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Association Between Acute Ischemic Stroke and Raised Serum Gamma Glutamyl Transferase

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ABSTRACT

The serum gamma-glutamyl transferase level predicts the development of cardiovascular illnesses. Serum gamma-glutamyl transferase levels have been linked to atherosclerosis in several investigations, indicating that gamma-glutamyl transferase may be utilized as an early indicator of atherosclerosis. **Objective:** To determine the association between acute ischemic stroke and raised serum gamma-glutamyl transferase. **Methods:** After obtaining ethical approval, in this case-control study, 310 patients fulfilling the selection criteria were included from the Medical Emergency Department of, KEMU/ Affiliated hospital, Lahore from August 2022 to February 2023. Informed consent was obtained. After matching for age (40-80 years) and gender (both male and female), 155 controls enrolled preferably the accompanying healthy attendants of the patients and 155 cases i.e. ischemic stroke patients. Venous blood samples were obtained from cases at the time of presentation in the Emergency Department for serum gamma-glutamyl transferase (GGT). Data was collected in structured proforma. Data scrutiny was done using SPSS version 26.0. Mean and standard deviation were used for quantitative variables and frequency for qualitative data. Data were stratified for effect modifiers, and $p \leq 0.05$ was taken as significant. **Results:** In the current study, the frequency of raised GGT was found more among cases as compared to controls i.e. 74% vs 20%, $p<0.00001$ and OR calculated was 11.5. **Conclusions:** It was concluded that a considerable percentage of patients had raised gamma-glutamyl transferase at the time of presentation with acute ischemic stroke. These results emphasize the need to keep an eye on GGT levels in ischemic stroke patients as a possible stroke marker.

INTRODUCTION

Stroke/cerebral vascular accident (CVA) remains the primary cause of disability and death worldwide. Hemorrhagic and ischemic strokes are its two forms. Just 20% of strokes are hemorrhagic, caused by blood vessel rupture, while the majority of strokes 80% are ischemic, due to disruption in blood supply to the brain caused by atherosclerosis/thrombosis [1, 2]. The most significant risk factors for CVA include being male, smoking, dyslipidemias, advanced age, diabetes (DM) and hypertension (HTN). There are other risk factors as well [3, 4]. Clinicians may be able to identify patients who are more likely to have a stroke and schedule early preventive therapies with the aid of risk factor identification [1]. It has long been believed that raised gamma-glutamyl transferase (GGT) is a sign of alcohol consumption and hepatobiliary dysfunction [5]. Cellular membrane-bound

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GGT protein promotes intracellular uptake of peptides and amino acids. It is essential for extracellular glutathione that is produced during regular metabolic activities to be absorbed within the cell, shielding it from oxidative damage. To restore normal glutathione levels, production of GGT is stimulated when oxidative stress lowers intracellular glutathione levels. On the other hand, during times of elevated oxidative stress, increased requirement for glutathione combined with inadequate glutathione availability causes oxidative stress to negatively impact cells [6]. According to recent research, GGT actively participates in oxidative and inflammatory pathways that lead to atherosclerosis. Atherosclerosis, cardiovascular disease, and stroke are all facilitated by oxidative stress, which also causes vascular damage and endothelial dysfunction [7]. Serum GGT levels and frequency of stroke are positively correlated, according to numerous research [8-10]. It makes GGT an affordable and easy addition to the list of accessible tests beneficial in primarily stratifying patient risk. According to one recent study, raised GGT, is related to a higher risk of CVA, irrespective of liver disease [11]. Within 24 hours of presentation, patients with ischemic stroke had considerably higher GGT levels, according to another study [12]. Further supported by another study, that raised GGT was found to be a potential risk factor for stroke [13]. Despite the well-established risk factors for ischemic stroke, there remains a need for additional biomarkers that can enhance early risk stratification and improve clinical outcomes. Recent studies suggest that elevated GGT, which may also be implicated in atherosclerosis, is a key contributor to ischemic stroke. However, the potential of GGT as a predictive biomarker for AIS has not been fully explored.

This study aimed to address this gap by investigating the association between elevated serum GGT levels and acute ischemic stroke (AIS), to identify a novel marker that could facilitate earlier intervention and reduce the burden of stroke.

