



STUDY OF PLASMA FIBRINOGEN IN ACUTE ISCHEMIC STROKE

Amol Dube

Assistant Professor Dept of obgy.,Indira Gandhi Govt. Medical College,Nagpur.

Madhuri Pandharipande

Associate professor Dept of Medicine Indira Gandhi Govt. Medical College,Nagpur.

Madhuri Patil

Assistant professor Dept of obgy.,Indira Gandhi Govt. Medical College,Nagpur

(ABSTRACT) Plasma fibrinogen is one of the important risk factor for Acute Ischemic Stroke (AIS). We studied plasma fibrinogen in cases of AIS, we determined the severity of stroke by NIH Stroke Scale (NIHSS) score and then correlated plasma fibrinogen and with severity and other risk factors for stroke. 60 consecutive cases AIS were included in the study. Plasma fibrinogen and NIHSS score were estimated. 60 age and gender matched controls were also included during study period. The plasma fibrinogen was significantly raised in cases with AIS than controls. Plasma fibrinogen was higher in males and hypertensive cases. Plasma fibrinogen more than 350 mg/dl was very highly significantly related to stroke. There was positive correlation between plasma fibrinogen and stroke severity by NIHSS score. In this mortality was 13% (7 out of 60) in cases had NIHSS score more than 21 and plasma fibrinogen more than 350 mg%.

KEYWORDS : plasma fibrinogen, ischemic stroke, NIHSS, hypertension

The term Brain attack has been introduced to stress the need for emergency hospitalization of stroke patients in the same way as Heart attack patients. Recent studies showed that the age-adjusted annual incidence rate was 105/100,000 in the urban community of Kolkata and 262/100,000 in a rural community of Bengal. There is also a wide variation in case fatality rates with the highest being 42% in Kolkata. [1] Total cholesterol, LDL cholesterol, obesity, hypertension and smoking are risk factors for stroke. Plasma fibrinogen which not frequently studied is an important risk factor for ischemic stroke. There is positive correlation between smoking & obesity with plasma fibrinogen. Hence life style modification may help in reducing levels of plasma fibrinogen. Incidence of stroke and myocardial infarction was higher with high plasma fibrinogen levels and when other risk factors were controlled plasma fibrinogen still stood as an important risk factor for stroke. [2] Higher plasma fibrinogen, total cholesterol and low HDL cholesterol were independent risk factors for TIA and minor ischemic stroke. [3] Indicators of an acute phase response (APR) in acute ischemic stroke have been shown to correlate with infarct size and predict stroke recurrence. Plasma levels of interleukin-6 (IL-6), fibrinogen, white blood cells (WBCs), and serum albumin were measured within 4±2 days of onset in 131 stroke patients who were free of apparent infections. Standard clinical predictors included initial National Institutes of Health Stroke Scale (NIHSS), infarct size on computed tomography (CT), and Glasgow scale. The individual correlations with 6-month Glasgow outcome were IL-6, 0.42; fibrinogen, 0.24; WBC, 0.35; albumin, 0.47; NIHSS, 0.53; infarct size, 0.19; and initial Glasgow, 0.57. (all P<.005) [4]

In the Framingham study, 1315 participants who were free of cardiovascular disease had fibrinogen levels measured. During the ensuing 12 years, cardiovascular disease developed in 165 men and 147 women. The risk of cardiovascular disease was correlated positively to antecedent fibrinogen values higher than 126 to 696 mg/dl. [5]

The NIHSS score strongly predicts the likelihood of a patient's recovery after stroke. A score of > 16 forecasts a high probability of death or severe disability whereas a score of < 6 suggest good recovery. [6] Since NIHSS score predicts severity of stroke we tried to correlate plasma fibrinogen with stroke severity.

