

Original Research Article

Serum gamma-glutamyl transferase level in acute stroke

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ABSTRACT

Background: Stroke is the second leading cause of death worldwide, causing 6.2 million deaths in 2011. Serum Gamma-Glutamyl Transferase (GGT) has been conventionally considered as a marker of excessive alcohol intake and/or liver dysfunction. There are accumulating evidences suggesting association of raised serum GGT level in stroke. So, this study was conducted to determine the association between the serum GGT level and stroke in population without history of alcohol consumption.

Methods: This cross-sectional comparative study was carried out at Department of General medicine, Veer Surendra Sai Institute of Medical Sciences and Research (VIMSAR), Burla from November 2016 to October 2018. 100 cases and 100 controls were included in this study. Cases were the patients admitted to Department of General Medicine, VIMSAR, Burla, presenting within 24 hours of first episode of stroke. Controls were the age (+/-5 years) and sex matched healthy attendants of the patients. Alcoholics or patients suffering from hepatitis, cirrhosis of liver, cholestasis or patients taking drugs like Phenytoin, Valproic acid, Carbamazepine etc or patients with past episode of stroke were excluded from this study. Serum GGT level of both cases and controls were measured and compared.

Results: In stroke patients, the mean serum GGT level was 54.95 IU/L with standard deviation of 20.54. In controls, the mean serum GGT level was 32.14 IU/L with standard deviation of 5.07. The p-value was less than 0.0001 i.e. highly significant.

Conclusions: Serum GGT level is significantly increased in stroke patients than healthy persons without stroke.

Keywords: Diabetes mellitus, Dyslipidemia, Gamma-Glutamyl transferase, Hypertension, Stroke

INTRODUCTION

Stroke is responsible for a high socioeconomic burden worldwide by increasing morbidity and mortality. Stroke is the second leading cause of death worldwide, causing 6.2 million deaths in 2011.¹ Over the past 4 decades, the rate of stroke incidence has decreased 42% in high income countries and increased over 100% in low-to-middle-income countries globally.² The crude stroke prevalence in different parts of India ranged from 44.29 to 559 per 1,00,000 persons during the past two decades.³ The cumulative incidence of stroke in India ranged from

105-152/1,00,000 persons per year during the past two decades in different parts of the country.³

According to World Health Organization (WHO), Stroke is defined as 'rapidly developing clinical signs of focal (at times global) disturbance of cerebral function, lasting more than 24 hours or leading to death with no apparent cause other than that of vascular origin.' The term 'global' is applied to patients in deep coma and to those with subarachnoid hemorrhage.⁴ Stroke is classified into two broad categories Ischemic stroke- caused by cerebral thrombosis or embolism and Hemorrhagic stroke- caused

by intra-cerebral hemorrhage or subarachnoid hemorrhage.

Gamma-Glutamyl transferase (GGT) is an enzyme that belongs to the family of Transferases. It catalyses the transfer of a Gamma-glutamyl group of a Gamma-glutamyl peptide such as Glutathione, to a peptide or amino acid type acceptor.⁵ GGT is usually considered as a marker of alcohol consumption.⁶

Some population-based studies have found that raised serum GGT level is associated with risk of stroke.⁷⁻⁹ They are the prospective cohort study by Pekka Jousilahti et al, the "EUROSTROKE PROJECT" by ML Bots et al and the study by Yuji Shimizu et al. The probable mechanism of raised serum GGT level in stroke is oxidative stress.¹⁰ Oxidative stress is usually associated with atherosclerosis. Some evidences are available indicating a direct relation between raised GGT activity and progression of atherosclerosis.¹¹ There is a paucity of studies in India regarding the relationship of serum GGT and stroke. Some studies found the association between self-reported alcohol consumption and raised serum GGT level with risk of stroke.⁷ But there may be misinterpretation in calculating the alcohol consumption level by self-report, because heavy drinkers may under-report their alcohol intake. Hence the present study was an effort to evaluate the relationship of serum GGT level with stroke in patients without history of alcohol consumption.

