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Original Research Article

Study of serum gamma glutamyl transferase in acute stroke - a single centre experience

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ABSTRACT

Background: Gamma-glutamyl transferase (GGT) is an enzyme involved in oxidative stress and inflammation, which are key mechanisms in the pathogenesis of stroke. Recent evidence suggests serum GGT levels may be associated with the risk and prognosis of acute ischemic stroke. This study aimed to investigate serum GGT levels in patients with acute stroke at a single center in India.
Methods: This case-control study included 100 patients (50 with acute stroke and 50 age and sex-matched controls). Patients aged 40 to 80 years and diagnosed with acute stroke (encompassing first-time occurrences of intracerebral hemorrhage, ischemic stroke, and subarachnoid hemorrhage) were included in the study. Serum GGT levels were compared between stroke patients and controls. The association of GGT with various risk factors was also analyzed among cases.
Results: The mean age of cases is 60.2±10.07 years. Hemorrhagic stroke was most common and found in 52% of cases. Mean serum GGT levels were significantly higher in stroke patients (55.2540±40.8909 U/l). Higher serum GGT levels were associated with male gender, presence of diabetes, hypertension, dyslipidemia and smoking and were found to be statistically significant ($p<0.005$). Age and stroke type were found to be not significantly associated with GGT levels.
Conclusions: In conclusion, our study findings indicate that elevated serum GGT levels are associated with an increased risk of stroke, particularly in male patients and those with hypertension, dyslipidemia, and diabetes. Further prospective studies are needed to establish the predictive value of GGT for stroke.

Keywords: Stroke, Gamma-glutamyl transferase, Hypertension, Dyslipidemias, Oxidative stress

INTRODUCTION

As per the World Health Organization (WHO), stroke stands as the primary cause of death following heart disease.[1] According to the Centers for Disease Control and Prevention (CDC), 1 in 6 cardiovascular disease deaths were due to stroke. Annually, over 795,000 Americans experience a stroke, including approximately 610,000 first

or new strokes, and nearly 185,000 strokes occur in individuals with a previous stroke.[2] Studies conducted within communities in India indicate a substantial disparity in stroke prevalence, ranging from 147 to 922 cases per 100,000 individuals.[3]

A stroke is a sudden neurological impairment lasting more than 24 hours, presumed to be of vascular origin, excluding transient ischemic attacks and trauma-related symptoms. Definitive stroke signs must last over 24 hours including unilateral or bilateral motor or sensory impairment, non-fluent speech, visual field impairment, diplopia, conjugate deviation, acute onset apraxia or ataxia, or perception deficit. Additional impairments encompass changes in consciousness, diminished visual function, and reduced blood circulation to specific brain regions—ischemic stroke results from artery occlusion, diagnosed through clinical examination and neuroimaging. Intra-cerebral hemorrhage involves bleeding into brain tissue, diagnosed clinically and confirmed by neuroimaging. Subarachnoid hemorrhage, characterized by arterial bleeding between meninges, is diagnosed through neuroimaging. Unspecified stroke applies when no diagnostic examination is performed. Fatal stroke results in death within 28 days, while non-fatal stroke survivors live beyond this period. This classification aids in precise diagnosis, research, and patient care.[4-6]

Various risk factors contribute to the occurrence of stroke, with aging, male gender, smoking, obesity, and dyslipidemia being particularly noteworthy.[7] The identification of these risk factors is crucial for clinicians as it enables the identification of individuals at a higher risk of stroke, facilitating the implementation of early interventions.[8] One such factor that has gained physicians' attention is gamma-glutamyl transferase (GGT) which is primarily recognized as an indicator of liver disease. Sequential investigations into the correlation between GGT and stroke have underscored the prospect of GGT serving as an innovative biomarker for predicting the occurrence of strokes.[9] The study aims to see whether serum GGT level has any influence on stroke without a history of alcohol consumption.

METHODS

This is a case-control study that was conducted over at the inpatient department (IPD) of the Department of General Medicine, Asansol District Hospital from October 2022 to October 2023. Patients aged 40 to 80 years and diagnosed with acute stroke (encompassing first-time occurrences of intracerebral hemorrhage, ischemic stroke, and subarachnoid hemorrhage) were included in the study. Exclusion criteria involved individuals with a prior history of stroke, those without acute stroke, and those with conditions or factors associated with elevated serum GGT levels. Serum GGT reference values: IFCC method <55 U/l for males and <38 U/l for females; Szasz method <49 U/l for males and <32 U/l for females, such as congestive cardiac failure, alcohol consumption, and specific drug use.[10,11]