Methodology**a) Study design :- case control study**

b) Study set up:- patient admitted in medicine wards and ICU at tertiary care teaching hospital. 60 consecutive cases were enrolled and age and gender matched controls were selected from hospital staff and volunteers. Hypertensive control cases were selected from patients attending hypertension clinic.

c) Inclusion criteria :- Computed tomography (CT) proven cases of acute ischemic stroke within 48 hours of onset of symptoms were selected as cases.

d) Exclusion criteria:- 1) Diabetes mellitus, 2) Seizure disorders, 3) Brain tumor, 4) Ischemic heart disease, 5) Valvular heart disease, 6) Chronic Alcoholics and cirrhosis, 7) anticoagulant drugs like warfarin, etc.

e) Study period:- one year (February 2004 to Feb 2005)

60 cases satisfying inclusion and exclusion criteria were included in study. 60 controls were also selected. History, General examination, detailed neurological examination was carried out. NIH stroke scale was applied and score determined. CT scan of head was done to rule out intracerebral bleed on admission itself. Laboratory investigations were sent within 24 hours of hospital admission including plasma fibrinogen estimation. Plasma fibrinogen level was estimated at hematology laboratory by modified CLAUSSE'S method and quantitative estimation done using Multifibrin -U reagent of Behring Werke A.G; Germany.

Statistical Analysis: Standard deviation and standard error of means was determined. Student 't' test applied and level of significance determined, p value calculated. Correlation coefficient 'r' determined. P value <0.05 was considered statistically significant. Computer software programme Epi-info version 3.3/2004 was used.

Observations

Plasma fibrinogen was highly significantly increased in cases 349±36.4 mg% (Range 290-420) as compared with controls 239.6±45.01 mg% (range 180-380); p<0.001. The plasma fibrinogen in males (n=36) was 352.11±7.46 higher significantly than females 345.83±11.46, p, 0.05.

Table 1) Age wise distribution of plasma fibrinogen levels in case and control (in mg/dl)

| Group | Age (in Years) | Cases(n=60) (mean PF±SD) | Control(n=60) (mean PF±SD) | 'p' value | 't' value |
|-------|----------------|--------------------------|----------------------------|-----------|-----------|
| I | 31-40 yr | 318±27.75 (n = 5) | 227±22.18 (n = 4) | <0.001 | 5.47 |
| II | 41-50 yr | 343.3±45.89 (n = 6) | 210±31.62 (n = 22) | <0.001 | 6.2 |
| III | 51-60 yr | 352.2±35.4 (n = 22) | 225±24.05 (n = 22) | <0.001 | 13.94 |
| IV | 61-70 yr | 353.3±36.04 (n = 27) | 265.2±43.24 (n = 25) | <0.001 | 7.31 |

It was observed that plasma fibrinogen level increases as age advances and difference in two age group was statistically highly significant.

Table 2) Comparison of Plasma fibrinogen in hypertensive and non-hypertensive

| | Hypertensive (n=40) | Non Hypertensive (n=20) | T value and P value |
|---------|---------------------|-------------------------|---------------------|
| Cases | 354.75±37.8 | 337.5±32.09 | T=1.85,p=NS |
| Control | 255±45.8 | 209±21.4 | T=5.29,p<0.001 |

There was no significant difference in plasma fibrinogen among hypertensive and non hypertensive cases of acute ischemic stroke. But plasma fibrinogen was significantly higher in hypertensive control $p < 0.001$ than non-hypertensive control. Total cholesterol, LDL-CHO, and triglycerides were significantly higher in cases as compared with control.

Table 3) NIHSS score on DAY 1 and plasma fibrinogen

| NIHSS score | No of cases n = 60 | Mean plasma fibrinogen mg% |
|-------------|--------------------|----------------------------|
| 0-6 | 6 (10%) | 315±16.43 |
| 7-12 | 18 (30%) | 360±24.6 |
| 13-42 | 36 (60%) | 380±40.05 |

Plasma fibrinogen [36024.6mg/dl] was significantly raised ($p < 0.001$) in the cases who had higherscore between 7-12 than those with score less than 6 (31516.43 mg/dl).

