



Assessment of Fibrinogen Level in Relation to Risk Factors in Stroke Types

KEYWORDS

FIBRINOGEN, STROKE, CT SCAN.

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ABSTRACT Background: Fibrinogen is important in the development of premature atherosclerosis. Hence, fibrinogen levels are to be measured in patients with stroke at the earliest and to be treated.

Aims and Objectives:

To study plasma fibrinogen levels and establish the coexistence of raised fibrinogen levels with other possible risk factors in stroke patients.

Study design: Cross sectional, case control observational study.

Materials and methods:

This study was conducted in 40 stroke patients confirmed by CT brain between May 2013 and August 2014. 40 age and sex matched controls were studied with regards to fasting lipid profile and plasma fibrinogen levels.

Statistical methods:

Chi-square test, Analysis of variance (ANOVA) and other suitable statistical methods were used. P value of < 0.05 is taken as significant.

Results: The Plasma Fibrinogen levels were significantly increased in both ischemic 465.5+/-66.984mg/dl (range 320–620 mg/dl) & hemorrhagic 409.65+/-67.9mg/dl (range 313-550 mg/dl) stroke groups of patients (more so in ischemic stroke patients) when compared to controls (300.75+/- 52.74mg/dl) (range 150-450 mg/dl P value <0.004 (statistically significant)

Conclusion: Increased Fibrinogen level acts as an independent risk factor in etiology of Stroke. Plasma Fibrinogen helps in predicting future adverse events.

Introduction

The term stroke is applied to a sudden focal neurologic syndrome, specifically the type due to cerebrovascular disease¹. 85% of the strokes are Ischemic and 15% are Hemorrhagic^{2,3,4,5,6,7,8}.

Fibrinogen is an acute phase reactant protein as well as clotting factor and has numerous other functions like being an essential cofactor for platelet aggregation¹¹, a determinant of blood rheology^{2,8,9,10} and a stimulant of smooth muscle cell migration and a catalyst for atherosclerosis proliferation^{11,12,13}. It also has been noted to cause local endothelial damage & haemostatic abnormalities due to platelet dysfunction (quantitative & qualitative) thus acting as a major risk factor in hemorrhagic stroke^{8,14,15}. A hypercoagulable state would seem to favor thrombotic stroke whereas local endothelial damage would favor hemorrhagic stroke^{14,16,17,18}.

Hyperfibrinogenemia, independently of other risk factors is known to be associated with macrophage infiltration into the fibro-fatty plaque, which in turn is related to vascular plaque rupture & thrombosis (Alessandro Mouriello et al,

Circulation 2000).¹⁹ thus fibrinogen is emerging as an independent & major risk factor for stroke, thrombo-atherosclerotic and peripheral vascular diseases.^{3,21,22}

It has also been observed that major risk factors, particularly Smoking further enhances the deleterious effects of elevated fibrinogen levels in aggravating the endothelial damage and haemostatic abnormalities^{3,20}. It has been shown that fibrinogen deposition in the intima of cerebral artery bifurcations precedes the deposition of LDL cholesterol and acutely elevated fibrinogen levels continue to be high in patients at risk for further cerebrovascular events.^{14,16,17, 23,24}. The hazard ratio (95%CI) associated with a 1-g/l increase in fibrinogen levels after adjustment for age, sex and cohort was 2.08(1.74-2.48) for ischemic stroke and 1.44(1.05 to 1.76) for haemorrhagic stroke²⁵.

In view of the above studies, fibrinogen levels were estimated retrospectively in stroke patients (both ischemic and hemorrhagic) not only to correlate the associated relative risk but also to compare it with other risk factors.

MATERIAL AND METHODS

Selection of patients:

The study was conducted in patients who presented with clinically first attack of stroke (proven by CT scan) with no previous history of similar complaints and admitted to the medicine ward of Gandhi Hospital, Secunderabad. 40 patients were selected as study group, which comprised of 20 patients (10 males & 10 females) with ischemic stroke and likewise, 20 patients (10 males & 10 females) with hemorrhagic stroke after taking exclusion criteria into consideration. 40 age & sex matched controls were selected from general population randomly for comparison.

Blood sample for plasma fibrinogen was taken within 24 hours of admission for subjects and controls. Fasting blood sample was collected for estimation of lipid profile on the next day of admission. Other investigations like Complete blood picture, Complete Urine examination, ESR, Random blood sugar, Blood urea, Serum Creatinine, Serum electrolytes, Liver function tests, ECG, Chest X-ray were done for all subject.

