A STUDY ON CLINICAL AND PROGNOSTIC SIGNIFICANCE OF GAMMA-GLUTAMYL TRANSFERASE IN PATIENTS WITH ACUTE STROKE

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ABSTRACT

BACKGROUND

Stroke is one of the major health problems in many countries. There is supporting evidence suggesting that Gamma-Glutamyl Transferase (GGT) enzyme has an active involvement in atherosclerosis through its oxidative and inflammatory mechanisms. With this background, we conducted a study among acute stroke patients with an aim and objective to evaluate the relationship between stroke and serum GGT levels and to assess the severity of various types of stroke in relation to the levels of serum GGT enzyme.

MATERIALS AND METHODS

A total of 50 acute stroke patients and 50 normal individuals as controls participated in the study. Stroke patients were advised for routine haematological investigations, serum GGT estimation and plain CT of brain.

RESULTS

Out of the 50 acute stroke patients who participated in our study, 32 patients had elevated levels of serum GGT and 3 patients had drastically elevated levels of GGT (>100 IU/L). A statistically significant relationship was found between ischaemic stroke and GGT with a p-value of 0.0418.

CONCLUSION

Gamma-glutamyl transferase estimation in acute stroke patients may serve as a reliable and feasible clinical test for the physician to initially stratify patient risk and provide prompt therapy.

KEYWORDS

Gamma-Glutamyl Transferase (GGT), Acute Stroke, Cerebrovascular Accident (CVA).

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BACKGROUND

A stroke or cerebrovascular accident is defined as the abrupt onset of a neurological deficit that is attributable to a focal vascular cause.[1] Stroke continues to be a major public health problem and it ranks as one of the top four causes of death in many countries.[2] It is responsible for the largest proportion of neurological disorders more often disabling than fatal causing both physical as well as mental crippling.[2,3]

Oxidative stress predisposes to vascular injury/endothelial dysfunction leading to atherosclerosis, cardiovascular disease and stroke.[4,5] It is a known fact that Gamma-Glutamyl Transferase (GGT) mediates intracellular uptake of extracellular glutathione, which is produced during normal metabolic processes and thus plays a vital role in protecting the cells from oxidative stress.[6] Gamma-glutamyl transferase, which is present on cellular membrane is responsible for intracellular ingress of amino acids and peptides in the form of γ-glutamyl peptides.[7]When oxidative stress occurs, decreased intracellular glutathione levels induce the formation of GGT enzyme in an attempt to maintain the normal intracellular glutathione level. But,at times of increased oxidative stress, there is an enhanced requirement for glutathione and because of the presence of inadequate amounts of glutathione, oxidative stress exerts severe harmful effects on the cells.[8,9] Several studies have found positive correlation between serum Gamma-Glutamyl Transferase (GGT) and stroke because of its involvement in oxidative stress pathway.[10,11] Paradoxically, there are also recent studies suggesting that GGT may also be involved in the generation of reactive oxygen species in the presence of iron or other transition metals thus triggering cell death.[12,13]

With this background, the present study was conducted with aim and objective to evaluate relationship between acute stroke and serum Gamma-Glutamyl Transferase (GGT) enzyme level and to assess the severity of various

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types of stroke in relation to the levels of serum GGT enzyme.

MATERIALS AND METHODS

The study was conducted in the Department of Internal Medicine, Thanjavur Medical College and Hospital, Tamilnadu, India, during December 2010 to November 2011 among patients admitted for acute stroke. The study protocol was approved by the ethical review committee of Tamil Nadu Dr. M.G.R. Medical University. Patients who reported within 2nd to 3rd day of acute Cerebrovascular Accident (CVA) were consecutively included in the study irrespective of their age and sex. The control group consisted of 50 normal individuals. Patients with chronic liver diseases, diseases of biliary tract/pancreas/gallbladder, carcinoma of prostrate or patients who are chronic alcoholics/alcohol dependents/binge alcoholics or patients who are on drugs like phenytoin, fibrates, barbiturates, rifampicin and oral contraceptives or patients with previous history of stroke/transient ischaemic attack or coronary artery disease/congestive cardiac failure were excluded from our study.