Table 4) Clinical profile of cases with type of stroke plasma fibrinogen value and NIHSS on day 1

| Clinical Type of stroke | No. of cases (n = 60) | Mean plasma (mg/dl) fibrinogen | Mean NIHSS score on day 1 |
|---|-----------------------|--------------------------------|---------------------------|
| Fasciobrachial Monoparesis | 3 (5%) | 330±10 | 5 |
| Hemiparesis or Hemiplegia | 17 (28.33%) | 341.76±33.58 | 11.58 |
| Hemiparesis / plegia with aphasia | 14 (23.33%) | 332.65±39.50 | 14.78 |
| Old CVE + Fresh CVE | 6(10%) | 361.66±35.44 | 20.66 |
| CVE with Coma with Hemiplegia | 9 (15%) | 392.21±25.87 | 21.25 |
| Cerebeller stroke (cerebellar syndrome) | 5 (8.33%) | 336±27.01 | 10.8 |
| Lacunar stroke | 6 (10%) | 351.66±19.40 | 11.66 |

It was observed that plasma fibrinogen was higher when stroke severity by NIHSS score was more.

Table 5) Multiple logistic Regression Analysis of Risk factors in Acute Ischemic stroke

| Risk factor | Adjusted (or) odd ratio | 95% CI | P value | Z value |
|--------------------------------|-------------------------|------------|---------|---------|
| 1) Plasma fibrinogen >350mg/dl | 20.61 | 4.59-92.49 | < 0.001 | 3.95 |
| 2) Total CHO >200mg/dl | 3.15 | 0.74-16.61 | 0.11 | 1.5 |
| 3) LDL-CHO >100mg/dl | 2.90 | 0.83-10.07 | 0.09 | 1.6 |
| 4) HDL-CHO <40mg/dl | 4.96 | 1.66-14.82 | < 0.01 | 2.86 |

After adjusting for other risk factors and then did multivariate analysis, increased plasma fibrinogen was very highly significantly ($p = 0.001$) associated with stroke, the other was low HDL-Cholesterol ($p < 0.01$). **Mortality** at the time of hospital discharge was 11.66%, including 4 males and 3 females. Mean age of cases was 58.57±5.56 years. Mean plasma fibrinogen in them was 395.7±22.9 mg%. Mean NIH stroke scale score was 21. Plasma fibrinogen values were more than 350 mg/dl in all cases and NIHSS score was > 20 (R - 20-22).

DISCUSSION

The present study was carried out in CT (Computed Tomography) proved cases of Acute Ischemic Stroke (AIS), who were in the age group of 30 to 70 years. 20 healthy controls and 40 hypertensive age matched controls were selected. In our study, plasma fibrinogen level was 349 ± 36.4 mg/dl in cases was comparable to Di Napoli (2001) and Mahesh Pai (2003) studies 413 103 and 338.68±49.1 mg% respectively.[7,8]

Mean age of cases in this study was 58.63 years range between (34 to 70 years) The plasma fibrinogen levels were found to increase significantly with increase in age ($P < 0.001$). In European study (2002) showed a positive association of age and fibrinogen level.[9]

Mean plasma fibrinogen levels were in males was higher as compared to females, the difference was statistically significant ($P < 0.05$). A.R. Kumar (Secundarabad- 2005) plasma fibrinogen were higher in males as compared with females.[10]

No significant difference was found in plasma fibrinogen level of hypertensive and non hypertensive cases of ischemic stroke. But Plasma fibrinogen was significantly higher in hypertensive control $p < 0.001$ than non-hypertensive. A. R. Kumar had found elevated fibrinogen levels associated with hypertension **Letcher RL** (1981) found fibrinogen levels were higher in patients with essential hypertension than normotensive control. [10,11]

All lipid subtypes are significantly raised in cases (stroke) than controls. There was positive correlation between fibrinogen and total cholesterol, LDL-cholesterol and Triglycerides in the present study but not with HDL-CHO.

