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Original Article

Relationship between Ischemic Stroke and Raised Gamma Glutamyl Transferase

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Abstract

Objectives: To demonstrate the relation between stroke due to vascular insufficiency and elevated serum Gamma-glutamyl transferase.

Methods: In this research 390 individuals were studied, 195 cases were patients who had first-ever event of acute ischemic stroke within a day. Remaining 195 were controls who were healthy individuals who accompanied the patients (within ± 5 years and of same sex). Frequency of raised GGT was compared between both groups.

Results: Out of this sample of 390 patients 88 (22.6%) had elevated GGT. 26.7% of patients (cases) and 18.5% subjects (controls) had raised GGT (p value greater than 0.05). Odds ratio was 1.44 ((at 95% CI, 0.992 to 2.103). Sex, age, smoking, BMI did not change outcome.

Conclusion: Hence we conclude that ischemic stroke and increased GGT has no association with each other.

Keywords: GGT, Ischemic stroke, CVA, Cardiovascular disease.

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Introduction

There is an ever rising socio-economic burden due to the increased morbidity and mortality associated with stroke particularly in older generations.[1,2] The determination of high risk factors may aid the doctors to prioritize patients who are at an enhanced risk.[3,4] Serum GGT is an important enzyme that is elevated in liver dysfunction and excessive alcohol intake. Research has shown that GGT may be a causative factor of CVD entailing stroke.[1,2,5]

Studies have shown that GGT causes atherosclerosis through oxidative and inflammatory mechanisms. GGT provides GTH (antioxidant) to the cells and thus it causes oxidative stress

Rationale of this study is that there is no local published literature available showing its association with stroke. In a study the number of stroke patients that had elevated GGT levels were higher than controls (28.8% v/s 16.9%). Patients with highest quartile of GGT levels had a 4-4.[5] times increased risk of developing ischemic stroke (95% Confidence Interval 2.39-9.11, p<0.001) This study will aid clinicians to identify patients at greater risk for ischemic stroke so that they can be managed better. Present study aimed to demonstrate the connection between elevated GGT and ischemic stroke.

Methods

This research was an observational study carried out at the Medical Emergency Department, Lahore General Hospital, Lahore. It was conducted for six months from 24th May to 30th Nov 2020. It was a Non-probability/ purposive sampling. At 95 % confidence interval and 80% power of study, taking frequency of raised GGT in groups with and without ischemic stroke 28.8% vs 16.9%,6 required sample size is 390 (195 in each group)

Inclusion Criteria

1. **Adults :** forty to eighty years
2. **Both genders:** men and women.
3. **Cases:** were patients who had first episode of ischemic stroke in lifetime presenting within one day
4. **Controls:** were healthy individuals without

history of CVD i.e. IHD, stroke and PVD and of same gender and age.

Exclusion Criteria

1. Recent surgery or trauma
2. Acute or Chronic liver disease determined by abnormal ALT and ultrasound.
3. Drug/alcohol abuser
4. Chronic kidney disease
5. Recurrent stroke

Operational Definition

Stroke is a medical emergency in which blood supply to the brain is temporarily or permanently interrupted resulting in diminished supply of Oxygen and nutrients to the brain cells which may result in cell death. If the focal neurological findings appear acutely it is termed as acute stroke while stroke that lingers on for more than six months is called chronic stroke.

GGT is an enzyme that is found in many organs of the body with particularly high content in liver. The normal range of GGT is 0-30IU/L. Level above 30IU in blood is considered abnormal and depicts liver disease. It is believed that elevated levels of GGT may have a strong association with stroke.

195 consecutive cases with ischemic stroke presenting to emergency department of Lahore General Hospital were enrolled in the study. Purpose of study was explained and consent was taken from all patients. 195 healthy attendants of patients of same age and gender were taken as controls. This was followed by CT brain and confirmation of diagnosis. Aseptic measures were taken and blood sample was taken from patients at the time of presentation. With the help of standard chemical analyzer serum GGT was measured. Data obtained was structured in performa along with information such as age, gender and elevated GGT. Additionally elevated HbA1c risk factors like smoking and derranged lipids was also reported. Data was analyzed using SPSS version 25. Mean with standard deviation was measured for age and serum GGT. Frequency and percentages of gender, raised GGT were calculated. Odds ratio was measured in both groups. Chi square test was applied. P value <.05 was taken as note able.