METHODS

This case-control study was done at the Emergency Department, of Mayo Hospital, Lahore over a six-month duration i.e. August 2022 to February 2023 after the acceptance of a proposal from Child Protection & Safeguarding Policy (CPSP) (Ref No: CPSP/REU/MED-2020-066-16551). 310 (155 in each group) selected via non-probability consecutive sampling and the sample size was calculated, by using a 5% significance level and 80% power of the study, the prevalence of raised GGT in groups with and without ischemic stroke was 28.8% vs 16.9% [11]. Data were collected in structured proforma containing background information. Patients 40-80 years of either gender presented with first ever episode of acute ischemic stroke as determined by history and CT scan within the last 24 hours (cases) and healthy attendants of patients without a history of cardiovascular disease (controls) Patients with recent surgery or trauma, any liver disease, those with history of alcoholic intake, creatinine >1.4 mg/ dl and with history of previous stroke were excluded. Venous blood samples were taken from cases and controls at presentation in emergency for Serum GGT. Patients with serum GGT level >27 IU/ ml were labelled as having raised GGT. Data were analyzed using SPSS version 26.0. Mean and SD were computed for quantitative variables and categorical variables were presented with frequency and percentage. OR calculated to check the association. Data stratified for effect modifiers age, gender, and DM. Post-stratification chi-square test calculated. Taking p-value<=0.05 is taken as significant.

RESULTS

There were more male patients in both groups i.e. 99 (64%) and 109 (70%) male vs 56 (36%) and 46 (30%) females in the case and control groups, respectively. In the case group, 50 (32%) patients and in the control group 23 (15%) were found to be diabetics. 35% were current smokers in the case and 19% in control group. 45% of cases and 22% among controls were found to have dyslipidemia. The mean age calculated was 55.41 + 9.17 years and 50.21 + 9.17 years among cases and controls, respectively and also exhibits that among cases 75 (48%) and in the control group 105 (68%) patients belong to age group <55 years and 80 (52%) in the case and 155 (100%) in control group belong to age >/=55 years (Table 1).

Table 1: Sociodemographic Characteristics of Study Groups

Variables	Case n=155	Control n=155
Age		
<55 years	75 (48%)	105 (68%)
>/=55 years	80 (52%)	50 (32%)
Total	155 (100%)	155 (100%)
Age (mean ± SD)	55.41 ± 9.17	50.21 ± 9.17
Gender		
Male	99 (64%)	109 (70%)
Female	56 (36%)	46 (30%)
Total	155 (100%)	155 (100%)
Diabetes Mellitus		
Yes	50 (32%)	23 (15%)
No	105 (68%)	132 (85%)
Total	155 (100%)	155 (100%)
Current Smokers		
Yes	55 (35%)	30 (19%)
No	100 (65%)	125 (81%)
Total	155 (100%)	155 (100%)
Current Smokers		
Yes	70 (45%)	35 (22%)
No	85 (55%)	120 (78%)
Total	155 (100%)	155 (100%)

The mean and SD of GGT i.e. 41.35 + 9.65 and 27.66 + 7.32 among cases and controls, p <0.0001 i.e. significant (Table 2).

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Table 2: Comparison of Descriptive Distribution of GGT Among Groups

GGT	Case n=155	Control n=155	p-value
Mean	41.35	27.66	<0.0001
SD	9.65	7.32	

The study showed a significantly raised frequency of raised GGT among cases as compared to controls i.e. 74% vs 20%, p<0.00001 and OR calculated was 11.5 (Table 3).

Table 3: Comparison of Frequency of Raised GGT among Case and Control Groups

Raised GGT	Case n=155	Control n=155	Total	p-value	Odds Ratio
Yes	115 (74%)	31 (20%)	146	<0.00001	11.5
No	40 (26%)	124 (80%)	164		
Total	155	155	310		

Data stratified for age, gender, and DM for raised GGT and compared among groups, showing statistically significant results i.e. p</= 0.05 for all stratified groups (Table 4).

Table 4: Data Stratification Concerning Effect Modifiers

DM	Raised GGT		p-value	Chi-Square
	Yes	No		
Yes				
Case	46	4	0.004	8.22
Control	15	8		
No				
Case	69	36	<0.00001	73.02
Control	16	116		
Age (Years)	Raised GGT		–	–
	Yes	No		
<55				
Case	40	35	<0.00001	41.85
Control	10	95		
>55				
Case	65	15	<0.00001	39.13
Control	13	37		
Gender	Raised GGT		–	–
	Yes	No		
Male				
Case	65	34	<0.00001	69.07
Control	11	98		
Female				
Case	50	6	<0.00001	42.31
Control	12	34		