Totally, 50 stroke patients who had first acute CVA and who were admitted within first 24-72 hours participated in this study. Careful history was taken and screened for risk factors like systemic hypertension, diabetes mellitus, obesity, Chronic Kidney Disease (CKD) and smoking. They were thoroughly examined clinically and a detailed neurological examination was done. For all patients, routine blood investigations including complete haemogram, glucose, urea, creatinine and lipid profile were done. CT scan of brain (plain) was done within 24-72 hours of admission and analysed for site of lesion, nature of lesion (infarct/haemorrhagic), if infarct whether single/multiple/massive and if haemorrhagic whether parenchymal or evident intraventricular extension was present. Random venous blood sample of 5 mL was collected and the sample was centrifuged. The serum was separated and analysed for gamma-glutamyl transferase estimation using the AutoAnalyzer, Turbochem 100 by Szasz method by using the assay kit, BioSystems Gamma-Glutamyl Transferase (Figure 1) based on the recommendations by Scandinavian Society for Clinical Chemistry and Physiology. The normal value of serum GGT for men was 7-40 IU/L and for women was 4-25 IU/L.

RESULTS

The data was tabulated and statistical analysis was done using SPSS software version 21. The paired t-test was done for determining the relationship in case of quantitative variables and Chi-square test in case of qualitative variables. The p-values were determined and 'p' value <0.05 was taken to denote significant relationship. Among the 50 stroke patients who participated in our study, 20 were females and 30 were males and 5 were in the age group of 31-40 years; 7 were between the age group of 41-50 years; 16 were in the age group of 51-60 years; 16 were between the age group of 61-70 years and 6 were more than 70 years of age. The highest GGT level was found among individuals above 70 years of age and the mean value was 78.6 ± 40 (Table 1). Of the 50 cases, 20 patients were hypertensive; 10 were diabetic; 11 were obese; 17 patients had dyslipidaemia; 2 had CKD and 14 patients were smokers; 7 cases were found to be both hypertensive and diabetic and 5 cases had all 3 risk factors including systemic hypertension, diabetes mellitus and obesity.

Out of the 50 acute stroke cases; 32 patients had elevated values of serum GGT and 3 patients had drastically elevated values of GGT (>100 IU/L) when compared to the control group. Maximum number of cases with elevated GGT was present in the age group of 51-60 years, followed by 61-70 years and above 70 years of age, all the 6 cases showed elevated GGT values. The association between GGT and age was statistically significant in our study with a p-value of 0.0472 (Table 1).

Out of the 30 male patients, 19 patients had elevated GGT values; 7 had normal GGT values and 4 patients had decreased GGT values. Among 20 female patients, 13 had elevated GGT levels; 5 had normal GGT levels and 2 had decreased GGT levels. There was no statistically significant relationship between elevated levels of GGT and sex (Table 2).

With respect to the risk factors including systemic hypertension, diabetes mellitus, obesity, CKD and smoking, a statistically significant correlation was found between systemic hypertension and GGT with a p-value of 0.0253, but the correlation with other risk factors was insignificant in our study (Table 3).

Regarding the distribution of cases with respect to the nature of stroke; out of the 50 cases, 40 patients had ischaemic stroke and 10 patients had haemorrhagic stroke. Among 40 cases with ischaemic stroke, 28 patients had elevated GGT values, 10 cases had normal values and 2 cases had decreased values of GGT (Table 4). Three infarct cases had grossly elevated values of GGT >100 IU/L who were found to have large infarcts or multi-infarcts in CT. Among 10 cases with ischaemic stroke; 4 cases had elevated GGT values, 3 cases showed normal values and 3 cases showed decreased GGT values. The mean value of GGT for patients with ischaemic stroke was 51.1 ± 24 and that for haemorrhagic stroke was 28.6 ± 20.5. In our study, the relationship between GGT and ischaemic stroke showed a p-value = 0.0418 suggesting a strong relationship between elevated levels of GGT and ischaemic stroke (Table 5).

DISCUSSION

Stroke is considered as one of the leading causes of death and disability worldwide. The prevalence rate of stroke in India varies widely from 147-922/1,00,000 based on numerous community-based studies.[14] In India, according to stroke factsheet updated in 2012 with age adjustment, the estimated prevalence rate for stroke was found to be between 84-262/1,00,000 in rural areas and between 334-424/1,00,000 in urban areas.[15] Mortality and morbidity associated with stroke can be reduced if patients at risk are identified early, thereby enabling the physician to plan

primary prevention strategies promptly. Gamma-glutamyl transpeptidase is a widely available biochemical test and there is supporting evidence suggesting a prognostic role of GGT in cerebrovascular diseases because of its active involvement in atherosclerosis through oxidative and inflammatory mechanisms.[8,9]

In our study, 64% of stroke patients had elevated levels of GGT when compared to the control group. Consistent results were found in a similar study conducted by Korantzopoulos P et al (2009) in individuals >70 years of age with first ischaemic/non-embolic stroke where stroke patients showed higher concentrations of GGT compared with control and there was positive associations between serum GGT and stroke.[16] The elevated levels of GGT in stroke patients could be due to the induced formation of GGT in response to decreased levels of intracellular glutathione at times of oxidative stress.

