Original Article

SERUM GAMMA GLUTAMYLTRANSFERASE AND THE RISK OF STROKE IN CHRONIC EXCESS ALCOHOLISM

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ABSTRACT

Background : Stroke continues to be the major public health problem. It ranks in the top four causes of death in most countries and is responsible for the large proportion of neurological disorders. More often disabling than fatal stroke is the leading cause of severe neurological disability. It results in enormous costs measured in both health-care expenses and lost productivity which is vital for a nation especially India where 12 percent of stroke cases are below 40 years of age (stroke in the young) with a case fatality rate of 1 percent. **Aim and Objective:** The aim is to analyze serum gamma glutamyltransferase (GGT) activity and Low Density Lipoprotein (LDL) concentration to achieve the objective of predicting the risk factors for stroke in chronic excess alcoholism. **Materials and Methods:** This is an age and sex matched comparative study. The study population includes two groups; group 1 consists of 50 persons with self- reported, chronic, regular excess alcohol intake (greater than 400g per week which approximately equal to 1400ml of brandy per week or just 200 ml per day) ; group 2 consists of stroke patients who have been taking alcohol similarly. Serum GGT and LDL were estimated and compared by Student's t-test and Pearson's correlations between the two groups. **Results:** The mean value of serum GGT and LDL were significantly increased in cases compared to the controls with p value 0.001 (GGT) and 0.021 (LDL). **Conclusion:** Chronic alcoholism increases the risk of stroke. Self-reporting of alcohol drinking under-estimates the true risk. Thus the use of GGT- the biological marker of alcohol drinking is a helpful tool for risk assessment. Excessive intake of alcohol, raised GGT level and increased LDL-cholesterol compound the risk for stroke.

Key words: Alcohol, Stroke, Cerebrovascular disease, Gamma glutamyltransferase, Low density lipoprotein.

INTRODUCTION

Serum gammaglutamyltransferase (GGT) activity is a low cost, highly sensitive laboratory test. Though it is currently considered as an index of hepato-biliary dysfunction and alcohol abuse, pathology studies have indicated it's possible role in the pathogenesis of atherosclerosis[1]. Furthermore epidemiology studies on a total of 218,561 subjects from unselected population or cohorts with ascertained disease have proven the role of GGT not only in predicting mortality but also the clinical evolution of cerebro-vascular and cardio-vascular diseases like stroke and myocardial infarction independently from the occurrence of hepatic disease, alcohol consumption and established risk factors in multivariable analysis. These data were further confirmed by another large epidemiological study involving 163,944 volunteers, confirming the predictive value of serum GGT activity on events like haemorrhagic and ischaemic stroke. This is found to be true in both genders with a clear dose-response relationship and with a stronger

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(from 1.5 to 2 fold) prognostic significance in participants less than 60 years.

The Euro-stroke analysis showed that risk of haemorrhagic stroke increase linearly with increase of GGT beyond the first quartile and it remain increased thereafter[2] and at high levels of GGT it is also independent of hypertension.[3] In cerebral infarction GGT level increase as a result of brain damage and this increment may be considered as a clinical and prognostic unfavourable index.[4] Moreover high elevations also seen in CSF which predict a poor outcome as a result of ischaemic stroke.[5] Large retrospective studies indicate that increased GGT activity are independently associated with more atherogenic lipid profile in the general population.[6] Recent studies have shown GGT is correlated highly and significantly with the components of metabolic syndrome. So elevated levels of GGT may not always indicate increased alcohol consumption, but may also suggest the existence of metabolic syndrome – a sure risk factor of atherosclerosis.[7] Studies of the impact of GGT on vascular diseases shows that GGT is associated with incident vascular events independently of alcohol intake as it plays one of the triggering effect in oxidative stress, however the underlying mechanism is unknown,[8] as for as vascular events are concerned and require future study.