J.F.Albucher (2000) in his study after multivariate analysis found low HDL Cholesterol as only lipid subtype which is independently associated with STROKE. We also found low HDL-CHO <40 mg% was significantly associated with ischemic stroke $p < 0.01$. [12]

Di Napoli et al (2001) in his study found positive correlation between levels with severity stroke assessed with CNSS (Canadian Neurological Stroke Scale). However no study is available to correlate plasma fibrinogen with clinical severity by NIHSS (National Institute of Health Stroke Scale) score, we made an attempt to find out their relationship. Plasma fibrinogen was in cases who had NIHSS score between 0 – 6, 7 – 12 and ± 13 was 316.6mg/dl, and 340.5 mg/dl and 358.8 mg/dl respectively. The difference was statistically highly significant ($P < 0.001$). There was positive correlation between plasma fibrinogen level and NIHSS score on day 1 ($r = 0.43$).

Conclusions

Plasma fibrinogen levels were highly significantly ($P < 0.001$) raised in cases of acute ischemic stroke as compared with controls. Hypertensive case and controls had higher plasma fibrinogen. Plasma fibrinogen positively correlated with total cholesterol, LDL cholesterol, and triglycerides but not with HDL cholesterol. Plasma fibrinogen levels were higher in men and smokers. Ischemic stroke cases with higher stroke severity by NIHSS score had higher plasma fibrinogen levels. Mortality was seen in cases with plasma fibrinogen higher than 350 mg% and NIHSS score more than 21

REFERENCES

- 1) Tapas Kumar Banjee,*Shyamal Kumar DAS(2006) Epidemiology of stroke in India Neurology Asia 2006; 11 :1 – 4
- 2) Lars Wilhelmsen, Kurt Svardstudd, Kristoffer. Bo Larsson, Lennart Welin, Gosta, Fibrinogen As A Risk factor for stroke and Myocardial Infarction” N. England. Journal of Medicine (1984), 311, 501-505
- 3) Nawab Qizilbash, Linda Jones, Charles Warlow and Jim Mann (1991) Fibrinogen And Lipid Concentrations As Risk Factors For Transient Ischaemic Attacks And Minor Ischaemic Strokes BMJ: Vol. 303, No. 6803 (Sep. 14, 1991), pp. 605-609
- 4) Wayne M. Clark, MS Nancy B. Beamer, Michael Wynn, Bruce M. Coull (1998) The initial acute phase response predicts long-term stroke recovery Stroke 1998, vol 7(2), 128-131
- 5) William B. Jannel, Philip A Wolf, William Plasma Fibrinogen and Risk of cardiovascular Disease. (The Framingham Study). JAMA (1987), 258, 1183-1186.
- 6) H.P. Adams, Jr., P.H. Davis, E.C. Leira, K.-C. Chang, B.H. Bendixen, W.R. Clarke, R.F. Woolson, M.D. Hansen (1999) Baseline NIH Stroke Scale score strongly predicts outcome after stroke: A report of the Trial of Org 10172 in Acute Stroke Treatment (TOAST). Neurology. 1999 Jul 13; 53(1):126-31
- 7) Mario Di, Napoli, Francesca Papa, Vittorico Bocola C-Reactive protein in Ischemic stroke Stroke 2001, 32(4) 917. 8) Pai Mahesh, Chandrashekar P. (2003) A study of plasma fibrinogen as a risk factor for ischemic stroke JAPI vol. 51, Dec. 2003, 1197
- 9) ML Bots, PC Elward, JT Salonen, A Frier (2002) Level of fibrinogen and risk of fatal and non fatal stroke, EUROSTROKE, a collaborative study among research center in Europe J. Epid. community Health, 2002, 56 (Supp.1) 114-118
- 10) A.R. Kumar, Satish, A Kumar, U. Raghawa, M. Joshi, K. Shanker (2005) A Study of plasma fibrinogen levels in stroke in ischemic and Haemorrhagic. JAPI vol. 53, April 2005.
- 11) Robert L. Letcher, Shu Chien, Thomas G. Pickering, Jean E. Sealey, John H. Laragh (1981) Direct relationship between blood pressure and blood viscosity in normal and hypertensive subjects: Role of fibrinogen and concentration American Journal of Medicine. 1981, vol 6, p1195-1202
- 12) J.F. Albucher, J. Ferrieres, J.B. Ruidavets, BP, Perret Serum Lipids in young patients with ischemic stroke – a case control study. J. Neuro. Neurosurg psychiatry 2000, vol 1, 69, 29-33