The plasma fibrinogen levels were estimated using Fibroquant kit^{31,46} after taking necessary precautions. The normal measuring range of fibrinogen levels is 150–400 'mg/dl.

Study Protocol:

A detailed history was taken either from the patient himself or the attendants and various risk factors like Hypertension, Smoking, Diabetes, and Alcoholism were considered. A detailed general examination including height, weight, BMI, markers of atherosclerosis and vital data including Pulse, Blood Pressure were noted. Detailed systemic examination was done to rule out any other systemic disease. A detailed neurological examination based on proforma was done and recorded.

All the exclusion criteria were taken into consideration and relevant data recorded in the proforma. **Exclusion criteria:** Patients with previous history of myocardial infarction or present myocardial ischemia., previous history of stroke or transient ischemic attack or seizure disorder. Recent infections (<3 weeks), Elevated ESR due to any cause. Traumatic lesions or Space occupying Lesions on CT scan. Head injury within 3 months. Liver diseases. Renal failure. Patients with meningitis, brain abscess or any chronic infection, Patients with temperature of >100 degrees F at the time of presentation, Patients with history of chronic rheumatic heart disease (due to imminent susceptibility to TIAs/ stroke).

RESULTS & DISCUSSION

Plasma fibrinogen levels were estimated in these subjects and compared with various risk factors associated with cerebrovascular accidents in these patients. Age of the patients varied from 40 to 70 years in both ischemic and hemorrhagic stroke subsets in the study. In ischemic stroke subset, 10 patients were in >60 years age group whereas 10 patients were in 45 to 60 years age group and in hemorrhagic stroke subset 7 patients were in >60 years age group where as 13 were in 40 to 60 years group in the study.

The Plasma Fibrinogen levels were significantly increased in both ischemic (465.5+/-66.984mg/dl) (range 320–620 mg/dl) & hemorrhagic (409.65+/-67.9mg/dl) range 313-550 mg/dl) stroke groups of patients (more so in ischemic stroke patients) when compared to controls (300.75+/-52.74mg/dl) (range 150-450 mg/dl P value <0.004 (statistically significant). (diagram-1)

In hemorrhagic stroke the plasma fibrinogen levels in males and females are 439.0+/-72.291mg/dl (range 350-550 mg/dl); and 380.38 +/-64.659mg/dl (range 313-550mg/dl) respectively and the P value are <0.00 (stat. sign) and < 0.04 (stat sign).

In ischemic stroke the plasma fibrinogen levels in males and females are 497.70 +/-66.353mg/dl (range 417-620 mg/dl) and 433.40 +/-61.616mg/dl (range 322-550 mg/dl) respectively and P value are <0.00 (stat. signif.) and < 0.00 (stat. signif.). (Table-1)

The Plasma Fibrinogen levels have increased (Table-2) in both males (497.70+/-66.353mg/dl in ischemic & 439.2+/-72.291mg/dl in hemorrhagic stroke) & females (433.4+/-61.60mg/dl in ischemic & 380.38+/-64.659mg/dl in hemorrhagic stroke) with preferential increase in males compared to females in both subgroups, suggests that fibrinogen levels varies with gender.²⁶

In hemorrhagic stroke high plasma fibrinogen levels (>400mg/dl) were seen in 4 out of 7 patients (57.14%) with age > 60 yrs and in 5 out of 13 patients (38.46%) with age 45-60yrs. High plasma fibrinogen levels (>400mg/dl) were recorded in 9 out of 20 patients (45%) of which 8 were males(88.8%) and 1 was female(11.1%).

In ischemic stroke high plasma fibrinogen levels (>400mg/dl) were seen in 10 out of 10 patients (100 %) with age > 60 yrs and in 8 out of 10 patients (80%) with age 45-60yrs. high plasma fibrinogen levels (>400mg/dl) were recorded in 18 out of 20 patients (90%) of which 10 were males(100%) and 8 were females(80%). Thus this study states that fibrinogen mediated risk in stroke ascends with age²⁰.

The Plasma Fibrinogen levels have increased with age in both ischemic (100% with age>60yrs & 80% with age 40-60yrs) & hemorrhagic (57.4% with age>60yr & 38.46% with age 40-60yr) stroke groups of patients.

On observation of isolated major risk factors (Table-3), the following descending order was noted in patients with ischemic stroke: High LDL cholesterol (90%), Hypertension (80%), Hypercholesterolemia (75%), Smoking (55%), Alcohol (30%) and Diabetes mellitus (20%). And in patients with hemorrhagic stroke, the risk factors followed the descending order: Hypertension (65%), Smoking (55%), Alcohol(50%) High LDL cholesterol (30%), Hypercholesterolemia (30%) and Diabetes mellitus (15%).