Heavy alcohol consumption is an important, un-recognised and independent risk factor of stroke in men and GGT as a biological marker of alcohol increased with increasing age until 70 years.[9] Studies indicate that GGT activities respond to ethanol intake in an age dependent manner, which should be considered in the clinical use of GGT measurement for detecting alcohol-use disorders.[10] It has been shown that BP level as well as prevalence and incidence of hypertension are higher in persons with serum GGT above normal than in normal controls.

This difference is more marked in persons who consume 30 ml or more alcohol per day. Thus elevated serum GGT may identify drinkers at higher risk for the development of alcohol - related hypertension and stroke.[11] Studies have concluded that initial level of GGT, after 36 and 72 hours reflect cerebral damage which may alert physicians not to attribute all unexplained high levels of GGT in stroke to alcohol.[12] There have also been important advances in the definition of the associations between serum GGT and conditions such as stroke and myocardial infarction that can be explained by oxidative stress along with other established risk factors. People with high serum GGT have higher mortality because it is an independent predictor of risk.[13]

This study aims to summarize the knowledge about clinical applications of GGT with regard to stroke with regular, excess intake of alcohol and to assess how far these studies can be combined into an integrated one. Alcoholism has been defined as the repeated ingestion of alcohol resulting in dependency, disease or harm. Dependency: It is characterized by drink orientated behaviour, tolerance to the cerebral effects of alcohol, continued drinking despite harm and withdrawal symptoms with abstinence. Excess alcohol consumption: It may be considered as regular alcohol intake at levels at which there is a high risk of harm particularly from organ injury. Where such intake is accompanied by actual harm the terms 'harmful drinking' or 'alcoholism' may be used (syn.alcohol abuse). A plasma level of ethanol

between 250 to 300 mg per 100 ml is termed intoxication. There is a high risk of harm from alcohol intake greater than 400g per week[14] which approximately equal to 1400ml of brandy-just 200ml per day. This approximation holds good for a genuine brand and if the drink is adulterated there is still more danger. By pharmacological definition alcohol is a drug and may be classified as a sedative, tranquilizer, hypnotic or anaesthetic depending upon the quantity consumed. Off all the drug alcohol is the only drug whose self-intoxication is socially acceptable.

Over the past years increasing percentages of young people have started to drink alcoholic beverages and their alcohol consumption has increased in quantity and frequency and the age at which drinking starts has declined. This situation is disturbing because the young people concerned may run a greater risk of alcoholic problem in later life and also in the short term, increased involvement in road accidents. According to current concept alcoholism is considered a disease and alcohol - a disease agent. The health problem for which alcohol is responsible is only part of the total social damage it causes.[15] A national survey found that about 31.9% of men and 2.2% of women drink alcohol and about 9.9% of men drink alcohol everyday in India. The overall prevalence in our state is about 40% and these surveys had been taken during 2005-06.[16]

MATERIALS AND METHODS

This is an age and sex matched comparative study. The study population includes two groups; group 1 consists of 50, self- reported, chronic, regular and excess alcohol drinking persons; group 2 consists of stroke patients who have been taking alcohol similarly. The alcohol content of "drink" is taken into account rather than the type/brand of drink as there is high variation of type of 'drink' among the same individual. Cases and controls are included irrespective of age with due consideration of excess alcohol drinking- more than 400mg/week (about 200ml of brandy/day or 1400ml of brandy in a week) Brandy being the commonest alcoholic drink among the 'drinker' which is available commonly in the market.

Inclusion Criteria

1. Patients with stroke and
2. Chronic, excess intake of alcohol (1400ml of brandy/week or regular intake of 200 ml of brandy every day).

Exclusion criteria

1. Persons with liver disease
2. Patients taking drugs like Phenytoin, Fibrates, Barbiturates, Rifampicin and Oestrogen-containing contraceptives.
3. Patients with carcinoma prostate[17]
4. Patients who are not willing to give informed consent, however, are excluded from the study.