DISCUSSION

According to the results of the current study, among cases 48% of patients and in the control group 68% of patients aged <55 years and 52% in case and 100% in control group aged >/=55 years. There were more male patients in both groups. In the case group 50 (32%) patients and in the control group 23 (15%) were found to be diabetic. 35% were current smokers in the case and 19% in the control group. 45% of cases and 22% among controls were found to have dyslipidemia. Furthermore, current results have shown significantly more frequency of raised GGT among cases as compared to controls i.e. 74% vs 20%, p<0.00001 and OR calculated was 11.5. Similar to the current study, one local study conducted has recently found to have high rates of hypertension (58%), dyslipidemia (26%), DM (34%), smoking (21%), ischemic heart disease (36%), obesity (19%), and other risk factors for stroke [14]. Previous studies have supported current study results, that increased frequency of raised GGT found in ischemic stroke patients, suggesting a possible relationship between GGT and cerebrovascular risk factors [15, 16]. In one previous study by Kalirawna *et al.*, unlike our results, no significant variance was found in age groups (p=0.741) or gender (p=0.1018) between case and controls. However, similar to our results, diabetes was notably higher in stroke patients compared to controls p=0.005 and an independent sample t-test revealed a significant difference in serum GGT levels between cases and controls [13]. According to current study results, GGT levels were found to be high among cases vs controls i.e. 41.35 + 9.65 vs 27.66 + 7.32urre, p<0.0001. Our results, further supported by another study by Ismail *et al.*, 2023, in which serum GGT level in case population noticed was 58.30 (U/L), and in the control group 17.48 (U/L) p-value<0.001 and implies increased level of serum GGT level in stroke patients [15]. Another Korean study by Lee *et al.*, found that higher serum GGT levels were found to be autonomously linked to the development of stroke in future [17]. According to a study by Gurbuzer *et al.*, patients with ischemic CVA with substantially greater regions of infarction had significantly higher mean GGT levels (p<0.05) [18]. However, the current study has not quantified the area of infarct. In another study by Korantzopoulos *et al.*, the proportion of ischemic CVA patients who showed up with elevated GGT levels (>27 IU/L) was higher than that of the control group. Individuals in the highest quartile of GGT levels had a 4.7-fold higher chance of having ischemic CVA (p<0.001) as compared to those in the lowest quartile. Even after adjusting for all possible confounding variables, this link held significance [19]. In contrast to the current study, however, Yang *et al.*, found that raised GGT levels in ischemic CVA patients were not linked with large-artery atherosclerosis stroke but with cardioembolic stroke [20]. However, in the current study, we have not studied the aetiology of ischemic stroke and have not divided our population to compare GGT levels. The current study has certain limitations, we have not studied stroke characteristics in detail, including infarct size. Further research will be needed in this area with a large sample size, including multi-centres to increase the generalizability of results.

CONCLUSIONS

It was concluded that higher GGT levels were found to be significantly associated with acute ischemic stroke as

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compared to the control group, reinforcing the relationship of raised GGT with acute ischemic stroke. This makes GGT, a potentially beneficial addition to an expanding panel of clinically available diagnostics that can be used to help with patient risk initialization.

Authors Contribution

Conceptualization: SK
Methodology: SK, QY, AJ, IUDYB, MUT, FR, UA, UH
Formal analysis: SK, WA, MQ
Writing review and editing: SK, QY, AJ, WA, IUDYB

All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

The authors declare no conflict of interest.

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REFERENCES

[1] Murphy SJ and Werring DJ. Stroke: causes and clinical features. Medicine. 2020 Sep; 48(9): 561-6. doi: 10.1016/j.mpmed.2020.06.002.

[2] Saini V, Guada L, Yavagal DR. Global epidemiology of stroke and access to acute ischemic stroke interventions. Neurology. 2021 Nov; 97(20_Supplement_2): S6-16. doi: 10.1212/WNL.0000000 0000012781.

[3] Alawneh KZ, Al Qawasmeh M, Raffee LA, Abuzayed B, Hani DA, Abdalla KM *et al.* A snapshot of Ischemic stroke risk factors, sub-types, and its epidemiology: Cohort study. Annals of Medicine and Surgery. 2020 Nov; 59: 101-5. doi: 10.1016/j.amsu.2020.09.016.

[4] Sarfo FS, Ovbiagele B, Akpa O, Akpalu A, Wahab K, Obiako R *et al.* Risk factor characterization of ischemic stroke subtypes among West Africans. Stroke. 2022 Jan; 53(1): 134-144. doi: 10.1161/STROKEAHA.120.032072.

[5] Imam YZ, Chandra P, Singh R, Hakeem I, Al Sirhan S, Kotob M, Akhtar N, Kamran S, Al Jerdi S, Muhammad A, Haroon KH. Incidence, clinical features, and outcomes of posterior circulation ischemic stroke: insights from a large multiethnic stroke database. Frontiers in Neurology. 2024 Feb; 15: 1302298. doi: 10.3389/fneur.2024.1302298.