Primary objective of this study was to determine the association between serum GGT level and acute stroke. Secondary objectives are:

- To compare the serum GGT level of different age groups in acute stroke
- To compare the serum GGT level between men and women in acute stroke
- To evaluate the association between serum GGT level and risk factors of stroke like diabetes mellitus, hypertension, Dyslipidemia and smoking and
- To compare the serum GGT level of acute ischemic stroke and acute hemorrhagic stroke patients.

METHODS

The present study was a hospital based, cross-sectional, comparative study carried out in the Department of General Medicine, Veer Surendra Sai Institute of Medical sciences and Research (VIMSAR), Burla in the state of Odisha from November 2016 to October 2018. Ethical clearance was obtained from VIMSAR Institutional Research and Ethics Committee (VIREC). The informed consent was taken from either the patients or their relatives.

About 100 cases and 100 controls were included in this study. Cases were the patients admitted to Department of

General Medicine, VIMSAR, Burla, presenting within 24 hours of first episode of stroke, confirmed by CT scan of brain. Controls were the age (+/-5 years) and sex matched healthy attendants of patients.

Inclusion criteria

- Age >14 years.

Exclusion criteria

- Patients with past history of stroke
- Patients having diseases or factors in which serum GGT level increases, like
 - History of alcohol consumption
 - Hepatitis, Cirrhosis of liver, Cholestasis
 - History of drug use like Phenytoin, Barbiturate, Carbamazepine, Valproic acid, Oral contraceptive pill, Methotrexate.

Detailed history regarding alcohol consumption, use of drugs, smoking, hypertension, diabetes mellitus, hyperlipidemia was collected from each patient. Then thorough clinical examination was performed. Each case was confirmed by non-contrast CT scan of brain. Different biochemical investigations like Liver function test (LFT), Fasting Blood sugar (FBS), Post prandial blood sugar (PPBS), Lipid profile, Serum Gamma-Glutamyl Transferase (GGT) were done. For serum GGT level estimation, random venous blood sample of 3 ml was collected from both cases and controls. Serum was separated by centrifugation of blood sample. The test instrument used was Auto-analyser Vitros-250. The Normal Range for serum GGT was taken as 25-43 IU/L.

Demographic data, biochemical investigations and reports of CT scan of brain were recorded in a structured proforma. The data were entered in Microsoft Office Excel 2007. Mean, standard deviation and P-value were calculated by using SPSS Version 23.0 (Statistical Package for Social Sciences, Inc., Chicago, III). P-value of <0.05 was considered as significant.

RESULTS

Baseline characters like age and sex of cases and controls were compared and represented (Table 1). Younger age group individuals were more in control group than cases where as number of middle aged and older individuals was more in cases. This difference reached statistical significance (P=0.002). There was no difference in sex wise distribution of cases and controls. Cases had 56% males and 44% females. Similarly Controls had 50% males and 50% females (P=0.39).

In cases, the mean serum GGT level is 54.95 with standard deviation (SD) of 20.54. In controls, the mean serum GGT level is 32.14 with standard deviation of 5.07. The P-value is less than 0.0001 i.e. highly significant. This implies serum GGT level is significantly increased in cases i.e. in stroke patients (Table 2).

Table 1: Baseline characters of case and controls.

Baseline characters	Case n (%)	Control n (%)	P-value
Age group (Years)			
15-40	14 (14%)	35 (35%)	0.002
41-65	67 (67%)	52 (52%)	
≥66	19 (19%)	13 (13%)	
Sex			
Male	56 (56%)	50 (50%)	0.39
Female	44 (44%)	50 (50%)	

Table 2: Comparison of serum GGT level between cases and controls.

Group	Serum GGT (IU/L)	
	Mean	Standard deviation
Case	54.95	20.54
Control	32.14	5.07
P-value	<0.0001	

The cases are divided into three age groups, 15-40 years (young age), 41-65 years (middle age) and ≥66 years (elder age). Serum GGT of (15-40) years age group has a mean of 37.07 IU/L with standard deviation of 9.16. Serum GGT of (41-65) years age group has a mean of 54.88 IU/L with standard deviation of 19.39. Serum GGT of ≥66 years age group has a mean of 68.36 IU/L with standard deviation of 21.05. So, serum GGT level is higher in ≥66 years age group than other age groups, with a p-value of less than 0.0001 i.e. highly significant. P-value was calculated by one way- ANOVA test (Table 3).