The sample size of 100 was determined based on epidemiological data for a case-control study. There were 50 participants in the two groups: group A, comprising individuals with acute stroke, and group B, featuring age and sex-matched control subjects without evident cerebrovascular and cardiovascular diseases. The sample size rationale employed a formula considering anticipated proportions and a power of 87%, and the sampling procedure involved categorizing the study population into specified groups. In this study, pretested and predesigned semi-structured questionnaires, as outlined in the study proforma, were administered, encompassing history, and general and systemic examinations, after obtaining consent from participants. The study tools included a patient proforma and standard hematological, biochemical, and radiological tests conducted for all enrolled patients. The history-taking process focused on factors such as alcohol consumption, use of GGT-altering drugs, smoking, hypertension, diabetes mellitus, and dyslipidemia. The general examination involved: measuring blood pressure, waist circumference, and waist-hip ratio. The systemic examination concentrated on the nervous and cardiovascular systems.

Various laboratory tests were performed, including complete blood count, liver function tests, prothrombin time, lipid profile, blood sugar levels, serum sodium, serum potassium, and serum creatinine. Radiological studies comprised ultrasound of the whole abdomen, echocardiography (ECG), carotid Doppler study (for ischemic stroke patients), and computed tomography (CT) scan of the brain. The study protocol was approved by the members of the clinical research ethics committee (CREC) of Burdwan Medical College (memo no. BMC/2380). Data collection, storage, and management involved entering information into a Microsoft excel spreadsheet and analyzing it using statistical package for the social sciences (SPSS) 20.0.1 and GraphPad Prism version 5. The statistical analysis included calculating means and standard deviations for numerical variables, counts and percentages for categorical variables, and medians with interquartile ranges for non-normally distributed numerical variables. Statistical tests such as Student's independent sample t-test and Chi-square test were employed as appropriate, with a significance level of $p \leq 0.05$.

RESULTS

A total of 100 patients (50 cases and 50 controls) were included in the study. They are both age and sex-matched. The mean age of cases is 60.2±10.07 years and the mean age of controls is 58.3±5.3 years. 51% were males and 49% were females. Among cases, 23% were smokers, 24% were diabetes, 38% were hypertensive and only 5% had dyslipidemia (serum triglyceride level ≥150 mg/dl or serum high density lipoprotein (HDL) >40 mg/dl in male

and >50 mg/dl in female is considered to be dyslipidemia). The basic characteristics of patients are described in Table 1.

Table 1: Basic characteristics of study participants (n=100).

Variables	Number of individuals (n=100)		Percentage
	Cases	Controls	
Age (in years)			
40-60	24	35	59
61-80	26	15	41
Gender			
Male	26	25	51
Female	24	25	49
Smoker			
Yes	23	18	41
No	27	32	59
Diabetes			
Yes	24	21	45
No	26	29	55
Hypertension			
Yes	38	37	75
No	12	13	25
Dyslipidaemia			
Yes	5	0	5
No	45	50	95

Among cases, hemorrhagic stroke was found in 52% (26), ischaemic stroke in 40% (20), and subarachnoid hemorrhage in 8% (4) (Figure 1). Mean serum GGT levels in cases and controls were 55.2540±40.8909 U/l and 17.4380±4.3468 U/l respectively. The difference in mean serum GGT in the two groups was statistically significant ($p<0.0001$). Association between variables and serum GGT levels among cases were described in (Table 2). Higher serum GGT levels were associated with male gender, presence of diabetes, hypertension, dyslipidemia and smoking and were found to be statistically significant ($p<0.005$). Age and stroke type were found to be not significantly associated with GGT levels.

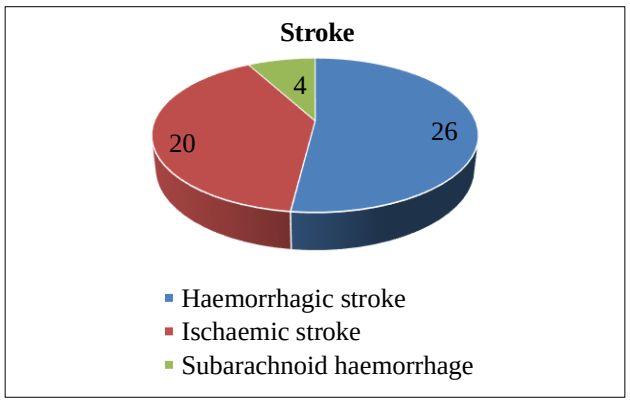

Figure 1: Type of stroke among cases (n=50).

Table 2: Association between variables and serum GGT levels among cases (n=50).

