucocyte activation, recruitment and adhesion to the endothelium.[12] These leucocytes obstruct the vessel together with monocytes /macrophages. Reperfusion, and systemic inflammatory process also stimulate theinflammatory response, which hampers the effect of thrombolytic therapy.[15]

In the normal conditions, the body responds to inflammatory and infective conditions, by means of cytokines, primarily IL-6 and IL-1. The most important acute phase reactants in cerebrovascular ischemia are C-reactive proteins (CRP), serum amyloid A protein, and fibrinogen.[16] There is hyperfibrinoginemia in patients with acute cerebral infarction together with leukocytosis and increased leukocyte aggregation.[14,17] This is due to infiltration of the vessel wall by fibrinogen, increase in blood viscosity and its, haemorrheological effects, increased platelet aggregation and thrombus formation. The binding of fibrinogen to ICAM-1 on the endothelial cells mediate the adhesion of platelets.[18] Fibrinogen is involved in the process of platelet aggregation. It crosslinks the platelets by binding the glycoprotein IIb-IIIa receptor on their surface. This has become more relevant with the advent of glycoprotein IIb-IIIa receptor inhibitors, which block this final common pathway of platelet binding. Hence, Measurement of plasma fibrinogen levels could potentially be more useful than those of other acute phase reactants

such as C-reactive protein, as fibrinogen is probably more specific to vascular disease.[17-19] Aspirin has a direct role in modifying CRP levels, thus raising the possibility of an anti-inflammatory action apart from its antiplatelet effect mediated via COX inhibition.[20] statins has a neuroprotective action by upregulation of endothelial NOS and inhibition of iNOS, an effect associated with augmented cerebral blood flow and reduced infarct size.[21] The diet rich in fruits and vegetables have a lower cardiovascular risk, possibly due to antioxidant nutrients: vitamin C, vitamin E, beta-carotene. They inhibit LDL oxidation and also by decreases fibrinogen and there by reduces the formation of atheroma.[22-26]

In this study, the mean fibrinogen level of hypertensive, diabetic, smokers, alcoholic, obese and hypercholesterolic patients among cases were higher than that of seen in control groups, which was statistically significant (p = 0.001).

Likewise, the mean fibrinogen level of normotensive, non diabetic, non smokers, non alcoholics, non obese and normal cholesterol patients in study group were higher than that of control group which was also statistically significant (p = 0.001). The mean fibrinogen level is higher in patients with higher NIHSS score i.e., very severe neurologic impairment and lowest in patients with mild impairment, NIHSS score <5.

After one month of acute ischemic stroke onset, the morbidity and mortality were assessed using Modified Rankin's Scale (MRS). It was found that the outcome was worse in cases with higher fibrinogen levels. Hence, it was clear that among the cases, the acute ischemic stroke was very severe in patients with higher fibrinogen levels. Also, the outcome at the end of one month was poor in patients with higher fibrinogen levels during stroke onset.

Conclusion

Serum fibrinogen level was higher in patients with acute ischemic stroke compared to controls. Among the patients with acute ischemic stroke, the higher serum fibrinogen level correlates with: Clinical severity assessed by National Institute Of Health Stroke Scale and Poor prognosis and stroke outcome at end of one month after stroke onset, assessed by Modified Rankin's Scale.

Fibrinogen is associated with risk factors for stroke. Therefore, elevated fibrinogen levels provide a mechanism for the risk factors to exert their effect. Fibrinogen is increased following an acute stroke as an acute phase reactant. Also, fibrinogen predicts vascular events in established atherosclerotic disorders. Hence, chronically raised fibrinogen in high risk individuals appears to be an independent risk factor for stroke. Measures such as cessation of smoking, weight reduction, increased physical activity and control of blood pressure decreases plasma fibrinogen level, thereby reduces stroke occurrence in high risk individuals in future.

Therefore, plasma fibrinogen measurement can be used as a screening for at risk persons for stroke and other vascular events and also as a prognostic marker following an acute stroke. The measures to decrease plasma fibrinogen levels can be included in preventive strategies against stroke.

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