Table 3: Comparison of serum GGT level between different age groups of cases.

Age group (Years)	Serum GGT(IU/L)	
	Mean	Standard deviation
15-40	37.07	9.16
41-65	54.88	19.39
≥66	68.36	21.05
P-value	<0.0001	

Serum GGT of male stroke patients has a mean of 58.41 IU/L with standard deviation of 21.12. Serum GGT of female stroke patients has a mean of 50.54 IU/L with standard deviation of 19.13. P-value is 0.057 i.e. not significant. This implies that, though mean serum GGT level is higher in male cases, there is no significant differences of serum GGT level between male and female cases (Table 4).

In this study, the patients having history of diabetes mellitus and treated with oral hypoglycemic agents or insulin, either regularly or irregularly, are considered as having diabetes mellitus. Serum GGT of diabetic cases has a mean of 74.84 IU/L with standard deviation of 17.05. Serum GGT of non-diabetic cases has a mean of

45.58 IU/L with standard deviation of 14.54. P-value is less than 0.0001 i.e. highly significant. This implies that serum GGT level is significantly higher in diabetic cases than non-diabetics (Table 5).

Table 4: Comparison of serum GGT level between male and female cases.

Sex	Serum GGT (IU/L)	
	Mean	Standard deviation
Male	58.41	21.12
Female	50.54	19.13
P-value	0.057	

Table 5: Relationship between serum GGT level and diabetes mellitus in cases.

Diabetes mellitus	Serum GGT (IU/L)	
	Mean	Standard deviation
Yes	74.84	17.05
No	45.58	14.54
P-value	<0.0001	

Hypertensive patients have a history of hypertension. They are taking oral anti-hypertensive drugs either regularly or irregularly. Non-hypertensive patients have no history of hypertension and they are not taking any type of anti-hypertensive medications. Serum GGT of hypertensive stroke patients has a mean of 61.47 IU/L with standard deviation of 19.65. Serum GGT of non-hypertensive stroke patients has a mean of 38.17 IU/L with standard deviation of 11.30. P-value is less than 0.0001 i.e. highly significant. This implies that serum GGT level is significantly higher in hypertensive cases than non-hypertensives (Table 6).

Table 6: Relationship between serum GGT level and hypertension in cases.

Hypertension	Serum GGT (IU/L)	
	Mean	Standard deviation
Yes	61.47	19.65
No	38.17	11.30
P-value	<0.0001	

Serum GGT level of dyslipidemic stroke patients has a mean of 67.94 IU/L with standard deviation of 15.98. Serum GGT level of non-dyslipidemic stroke patients has a mean of 46.98 IU/L with standard deviation of 18.98. P-value is less than 0.0001 i.e. highly significant. This implies that serum GGT level is significantly higher in cases with dyslipidemia than without dyslipidemia (Table 7).

Serum GGT level of smoker cases has a mean of 71.73 IU/L with standard deviation of 18.98. Serum GGT level

of non-smoker cases has a mean of 47.75 IU/L with standard deviation of 16.71. P-value is less than 0.0001 i.e. highly significant. This implies that serum GGT level is significantly higher in smoker cases than non-smokers (Table 8).

Table 7: Relationship between serum GGT level and Dyslipidaemia in cases.

Dyslipidema	Serum GGT(IU/L)	
	Mean	Standard deviation
Yes	67.94	15.98
No	46.98	18.98
P - value	<0.0001	

Table 8: Relationship between serum GGT level and smoking in cases.

Smoking	Serum GGT(IU/L)	
	Mean	Standard deviation
Yes	71.73	18.98
No	47.75	16.71
P - value	<0.0001	

Among 100 stroke cases, 58% patients had ischemic stroke and 42% hemorrhagic stroke patients. Serum GGT level of ischemic stroke patients has a mean of 53.65 IU/L with standard deviation of 17.30. Serum GGT level of hemorrhagic stroke patients has a mean of 56.73 IU/L with standard deviation of 24.44. P-value is 0.23 i.e. not significant. This implies that serum GGT level has no relation with type of stroke, though mean serum GGT level is higher in haemorrhagic stroke patients than ischemic stroke patients (Table 9).