Variables	N	Mean serum GGT levels	P value
Age (in years)			
40-60	24	63.4	0.1756 (not significant)
61-80	26	47.6	
Gender			
Male	26	63.9	0.0497 (significant)
Female	24	45.8	
Diabetes			
No	26	44.1	0.0444 (significant)
Yes	24	67.2	
Hypertension			
No	12	26.5	0.0042 (significant)
Yes	38	64.3	
Dyslipidemia			
No	45	46.7	<0.0001 (significant)
Yes	5	132.0	
Smoking			
No	27	44.32	0.0392 (significant)
Yes	23	68.08	
Type of stroke			
ICH	30	61.85	0.1643 (not significant)
INF	20	45.35	

DISCUSSION

This study examined various stroke types within the study population, and it is found that 52% of the cases were hemorrhagic strokes, 40% were ischemic strokes, and 8% were subarachnoid hemorrhages. Similar results were found in a study conducted in eastern India, with a potential explanation lying in the diverse patient admissions from the catchment areas of West Bengal, Bihar, and Jharkhand. Strikingly, the imaging results from the Kolkata study indicated a higher prevalence of cerebral infarction (68%) compared to cerebral hemorrhage (32%). This disparity highlights the regional differences in stroke subtypes, possibly influenced by the unique demographic and geographical characteristics of the population under study.[12] An intriguing aspect of the current study is the careful exclusion of alcoholic patients from both case and control groups, aiming to isolate the influence of alcohol consumption on the results related to serum GGT levels. The findings indicate a significant association between serum GGT levels and acute stroke, prompting further investigation into the role of GGT as either a risk factor or a marker for acute stroke. The significance of this association was underscored by a statistically significant difference in serum GGT levels between cases and controls, emphasizing the potential relevance of GGT in the context of acute stroke.

Our study findings align with the observations of the Eurostroke project by Bots et al and a study conducted by Jousilathi et al, both of which demonstrated a correlation

between elevated serum GGT levels and an increased risk of stroke.[13,14] Notably, the associations identified in these studies remained independent of factors such as hypertension, total cholesterol, drug use, and a history of myocardial infarction. The present study aligns with these broader findings, contributing to the growing body of evidence supporting the association between serum GGT levels and heightened stroke risk. Furthermore, our study explored the complex relationship between serum GGT levels and various demographic and clinical factors. While serum GGT levels were higher in the age group of 40-60 years compared to those aged 61-80 years, the difference did not reach statistical significance. A gender-based analysis revealed a statistically significant difference, with males exhibiting higher serum GGT levels than females. This observation dovetails with existing research suggesting a potential link between increased smoking prevalence in males and higher oxidative stress, leading to elevated serum GGT levels.

Our study also revealed a statistically significant association between serum GGT levels and diabetes, supporting previous research by Perry et al and Sabanayagam et al.[15,16] These studies indicated that elevated serum GGT levels serve as an independent risk factor for non-insulin-dependent diabetes mellitus (NIDDM) and are positively associated with diabetes, irrespective of confounding factors such as alcohol consumption, body mass index (BMI), and hypertension. A noteworthy finding in the study highlighted a significant correlation between serum GGT levels and hypertension, with hypertensive patients exhibiting higher GGT levels compared to non-hypertensive individuals. This aligns with the results of studies by Yamda et al and Jousilathi et al, both of which demonstrated a positive association between serum GGT levels and hypertension.[17,18]

The potential link between serum GGT levels and atherosclerosis was also explored, with findings suggesting that GGT might be a risk factor for stroke independent of alcohol consumption. Our study also reported the association between serum GGT levels and dyslipidemia, revealing a statistically significant difference in GGT levels between dyslipidemic and non-dyslipidemic patients. Finally, the study explored the relationship between stroke type and serum GGT levels, revealing no statistically significant correlation. While ischemic stroke exhibited a mean serum GGT level of 45.35 U/l, non-ischemic stroke (comprising intracerebral hemorrhage and subarachnoid hemorrhage) demonstrated a slightly higher mean GGT level of 61.86 U/l. This finding deviates from the Eurostroke project, which suggested a more pronounced association between elevated serum GGT levels and hemorrhagic stroke compared to cerebral infarction.[13]

Limitations

There are several limitations to this study. Firstly, the study design is an observational case-control study, whereas most research indicating serum GGT as a risk factor for stroke involves prospective studies that follow a cohort over several years to observe stroke incidence. Additionally, serum GGT levels may increase in post-stroke patients in cerebrospinal fluid. Secondly, the sample size is relatively small, comprising only 50 cases and 50 controls, which can influence the results. Thirdly, the diabetic and hypertensive patients included in the study are known to have these conditions but may or may not be taking their prescribed medications, which could affect the findings. Lastly, alcoholic patients were excluded based solely on their self-reported history, which may lead to underreporting and influence the study's outcomes.

CONCLUSION

In conclusion, our study findings indicate that elevated serum GGT levels are associated with an increased risk of stroke, particularly in male patients and those with hypertension, dyslipidemia, and diabetes. Further prospective studies are needed to establish the predictive value of GGT for stroke.

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