Confirmed stroke patients in the ward by clinical and MRI methods are included (cases). Persons with similar 'drinking' habits were selected in the same age group but without stroke (controls).

ETHICAL COMMITTEE APPROVAL:

The study was presented in the ethical committee, Stanley Medical College and formal approval was obtained.

SAMPLE COLLECTION AND ANALYSIS:

After taking informed consent from the patients and controls, they were selected by alcohol screening (vide infra) and a random venous blood sample of 5 ml was collected; the sample

centrifuged; serum separated and analyzed for the following;

1.Gamma glutamyltransferase (GGT),
2. Low-Density Lipoproteins (LDL)

ALCOHOL SCREENING QUESTIONNAIRE

A number of groups including the National Institute on Alcohol Abuse and Alcoholism (NIAAA), the US Preventive Task Force and The American Academy of Family Physicians reviewed the issue of screening and have recommended screening of adult and adolescent patients for problematic use of alcohol. The most effective method for detecting alcohol problems is to elicit an alcohol history by asking quantity and frequency questions in a routine manner and using a standardized screening questionnaire. Apart from routine screening the standardized questionnaire are CAGE (Cut-down, Annoyed, Guilty, Eye Opener) and AUDIT (Alcohol Use Disorder Identification Test). The cases and the controls have been screened first by the CAGE. Then a numerical scoring given by screening them by the AUDIT method. The AUDIT focuses on social and behavioural aspect of alcohol problem and provides greater accuracy than do frequency questions, lab test or clinical detection. More than 8 point: Positive for an alcohol use-disorder for both men women.

Measurement of GGT was done by the method of Rosalki & Tarlow, measuring the enzyme activity using spectrophotometer at 405nm. The LDL was measured directly by reagent kit for direct LDL-C assay (cholestest) was obtained from Deiichi Pure Chemicals Co. Ltd, Tokyo, Japan.

RESULTS AND STATISTICAL ANALYSIS

The total number of subjects included for the study was 100. Out of this 100, 50 were cases i.e. stroke patients with chronic, regular and excess intake of alcohol and 50 persons served as controls i.e. persons with similar intake of alcohol but without stroke.

The students 't' tests were used to find out the test of significance (p value) of both cases and controls in each age group and are presented in table 1 & 2 along with mean and standard deviation. Table 3 shows the GGT and LDL levels in cases and controls.

Table – 1 GGT levels in different age groups

Age Group	Test	Group	N	Mean	SD	'p' value
31-40	GGT(mg/dl)	Control	3	30.67	0.577	0.039
		Cases	3	37.33	3.786	
41-50		control	17	51.24	21.029	0.049
		cases	17	67.12	26.019	
51-60		control	22	51.95	24.285	0.028
		cases	22	70.91	30.678	
61-70		control	7	50.29	21.523	0.001
		cases	7	128.00	39.251	
More than 70		Control	1	144.00		
		Cases	1	162.00		

Table -2 LDL levels in different age groups

Age Group	Test	Group	N	Mean	SD	'p' value
31-40	LDL(mg/dl)	control	3	51.00	7.000	0.289
		cases	3	59.33	9.504	
41-50		control	17	75.88	33.134	0.220
		cases	17	92.35	43.000	
51-60		control	22	85.23	28.382	0.046
		cases	22	101.73	33.675	
61-70		control	7	92.57	27.122	0.583
		cases	7	101.00	28.787	
More than 70		control	1	103		
		cases	1	170		

Table -3

Variable	Study group		Control group		'p' value
	Mean	SD	Mean	SD	
GGT(mg/dl)	82.04	25.59	77.42	38.46	0.001
LDL (mg/dl)	97.26	37.55	81.38	29.94	0.021

DISCUSSION

The two groups have been compared of their chronic alcoholism by using GGT as a biological marker of alcohol intake. A significant relationship exists between the study and the control groups in all age groups (tables 1, 2 & 3 especially in the age group between 51-60). The retrospective studies on

possible association between alcohol intake and stroke have also revealed that heavy alcohol consumption is an important and under- estimated independent risk factor for stroke.[18]