Table 9: Relationship between serum GGT level and type of stroke.

Type of stroke	Serum GGT (IU/L)	
	Mean	Standard deviation
Ischemic stroke	53.65	17.30
Hemorrhagic stroke	56.73	24.44
P-value	0.23	

DISCUSSION

In this study, among the stroke patients, 58% are ischemic stroke and 42% are hemorrhagic stroke. In a population-based stroke survey in Mumbai done by Dalal PM et al, 80.2% of patients with first-ever stroke were ischemic strokes and 17.6% were hemorrhagic strokes.¹² In a study conducted by Sridharan S E et al in Trivandrum stroke registry, 83.6% were ischemic strokes and 16.4% were hemorrhagic strokes.¹³ Das S K et al in a study in Kolkata showed cerebral infarction in 65.06% cases and haemorrhage in 34.93% cases. Ratio of infarction: haemorrhage was 1.86.¹⁴ In this study, the

ratio of infarction: haemorrhage was 1.38. The decrease in the ratio is due to the increase in the number of hemorrhagic strokes, which may be due to exclusion of some stroke patients from this study due to associated alcoholism, chronic liver disease etc.

This study shows that serum GGT level is significantly higher in cases i.e. stroke patients (mean 54.95 IU/L with standard deviation of 20.54) than controls (mean 32.14 IU/L with standard deviation of 5.07) with a p-value of less than 0.0001. In a study done by Pekka Jousilahti et al, showed a similar finding like ours. They concluded that the relationship between serum GGT and stroke remained statistically significant, even after adjustment for smoking, serum cholesterol, body mass index and systolic blood pressure.⁷ The "EUROSTROKE PROJECT" conducted by M L Bots et al also supports the above result. They observed that an increased serum GGT level is associated with increased risk of stroke.⁸ In a meta- analysis done by Xiao- Wei Zhang et al also found similar result. They found that a high level of serum GGT is significantly associated with increased risk of stroke.¹⁵

Serum GGT level is significantly higher in elder age group (≥ 66 years) than young age group (15-40 years) and middle age group (41-65 years) with a p-value of less than 0.0001 in our study. Serum GGT of elder age group has a mean of 68.36 IU/L with standard deviation of 21.05. Serum GGT of middle age group has a mean of 54.88 IU/L with standard deviation of 19.39. Serum GGT of young age group has a mean of 37.07 IU/L with standard deviation of 9.16.

In present study, there is no significant difference of serum GGT level in male and female, with a p-value of 0.057. Serum GGT of male stroke patients have a mean of 58.41 IU/L with standard deviation of 21.12 and that of female stroke patients have a mean of 50.54 IU/L with standard deviation of 19.13. This observation is against the result of the Japanese study conducted by Yuji Shimizu et al. They concluded that serum GGT is positively associated with risk of total stroke for women but not men. The multivariate hazard ratios of total stroke for the highest quartile of GGT compared with the lowest quartile were 1.56 for women and 1.37 for men.⁹ This observation is also against the result of the study by Mijovic V et al, in 929 volunteer blood donors. They noticed that males had consistently higher levels of serum GGT compared to females.¹⁶ In "EUROSTROKE PROJECT" conducted by M L BOTS et al, male sex was positively and significantly related to serum GGT.⁸ A study conducted by Nurbanu Gurbuzer et al observed that the mean serum GGT level did not differ significantly between males and females, with a p-value of 0.918, which is similar to our finding.¹⁷

Present study shows that serum GGT level is significantly higher in stroke patients with diabetes than non-diabetics, with a p-value of less than 0.0001. Serum GGT of

diabetic patients has a mean of 74.84 IU/L with standard deviation of 17.05, whereas that of non-diabetic patients has a mean of 45.58 IU/L with standard deviation of 14.54. In contrast to our result, Nurbanu Gurbuzer et al found that the mean serum GGT level did not differ significantly between diabetics and non-diabetics.¹⁷