Results

In this study, 390 patients were taken ranging from 40 to 70 years with mean age of 53.68 ± 9.47.

277 patients (58.2%) taken in the study were less than 55 years while 163 (41.8%) were either 55 years or more in age.

288 patients (73.8%)in study sample were men and 102 (26.2%) were women.

Sampled population (n=390) were equally distributed between case and control groups.

88 (22.6%) patients from sample size of 390 had elevated GGT.

62 subjects (15.9%) had HbA1C level beyond 7% while 328 patients (84.1%) had it equal to or below 7%.

Most of the 390 population, that is 363 patients (93.1%) were non-smokers while 21 patients (6.9) were smokers at the moment

Only 59 patients (15.1%) were found to have deranged Lipid profile.

When we cross tabulated raised GGT and study groups (cases and control) and applied chi square test it was found that there was equal distribution of elevated GGT among cases and controls (26.7% v/s 18.5%).

Upon stratification of raised GT with gender, non-significant results (p=0.130) were found in males (cases and controls) and similar result was established in female patients. (p=0.246) cases and controls.

Upon stratification of GGT with age group, patients with age below 55 years(cases and controls) showed up non-significant results (p=0.155) and similar results were seen in age group above 55 years (p=0.053) (cases and controls)

On stratification of sample population (cases and controls) with HbA1c>7% and elevated GGT, non-significant results (p=0.644) was found.

Similar non-significant result was obtained upon stratification of cross tabulated sample group with current smokers (p=0.596).

There was no patient with dyslipidemia found to have elevated GGT

Discussion

GGT is found in cytosol and cell membrane. Glutathione is the major substrate. During stress the level of intracellular glutathione decreases which causes the formation of GGT enzyme to sustain its levels. The requirement of glurtathione increases with increase in oxidative stress and its deficiency results in more devastating effects.

In this study, cases (26.7%) and controls (18.5%) had elevated GGT. This shows that there is a more likely higher frequency of elevated GGT in patients with first episode ishaemic stroke. The result was reinforced by previous studies. In a study, percentage of raised GGT levels (>27IU/L) in stroke patients was greater than controls (28.8% vs. 16.9%).

According to previous theory, oxidative stress and related decrease in glutathione levels induce activity of GGT. Independent of alcohol consumption and presence of a liver disease, the predictive role of GGT activity in the development of new cases of diabetes, hypertension, and ischemic stroke has been established.[8–12]

The Vorarlberg Health Monitoring and Promotion Program (VHM&PP) study conducted by Ruttmann et al has investigated the association between GGT and cardiovascular mortality. In this study association between GGT levels and cardiovascular mortality in both female and male was discovered. In this study, the correlation between GGT and cardiovascular disease was observed, but no significant data demonstrating the correlation between GGT levels and stroke (both hemorrhagic and ischemic types) could be obtained statistically. In another study GGT levels were raised in the ischemic stroke group as compared to the control group. Anyway, there was not much difference in the distribution of raised GGT values in either gender.

D'Ambrosio et al..and Korantzopoulos et al. discovered positive correlation between serum gamma-glutamyl transferase and functional impairment in elderly after acute ischemic. The association between oxidative stress and development of stroke has already been known. Hence, the association between oxidative stress, subclinical inflammation and GGT can result in the development of stroke.

In previous study, higher GGT levels were detected in the acute ischemic stroke group in comparison to the control group. Also there were raised levels of GGT in cases with hypertension, increased LDL-cholesterol, and triglyceride levels which indicate the role of oxidative stress. It has also been observed positive relationship between the size of lacunar infarct and elevated GGT.

But contrary to earlier studies, the difference in result was non-significant (p value > 0.05). Odds ratio came out to be 1.44 and ranged from 0.992 to 2.103 (at 95% Confidence interval). This proves that raised GGT was equally distributed between cases and controls.