In this study, 80% of patients had ischaemic stroke and 20% of patients had haemorrhagic stroke. Similar to our study, Dalal PM et al (2008) have reported 80.2% of patients with ischaemic strokes and 17.7% with haemorrhagic strokes in their population-based stroke survey in Mumbai.[16] In our study, we observed that among ischaemic stroke patients; 70% of individuals had elevated GGT levels and 7.5% of individuals had grossly elevated GGT levels >100 IU/L and among haemorrhagic stroke patients; 40% of individuals had elevated GGT levels. Also, there was a strong relationship between elevated levels of GGT and ischaemic stroke with a significant p-value of 0.0419 (p-value <0.05). This could be because of the pathogenic role played by GGT in the evolution and instability of atherosclerotic plaques in the arterial wall.

D'Ambrosio et al (2013) reported that elevated GGT levels can predict functional impairment in elderly adults after ischaemic stroke.[10] Nurbanu Gubuzer et al (2014) in their study found statistically significant relationship between mean values of GGT and infarct area and a prominent increase was seen in cases with relatively large areas of infarct among patients with ischaemic stroke.[17] Similar observation was found in our study also.

Bots ML et al (2002) in the EUROSTROKE project found that patients with raised levels of GGT had 26% increased risk for acute stroke, but contrastingly in the EUROSTROKE analysis, it was found that an elevated GGT as a marker of alcohol consumption is associated with increased risk of stroke in particular haemorrhagic stroke.[18] Umar Farooq Dar et al (2016) reported that there is no association between raised gamma-glutamyl transferase and ischaemic stroke as the frequencies of raised gamma-glutamyl transferase were comparable among cases and controls in their study.[19]

Nurbanu Gubuzer et al have reported that mean GGT values were higher in the subgroup with the risk factors of hypertension and dyslipidaemia and significant correlation was found between the two risk factors and elevated GGT.[17] Josephine Latha P et al (2015) also reported of a significant relationship between GGT levels and waist circumference, hypertension and dyslipidaemia.[20] But, in our study, a statistically significant relationship was found only between hypertension and elevated GGT in stroke patients. This suggests that there may be a positive association between GGT and hypertension with respect to atherogenesis in stroke.

So, the estimation of serum gamma-glutamyl transferase level may serve as a reliable biochemical test enabling the physician and neurologist in planning primary treatment strategies promptly and preventing the complications of acute stroke. For the general practitioners, this feasible haematological test may be useful in early stratification of individuals at risk for stroke and in early referral to a tertiary health care unit. The drawback of our study is that a further study with a large population study is required to determine the correlation between severity of infarct and level of serum GGT.

CONCLUSION

The results of our study demonstrate that GGT is elevated in patients with acute stroke. The positive relationship between elevated levels of GGT and stroke patients suggest that the estimation of serum gamma-glutamyl transferase level may serve as a reliable, feasible and cost-effective biochemical test, which enables the physician to provide prompt therapy for acute stroke patients prevent the associated morbidity and mortality and provide a good quality of life for the patient.

Figure 1

Age Group	Serum GGT Levels (IU/L)	
	Mean	**S.D.**
Up to 40 yrs.	55.2	27.2
41-50	32.2	23.6
51-60	49	39.7
61-70	35.5	24.9
71 and above	78.6	40
Total	**46.6**	**34.2**
p-value	**0.0472, Significant**	

Table 1. Statistical Analysis showing Mean Values of GGT and Relationship between GGT and Different Age Groups

Sex	Serum GGT Values (IU/L)	
	Mean	**S.D.**
Male	46.6	33.7
Female	46.6	35.8
'p'	0.7438, not significant	

Table 2. Statistical Analysis showing Relationship between Sex and Serum GGT Values

Risk Factor	Serum GGT Values in Stroke Patients (IU/L)				'p'
	With Risk Factor		Without Risk Factor		
	Mean	S.D.	Mean	S.D.	
Hypertension	69.6	40	42.8	32.1	0.0253, significant
Type 2 DM	74	55.8	44.2	31.5	0.1425, not significant
CKD	34.4	39.6	47.1	34.3	0.7289, not significant
Obesity/dyslipidaemia	70.1	49	44	31.8	0.1411, not significant
Smoking (among males)	51.5	53	45.4	28.5	0.856, not significant

Table 3. Statistical Analysis Showing the Relationship between Risk Factors and Serum GGT Values

	Elevated GGT	Normal GGT	Decreased GGT
Ischaemic Stroke	28	10	2
Haemorrhagic Stroke	4	3	3

Table 4. Distribution of Cases with Elevated GGT Levels in Ischaemic/Haemorrhagic Stroke

Type of Stroke	Serum GGT Levels (IU/L)	
	Mean	S.D.
Ischaemic stroke	51.1	24.0
Haemorrhagic stroke	28.6	20.5
p-value	**0.0418**	

Table 5. Statistical Analysis showing Relationship between Type of Stroke and Serum GGT Levels

The relationship between GGT and ischaemic stroke showed a p-value = 0.0418 suggesting a strong relationship between GGT and ischaemic stroke.