Alcohol use is generally associated with an approximate dose dependent risk factor for stroke. and the activity of GGT is in an age dependent manner which is appreciable from table 1 & 2 as there is progressive increase of serum GGT with age. Older people who showed maximum elevations of GGT in both groups might have been started drinking at an early age and because of long duration of alcohol intake they showed maximum elevations. The long-term mortality among young stroke patients is mainly due to life-style factors such as high consumption of alcohol.[19]

Out of 50 patients in the study group 3 are in the age group between 31-40 (table 1 & 2) who constitute stroke in the young. In India out of all stroke cases, 12% are in the potential young age group. So a change of life-style would be the prime aspect in terms of primary prevention of stroke. It has been suggested that non-penetrating arterial trauma, haemoconcentration and hyper-coagulability are commonly associated with extensive drinking, which can result from prolonged neck posturing during drunken stupor.[20]

Even though there is no optimal single laboratory marker for alcohol consumption, the serum GGT level may reflect the usual drinking habits better than self-reporting.[21] In this study out of 50 study group, 27 cases have raised GGT levels, and in the control group, out of 50 persons, 14 have elevated GGT levels. From these observations it can be said that since these people (controls) also have been taking alcohol they are at possible risk of developing the disease. There exists a strong correlation between serum GGT and the LDL in both cases and controls. In both groups it shows significant associations (table 3 especially in the age group 51-60 (table 2). The non-significance of this association in other age groups could be due to lesser number of candidates taken up for the study. Retrospective studies also revealed that increased GGT activity is independently associated with a more atherogenous lipid profile in the general populations. Studies have revealed that one of the mechanism of association between GGT and LDL is that serum GGT is partially adsorbed onto the circulating LDL which can carry GGT activity inside the atheromatous plaques. Moreover active GGT is co-localized with oxidized LDL and free iron is present at levels sufficient to catalyse LDL oxidation[22]

Studies have shown that intake of more that 2 drinks (60 ml) per day may be associated with higher risk of ischaemic stroke.[23] and consumption of more than 60g of alcohol (140 ml) per day is associated with an increased risk of ischaemic as well as haemorrhagic stroke.[24] In this study both cases and control persons have been taking alcohol enough to be remaining at-risk status.

In India on the whole 31.9% of men and 2.2% of women consume alcohol. The corresponding figure in our state is 41.5% and 0.1% respectively. Among them it is the younger generation- in the age group between 20-34 and 35-49 who are active drinkers. 7% of men and 13.1% of women drink alcohol every day, in the age group of 20-34. At the same time 13.9% men and 18.1% of women drink alcohol every day in the age group of 35-49. It is this trend which is alarming in these age groups who are in at-risk category. There is a definite prevalence of drinking (2.3%) in pregnant women also. Moreover there is variation in drinking among

educated and un-educated, type of alcoholic beverage and religion to religion among both genders. So this study has a definite scope to be carried upon further in these aspects especially in the age group of 20-35 using GGT as marker.

There may be a positive association between GGT and Blood pressure with respect to atherogenesis in general, and stroke in particular which is also an area for further study. As there are possibilities of GGT associated with atherogenesis independent of alcoholism (and hence ischaemic stroke), this aspect also can be studied further.

CONCLUSION

The present study supports the hypothesis that excessive alcohol drinking increases the risk of stroke. Self-reporting of alcohol drinking under-estimates the true risk. Thus the use of GGT- the biological marker of alcohol drinking is a helpful tool for risk assessment. Excessive intake of alcohol, raised GGT level and increased LDL-cholesterol compound the risk for stroke. A better understanding of the mechanism between alcohol drinking, biological markers, and the risk of stroke is an important issue for the primary prevention of stroke.

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