Serum GGT level is significantly higher in hypertensive stroke patients than non-hypertensives, with a p-value of less than 0.0001 in this study. Serum GGT of hypertensive cases has a mean of 61.47 IU/L with standard deviation of 19.65 and that of non-hypertensive cases has a mean of 38.17 IU/L with standard deviation of 11.30. Nurbanu Gurbuzer et al, in their study showed similar result. They found that the serum GGT level was significantly higher in hypertensive patients than non-hypertensive patients with a p-value of 0.028.¹⁷ The "EUROSTROKE PROJECT" conducted by M L BOTS et al, also supports our study. They found that hypertension was significantly and positively related to serum GGT.⁸

In our study serum GGT level is significantly higher in stroke patients with dyslipidemia than those without dyslipidemia, with a p-value of less than 0.0001. Serum GGT level of dyslipidemic patients has a mean of 67.94 IU/L with standard deviation of 15.98 and that of non-dyslipidemic patients has a mean of 46.98 IU/L with standard deviation of 18.98. Nurbanu Gurbuzer et al found a similar result with significantly higher GGT levels in patients having increased LDL-cholesterol and triglyceride levels.¹⁷ The "EUROSTROKE PROJECT" conducted by M L BOTS et al also supports this result. They observed that total cholesterol level was positively and significantly related to serum GGT level.⁸

This study shows that serum GGT level is significantly higher in smoker stroke patients than non-smokers, with a p-value of less than 0.0001. Serum GGT level of smoker patients has a mean of 71.73 IU/L with standard deviation of 18.98 whereas that of non-smoker patients has a mean of 47.75 IU/L with standard deviation of 16.71. The study conducted by Pekka Jousilahti et al supports this result. They noticed a strong correlation between serum GGT and smoking, with a p-value of less than 0.001 in both male and female. Serum GGT level was significantly higher in smokers.⁷

In the present study, serum GGT level has no statistically significant relation with types of stroke, though the mean serum GGT level is higher in hemorrhagic stroke patients than ischemic stroke. Serum GGT level of hemorrhagic stroke patients has a mean of 56.73 IU/L with standard deviation of 24.44 and that of ischemic stroke patients has a mean of 53.65 IU/L with standard deviation of 17.30. The "EUROSTROKE PROJECT" conducted by M L BOTS et al does not support this result. They found that the risk of hemorrhagic stroke increased linearly with increase in serum GGT, but for ischemic stroke no clear significant association was observed.⁸ In contrast to our

study Pekka Jousilahti et al, found that raised serum GGT levels were associated with the increase risk of total stroke and ischemic stroke in both men and women. The risk ratios (logarithmic transformation of GGT) in men and women were 1.45 and 1.48 for total stroke and 1.51 and 1.59 for ischemic stroke, respectively. Among men, there was also a significant association (RR 1.91) between serum GGT level and the risk of intracerebral hemorrhage, but among women a significant association was not found between serum GGT and the risk of intracerebral hemorrhage.⁷

Serum Gamma-Glutamyl Transferase (GGT) has been conventionally considered as a marker of excessive alcohol intake and/or liver dysfunction. From this study we conclude that: Serum GGT level is significantly increased in stroke patients than non-stroke patients. Elder age group (≥ 66 years) has a significantly higher GGT level than young and middle age group. There is no significant difference of serum GGT level between male and female cases. Serum GGT level is significantly higher in diabetics than non-diabetics. Hypertensive stroke patients has significantly higher GGT level than non-hypertensives. In stroke patients with dyslipidemia serum GGT level is significantly higher than those without dyslipidemia. Serum GGT level is significantly higher in smoker stroke patients than non-smokers. Although the mean serum GGT level is higher in hemorrhagic stroke patients than ischemic stroke patients, there is no significant difference of serum GGT level between ischemic stroke and hemorrhagic stroke.

More prospective studies with large sample size are required to establish the causal relationship of raised serum GGT and stroke.

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