In controls, serum lipid profiles have shown that total cholesterol was 185.4+/-25.86mg/dl; LDL was 100.2+/-29.86mg/dl; HDL was 44.5+/-2.86mg/dl.

In ischemic stroke 13 out of 18 pts (72.22%) with Hypercholesterolemia (males 80%; females 62.5%); the total cholesterol levels male patients and female were 219.20+/-17.756 mg/dl and were 223.80+/-38.881mg/dl; 16 out of 18 pts (88%) with high LDL (males 80% females 75%) : LDL was 123.0+/-14.907 mg/dl in males and 140.20+/-35.118mg/dl in females; In males HDL was 35.04+/-1.796 mg/dl mg. In female patients, HDL was 42.90+/-2.188mg/dl. Respectively.

In hemorrhagic stroke male patients, 1 out of 9 pts.(11.1%) with Hypercholesterolemia (males 14.1%); noted the total cholesterol levels were 185.25+/-26.119mg/d ; LDL ch was 106.29+/-17.638mg/dl; HDL ch was 43.88 +/-3.681mg/dl.

And In female patients, the total cholesterol levels were 181.00+/-31.475mg/dl ; LDL ch was 140.20+/-35.118mg/dl; HDL ch was 47.40+/-2.477mg/dl.respectively.(Table-4)

Both Total Cholesterol and LDL cholesterol were significantly raised in conjunction with the elevated plasma fibrinogen levels (Table-5) in both ischemic & haemorrhagic stroke groups of patients but no significant correlation was noted with Triglycerides and HDL cholesterol.(Diagram-2)

In ischemic stroke high plasma fibrinogen levels were observed in 11out of 13 patients (84%) with Hypertension (males 100% females 71%) and in hemorrhagic high plasma fibrinogen levels were observed in 6 out of 13 patients (46.15%) with Hypertension (males 71.42% females 16.6%) respectively hence Hyperfibrinogenemia in association with Hypertension has contributed for significant increase in the risk of both ischemic (474.54mg/dl) & haemorrhagic (446mg/dl) strokes

Hyperfibrinogenemia noted in 3 out of 4 patients (75%) with Diabetes mellitus(males 100%females 50%) in ischemic stroke where as in haemorrhagic stroke 2 out of 3 patients (66.6%) with Diabetes Mellitus(males 100%, females 0%)respectively hence Hyperfibrinogenemia was also associated with Diabetes in both ischemic (553.02mg/dl) & haemorrhagic (452m/ldl) stroke groups where fibrinogen has been implicated as a risk factor for various vascular complications in diabetes.

In this study, 4 out of 20 patients in the ischemic stroke group as well as haemorrhagic stroke group had no specific major conventional risk factor like Hypertension, Hypercholesterolemia, High LDL cholesterol, Smoking or Diabetes too.

Of these 4 patients, 2 patients (1 male & 1 female) had elevated plasma fibrinogen levels in ischemic stroke group as well as haemorrhagic stroke group which suggest that Hyperfibrinogenemia may be considered an independent risk factor for both ischemic and haemorrhagic strokes. A good number of patients in both ischemic & haemorrhagic stroke groups with no conventional major risk factors had elevated plasma fibnogen levels suggesting hyperfibrinogenemia to be an independent risk factor for stroke.

Elevated Fibrinogen levels were seen in all smokers11 out of 11 patients (100%) in ischemic (508.95mg/dl) & 5 out of 8 patients (62.5%) in hemorrhagic strokes (473.23mg/dl) suggesting(Table-6) a strong association of hyperfibrinogenemia with smoking particularly in ischemic strokes.(Pearson chi-square test p values are 0.002) This indicates that smoking and fibrinogen leads to atherosclerosis and increased blood viscosity, which clearly correlates fibrinogen and smoking synergy, Similarly alcohol is also associated with stroke particularly ischemic stroke when assessed by pearson chi-square test the P-vlue shows(P<.001)(Table-7).

Other risk factors are not particularly associated significantly with stroke.

Limitations

1. Small sample size and as it is an observational study and therefore no conclusion can be made as far as any cause and effect relationship.
2. The follow-up of the patients should be done for prognostication of these stroke patients for recurrent events or complications based on higher fibrinogen

levels is beyond the scope of this study.