[6] Brennan PN, Dillon JF, Tapper EB. Gamma-Glutamyl Transferase (γ-GT)–an old dog with new tricks?. Liver International. 2022 Jan; 42(1): 9-15. doi: 10.1111/liv.15099.

[7] Jeon J, Kim DH, Kim W, Choi DW, Jung KJ, Jang SI. Dose-response relationship between gamma-glutamyltransferase and the risk of atherosclerotic cardiovascular diseases in Korean adults. Atherosclerosis. 2020 Jan; 292: 152-9. doi: 10.1016/j.atherosclerosis.2019.11.004.

[8] Li S, Wang A, Tian X, Zuo Y, Meng X, Zhang Y. Elevated gamma-glutamyl transferase levels are associated with stroke recurrence after acute ischemic stroke or transient ischemic attack. Central Nervous System Neuroscience & Therapeutics. 2022 Oct; 28(10): 1637-47. doi: 10.1111/cns.13909.

[9] Corti A, Belcastro E, Dominici S, Maellaro E, Pompella A. The dark side of gamma-glutamyltransferase (GGT): Pathogenic effects of an 'antioxidant'enzyme. Free Radical Biology and Medicine. 2020 Nov; 160: 807-19. doi: 10.1016/j.freeradbiomed.2020.09.005.

[10] Neuman MG, Malnick S, Chertin L. Gamma glutamyl transferase–an underestimated marker for cardiovascular disease and the metabolic syndrome. Journal of Pharmacy & Pharmaceutical Sciences. 2020 Apr; 23: 65-74. doi: 10.18433/jpps30923.

[11] Ruban A, Daya N, Schneider AL, Gottesman R, Selvin E, Coresh J *et al.* Liver enzymes and risk of stroke: the atherosclerosis risk in communities (ARIC) study. Journal of Stroke. 2020 Sep; 22(3): 357. doi: 10.5853/jos.2020.00290.

[12] Rathor E, Arasada C, Kulkarni A, Shaikh MA. Study of Serum Gamma-Glutamyl Transferase Levels in Patients With Acute Ischemic Stroke. Cureus. 2024 Jul; 16(7): e65336. doi: 10.7759/cureus.65336.

[13] Kalirawna TR, Rohilla J, Bairwa SS, Gothwal SK, Tak P, Jain R. Increased concentration of serum gamma-glutamyl transferase in ischemic stroke patients. Brain Circulation. 2021 Apr; 7(2): 71-6. doi: 10.4103/bc.bc_47_20.

[14] Aslam F, Maqsood A, Rauf A, Nawaz K, Aslam A. Frequency of risk factors for stroke in young Pakistani population. Pakistan Journal of Neurological Sciences. 2023 Dec; 18(04): 24-30. doi: 10.56310/pjns.v18i04.294.

[15] Ismail QM, Prasad MK, Marandi S, Guria RT, Dungdung A. Serum gamma-glutamyl transferase level as a risk factor in acute stroke. Journal of Family Medicine and Primary Care. 2023 Dec; 12(12): 3172-9. doi: 10.4103/jfmpc.jfmpc_750_23.

[16] Kim K, Jung H, Di Giovanna E, Jun TJ, Kim YH. Increased risk of ischemic stroke associated with elevated gamma-glutamyl transferase level in adult cancer survivors: a population-based cohort study. Scientific Reports. 2023 Oct; 13(1): 16837. doi: 10.1038/s41598-023-43839-8.

[17] Lee SM, Ha E, Ryoo JH. Serum gamma-glutamyltransferase levels predict the development of cerebral infarction in the Korean population. Neuropsychiatric Disease and Treatment. 2021 Aug;

DOI: https://doi.org/10.54393/pjhs.v5i09.2031

17: 2749-56. doi: 10.2147/NDT.S326450.

[18] Gurbuzer N, Gozke E, Ayhan Basturk Z. Gamma-glutamyl transferase levels in patients with acute ischemic stroke. Cardiovascular Psychiatry and Neurology. 2014 Aug; 2014(1): 170626. doi: 10.1155/2014/170626.

[19] Korantzopoulos P, Tzimas P, Kalantzi K, Kostapanos M, Vemmos K, Goudevenos J *et al*. Association between serum γ-glutamyltransferase and acute ischemic nonembolic stroke in elderly subjects. Archives of Medical Research. 2009 Oct; 40(7): 582-9. doi: 10.106/j.arcmed.2009.07.012.

[20] Yang W, Kang DW, Lee SH. Effects of gamma-glutamyl transferase on stroke occurrence mediated by atrial fibrillation. Journal of Clinical Neurology. 2020 Jan; 16(1): 60-5. doi: 10.3988/jcn.2020.16.1.60.