Limitation of current study includes

- A small sample size for a relatively common phenomenon
- Consecutive non probability sampling leading to non-generalization of results
- A single center study and population presenting here are not representative

There are two major types of stroke:

- Thromboembolic Stroke also referred as ischaemic stroke due to thrombosis, embolism, or systemic hypo-perfusion
- Hemorrhagic Stroke which may result due to intracerebral or subarachnoid hemorrhage.

Ischemic cerebral infarction accounts for almost 80 percent of strokes while remaining 20 percent may be due to cerebral hemorrhage. Another cause of stroke is due to venous stasis due to occlusion of veins that drain the blood of brain. Blood disorders may also lead to stroke but are not a common source. Stroke might also ensue due to embolism resulting from thrombosis formed due to increased coagulability.

Atherosclerosis is the most common cause of ischemic stroke followed by vasoconstriction (eg, with migraine)

Blood supply through arteries is dependent on various factors including blood pressure, blood viscosity and collateral flow.

Microatheromas can block small penetrating arteries called atheromatous branch disease).[7]

Symptoms of stroke depend upon the area rendered ischemic[8]. The source and composition of embolus determines the treatment and outcome.

Studies have shown that complex aortic atherosclerosis causes recurrent stroke.[9,10]

In authors opinion, large protruding and mobile plaques in the ascending aorta and arch are a significant cause of stroke.[11]

The most common causes of ICH are prolonged elevated blood pressure, injury, bleeding disorder, drug abuse (mostly amphetamines and cocaine), and vascular malformations.[12]

Symptoms of SAH are sudden as compared to ICH which has a gradual onset. Onset headache and vomiting occurs in hemorrhagic stroke and is less common ischemic stroke.[13]

The rate of cerebral blood flow depends on the diameter of the blood vessels14 which determines the resistance offered to the blood to flow in the blood vesels. The smooth muscle in cerebral vessels and the endothelial cells that release nitric oxide also seem to play a role in auto-regulation. Cerebral auto-regulation is hampered in ischemic stroke.[14,15] Patients who have persistent elevated blood pressure, auto-regulation takes place at higher arterial pressure.

Brain ischemia finally results in cell death. It causes exhaustion of energy in the form of ATP, intracellular accumulation of Oxygen free radicals and water, changes in the concentration of Na, K, Ca and lactate, acidosis and activation of proteolysis. ROS damage cellular components where WBCs migrate and release cytokines to attract additional cells.

Brain ischemia initiates a series of events that result in

the death of cell, this includes exhaustion of energy in the form of ATP, alterations in the concentrations of Na, K, Ca, pH, and accumulation of oxygen free radicals and water inside cells, all of this culminating in the activation of proteolysis.[16] ROS can react with and destroy cellular components. Inflammation results in the migration of WBCs to damaged tissue which results in the release of cytokines and further attracts inflammatory cells. In severe conditions cytokine level might reach to toxic levels.[17]

In genome-wide association studies (GWAS) it was established that three loci (PITX2, ZFHX3, and HDAC9) have significance for ischemic stroke.

Another factor that might be associated with stroke is ethnicity. For example, Africans are more prone to stroke than Caucasians. A study of 1398 individuals with sickle cell anemia was conducted and twelve genes appeared to interact with the mutated hemoglobin and controlled the risk of stroke.[18]

Patients suffering from a stroke might present with other illnesses as well, hence, a broad preliminary assessment is required.[19]

Early diagnosis of ICH or SAH can be life saving.[19]

Hyperglycemia results in poor functional outcome.[20]

Many reports suggest that cerebral blood perfusion is maximum when patient is in a lying position[29]. Hence it is advised for non-hypoxic patients to lay supine because intracranial flow velocity is maximum at this position.[21]

Conclusion

It is proved from the study that there is no association between elevated GGT and ischaemic stroke(Null Hypothesis) as the frequency of raised GGT between cases and controls was almost same. Odds ratio turned out to be 1.44 ((at 95% CI, 0.992 to 2.103).

Conflict of Interest None

Funding Source None

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