CONCLUSIONS

- 1) The plasma fibrinogen levels were significantly elevated in patients with ischemic as well as haemorrhagic strokes.
- 2) There is a preferential increase in males compared to females in both ischemic & haemorrhagic stroke groups and rising fibrinogen levels with age have been noted characteristically.
- 4) Elevated fibrinogen levels were seen in association with Hypertension, Smoking, Diabetes, Elevated Total Cholesterol & High LDL Cholesterol in both stroke groups.
- 5) Hyperfibrinogenemia can be considered as an independent risk factor for ischemic as well as haemorrhagic stroke as some patients in both groups had no conventional risk factors but had elevated plasma fibrinogen levels.
- 6) The association of plasma fibrinogen with risk of total stroke and stroke sub types are well established with our study hence plasma fibrinogen probably acts as a prognostic marker for future vascular events.

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Table-1:One sample test for fibrinogen

Control group	Test Value = 300.75						
	t	df	Sig. (2-tailed)	Mean Difference	95% Confidence Interval of the Difference		
	Lower	Upper	Lower	Upper	Lower	Upper	
1.00 Hemorrhage Male	FI-BRINOGEN	6.048	9	.000	138.250	86.54	189.96
2.00 Ischemic Male	FI-BRINOGEN	9.386	9	.000	196.950	149.48	244.42
3.00 Hemorrhage Female	FI-BRINOGEN	3.894	9	.004	79.630	33.38	125.88
4.00 Ischemic Female	FI-BRINOGEN	6.808	9	.000	132.650	88.57	176.73

Table-2: One-Sample statistics for plasma fibrinogen

FIBRINOGEN	N	Mean		Std. Deviation		95% Confidence Interval for Mean		Minimum	
		Lower Bound	Upper Bound	Lower Bound	Upper Bound	Lower Bound	Upper Bound	Lower Bound	Upper Bound
2.00 Ischemic Male	10	497.76	62.513	33.983	498.29	541.07	417	620	
3.00 Hemorrhage Female	10	393.38	84.870	33.847	334.13	428.83	314	545	
4.00 Ischemic Female	10	410.40	80.818	19.483	399.32	417.48	323	550	
Total	40	417.62	76.376	12.076	403.18	442.05	314	620	

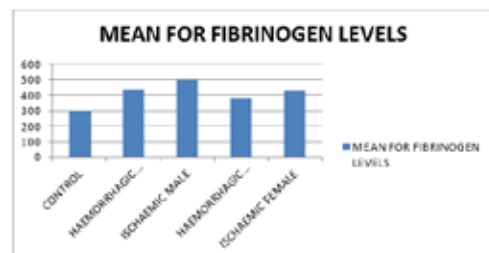


Figure 1 mean fibrinogen levels

Table -3:Fibrinogen values in association with major risk factors

Hyperfibrinogenemia	total N=20	Ischemic		total (N=20)	Haemorrhagic	
		M(N=10)	F(N=10)		M(N=10)	F(N=10)
Htn	11/13	6/6	5/7	6/13	5/7	1/6
Smoking	11/11	9/10	2/2	5/11	5/8	0/3
Dm	3/4	2/2	1/2	2/3	2/2	0/1
High TC	13/15	8/8	5/7	1/6	1/3	0/3
High LDL	16/18	10/10	6/8	1/6	1/2	0/4
Alcohol	6/6	6/6	0	6/10	6/7	0/3
No risk factor	2/2	1/1	1/1	2/2	1/1	1/1

Table-4:One-Sample Statistics of total cholesterol& LDL cholesterol& HDL cholesterol

Group		N	Mean	Std. Deviation	Std. Error Mean
1.00 Hemorrhage Male	TC	10	185.25	26.119	8.259
2.00 Ischemic Male	TC	10	219.20	17.756	5.615
3.00 Hemorrhage Female	TC	10	181.00	31.475	9.953
4.00 Ischemic Female	TC	10	223.80	38.881	12.295
1.00 Hemorrhage Male	LDL	10	106.29	17.638	5.578
2.00 Ischemic Male	LDL	10	123.00	14.907	4.714
3.00 Hemorrhage Female	LDL	10	115.30	31.496	9.960
4.00 Ischemic Female	LDL	10	140.20	35.118	11.105
1.00 Hemorrhage Male	HDL	10	43.88	11.640	3.681
2.00 Ischemic Male	HDL	10	35.04	5.678	1.796
3.00 Hemorrhage Female	HDL	10	47.40	7.834	2.477
4.00 Ischemic Female	HDL	10	42.90	6.919	2.188