REFERENCES

[1] Smith WS, English JD, Johnston SC. Cerebrovascular diseases. In: Fauci AS, Kasper DL, Longo DL, et al, eds. Harrison's principles of internal medicine. 17th edn. New York: McGraw-Hill 2008. p. 2513.

[2] Hatano S. Experience from a multicentre stroke register: a preliminary report. Bulletin of the World Health Organization 1976;54(5):541-553.

[3] Bogouisslausky J, Liu M, Moncayo J, et al. Stroke. In: Aarli JA, Aranzini G, Bertolote JM, et al, eds. Neurological disorders: public health challenges. Geneva, Switzerland: World Health Organisation 2006.

[4] Francesco C, Speranza R, Carmine S, et al. Endothelial dysfunction and stroke. Journal of Cardiovascular Pharmacology 2001;38(2):S75-S78.

[5] Rajendran P, Rengarajan T, Thangavel J, et al. The vascular endothelium and human diseases. Int J Biol Sci 2013;9(10):1057-1069.

[6] Sies H. Glutathione and its role in cellular functions. Free Radic Biol Med 1999;27(9-10):916-921.

[7] Lushchak VI. Glutathione homeostasis and functions: potential targets for medical interventions. Journal of Amino Acids Article ID (736837) 2012;(2012):26.

[8] Emdin M, Pompella A, Paolicchi A. Gamma-Glutamyltransferase, atherosclerosis and cardiovascular disease. Triggering oxidative stress within the plaque. Circulation 2005;112(14):2078-2080.

[9] Paolicchi A, Emdin M, Ghliozeni E, et al. Images in cardiovascular medicine. Human atherosclerotic plaques contain gamma-glutamyl transpeptidase enzyme activity. Circulation. 2004;109(11):1140.

[10] D'Ambrosio D, Gargiulo G, Della-Morte D, et al. Gamma-glutamyltransferase predicts functional impairment in elderly adults after ischemic stroke. Journal of the American Geriatrics Society 2013;61(6):1040-1041.

[11] Korantzopoulos P, Tzimas P, Kalantzi K, et al. Association between serum gamma-glutamyltransferase and acute ischemic nonembolic stroke in elderly subjects. Arch Med Res 2009;40(7):582-589.

[12] Cosentino F, Still JC, Katusic ZS. Endothelial L-arginine pathway and relaxations to vasopressin in canine basilar artery. Am J Physiol 1993;264(2 Pt 2):H413-418.

[13] Whitfield JB. Gamma-glutamyl transferase. Crit Rev Clin Lab Sci 2001;38(4):263-355.

[14] Prasad K, Vibha D, Meenakshi. Cerebrovascular disease in south Asia-Part I: a burning problem. JRSM Cardiovasc 2012;1(7).

[15] Bharucha NE, Bharucha EP, Bharucha AE, et al. Prevalence of stroke in the Parsi community of Bombay. Stroke 1988;19(1):60-62.

[16] Dalal PM, Malik S, Bhattacharjee M, et al. Population-based stroke survey in Mumbai, India: incidence and 28-day case fatality. Neuroepidemiology 2008;31(4):254-261.

[17] Gurbuzer N, Gozke E, Basturk ZA. Gamma-Glutamyl transferase levels in patients with acute ischemic stroke. Cardiovascular Psychiatry Neurology Article ID 170626 2014;(2014):4.

[18] Bots ML, Elwood PC, Salonen JT, et al. Level of fibrinogen and risk of fatal and non-fatal stroke. EUROSTROKE: a collaborative study among research centres in Europe. J Epidemiol Community Health 2002;56(Suppl 1):14-18.

[19] Dar UF, Ali S, Sirhindi GA, et al. Association between ischemic stroke and raised serum gamma-glutamyl transferase. P J Med Health Sciences 2016;10(1):130-132.

[20] Latha JP, Ganesan S. Correlation of serum gamma-glutamyl transferase with atherogenic dyslipidemia in obese individuals. Scholars Journal of Applied Medical Sciences 2015;3(1F):387-391.