DIAGRAM-2:fibrinogen in relation to cholesterol

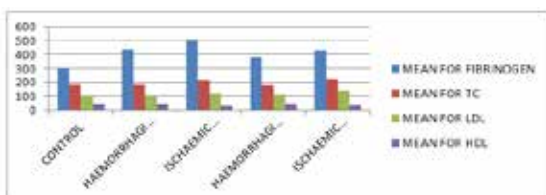


Table-5:One sample test for total cholesterol & LDL

cholesterol & HDL cholesterol

group	Total cholesterol		Test Value = 185.4				
	t	Df	Sig. (2-tailed)	Mean Difference	95% Confidence Interval of the Difference		
	Lower	Upper	Lower	Upper	Lower	Upper	
1.00 Hemorrhage Male	TC	-.018	9	0.986	-.150	-18.83	18.53
2.00 Ischemic Male	TC	6.020	9	.000	33.800	21.10	46.50
3.00 Hemorrhage Female	TC	-.442	9	.669	-4.400	-26.92	18.12
4.00 Ischemic Female	TC	3.123	9	.012	38.400	10.59	66.21

group	LDL cholesterol		Test Value = 100.2				
	t	Df	Sig. (2-tailed)	Mean Difference	95% Confidence Interval of the Difference		
	Lower	Upper	Lower	Upper	Lower	Upper	
1.00 Hemorrhage Male	LDL	1.092	9	.303	6.090	-6.53	18.71
2.00 Ischemic Male	LDL	4.837	9	.001	22.800	12.14	33.46
3.00 Hemorrhage Female	LDL	1.516	9	.164	15.100	-7.43	37.63
4.00 Ischemic Female	LDL	3.602	9	.006	40.000	14.88	65.12

Group	HDL cholesterol		Test Value = 44.5				
	t	df	Sig. (2-tailed)	Mean Difference	95% Confidence Interval of the Difference		
	Lower	Upper	Lower	Upper	Lower	Upper	
1.00 Hemorrhage Male	HDL	-.168	9	.870	-.620	-8.95	7.71
2.00 Ischemic Male	HDL	-5.269	9	.001	-9.460	-13.52	-5.40
3.00 Hemorrhage Female	HDL	1.171	9	.272	2.900	-2.70	8.50
4.00 Ischemic Female	HDL	-.731	9	.483	-1.600	-6.55	3.35

		Group				Total
		1.00 Hemorrhage Male	2.00 Ischemic Male	3.00 Hemorrhage Female	4.00 Ischemic Female	1.00 Hemorrhage Male
Smoke	no	n 2	1	7	8	18
	Row %	11.1%	5.6%	38.9%	44.4%	100.0%
	Col %	20.0%	10.0%	70.0%	80.0%	45.0%
	n 8	9	3	2	22	
yes	Row %	36.4%	40.9%	13.6%	9.1%	100.0%
	Col %	80.0%	90.0%	30.0%	20.0%	55.0%
	n 10	10	10	10	40	
	Row %	25.0%	25.0%	25.0%	25.0%	100.0%
Total	Col %	100.0%	100.0%	100.0%	100.0%	100.0%

		Alcohol * group				Total
		1.00 Hemorrhage Male	2.00 Ischemic Male	3.00 Hemorrhage Female	4.00 Ischemic Female	1.00 Hemorrhage Male
Alcohol	no	n 2	4	8	10	24
	Row %	8.3%	16.7%	33.3%	41.7%	100.0%
	Col %	20.0%	40.0%	80.0%	100.0%	60.0%
	n 8	6	2	0	16	
yes	Row %	60.0%	37.5%	12.5%	.0%	100.0%
	Col %	80.0%	60.0%	20.0%	.0%	40.0%
	n 10	10	10	10	10	40
	Row %	25.0%	25.0%	25.0%	25.0%	100.0%
Total	Col %	100.0%	100.0%	100.0%	100.0%	100.0%

TABLE-7:Chi-Square Tests for smoke

	Value	Df	Asymp. Sig. (2-sided)
Pearson Chi-Square	14.949(a)	3	.002
Likelihood Ratio	16.316	3	.001
N of Valid Cases	40		
a. 4 cells (50.0%) have expected count less than 5. The minimum expected count is 4.50			
Chi-Square Tests for alcohol group			
Pearson Chi-Square	16.667(a)	3	.001
Likelihood Ratio	20.365	3	.000
N of Valid Cases	40		
a. 4 cells (50.0%) have expected count less than 5. The minimum expected count is 4.00.			

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