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Is serum gamma-glutamyl transferase a good marker of alcohol intake in stroke patients?

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Summary: Serial serum gamma-glutamyl transferase (GGT) levels were estimated in 23 consecutive patients admitted to hospital with a diagnosis of acute stroke. The proportion of patients with elevated GGT levels in the initial, 36-hour and 72-hour samples was 13%, 30% and 24% respectively, suggesting a transient rise following a stroke. Patients with a history of diabetes mellitus had an initial serum GGT level 21 IU/l (95% confidence interval 6 to 37) higher than non-diabetics.

We conclude that GGT levels after a stroke may reflect a history of diabetes and cerebral damage as well as the usual more established causes. Physicians, therefore, should be wary of attributing all unexplained high GGT levels in stroke patients to alcohol.

Introduction

Gamma-glutamyl transferase (GGT) is an enzyme found in endothelial cell membranes where it appears to mediate peptide transport. Estimation of GGT levels is widely used in clinical practice as a marker of heavy alcohol drinking as well as for liver and biliary tract disease. In a prospective case-control study of the relationship between alcohol intake and stroke, Gill noted a higher proportion of stroke cases with elevated GGT levels compared with matched control patients.[1] A similar trend was not seen with elevated red cell mean corpuscular volume, another clinically useful marker of excessive drinking. These results raised the possibility that elevated GGT levels following a stroke may reflect factors other than alcohol abuse. To examine the possibility that GGT is released by the damaged brain, serial serum GGT levels were assayed in a series of patients during the first 5 days after an acute stroke. GGT has been shown to be normally present in low concentrations in cerebrospinal fluid and to be elevated accompanying brain damage.[2] Since, at the time of a stroke, there is disruption of the blood-brain barrier, it was postulated that a rise in serum GGT may be seen as a direct result of the stroke itself.

Methods

The study was performed at Dudley Road Hosptial, Birmingham, a District General Hospital, serving a population of approximately 300,000 people. Consecutive patients with a diagnosis of acute stroke admitted under one medical firm were assessed for inclusion into the study. Stroke was diagnosed by one physician (KP) using World Health Organisation criteria: 'rapidly developing signs of focal and at times global loss of cerebral function, with symptoms lasting more than 24 hours or leading to death, with no apparent cause other than that of vascular origin'.[3] All stroke sub-types (cerebral haemorrhage or infarction) were eligible for inclusion. Recruitment was completed over 6 months.

Patient exclusion criteria were: those with a doubtful diagnosis of a stroke and those presenting more than 24 hours after the onset of stroke. Patients with a history of biliary tract or liver disease, or who were receiving enzyme-inducing medication (for example anticonvulsants) and patients reporting regular alcohol consumption of greater than 70 units per week were excluded from the study, but there were no other grounds for exclusion.

Patients or, where necessary, their relatives, were interviewed at presentation and details of age, sex, past medical history, drug use and alcohol habit were recorded. Alcohol consumption was assessed as the usual number of units of alcohol consumed per week (one unit = 8 to 10 grammes of alcohol = 1/2 pint beer, a tot of spirits, a glass of wine or a glass of fortified wine). Those reporting no regular weekly alcohol consumption were classed as non-drinkers, those consuming 1 to 29 units/week were classified as light drinkers and those consuming 30 to 69 units/week were classified

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as heavy drinkers. GGT levels were measured as soon as possible after presentation, i.e. between 3 and 24 hours following the onset of stroke (with an aim of 12 hours), then at 24–48 hours (aim 36 hours) and on the fifth day.

The estimate of serum GGT activity was performed according to manufacturer's instructions on a COBAS – Bio analyser, with a Boehringer-Manheim diagnostic kit which uses L-G-glutamyl-3 carboxy-4-nitroanilide as substrate. Reference ranges for GGT levels were in line with the manufacturers recommendations and those in use by the laboratory (11 to 50 IU/l in men, 7 to 32 IU/l in women).

Ethical committee approval was obtained for the study and patients or their relatives asked if they agreed to the additional blood tests being performed.

Confidence intervals for the difference between means were calculated using the pooled estimate of the standard error of the difference. Exact confidence intervals for the proportion with elevated GGT levels were obtained from tables of the binomial distribution.

Results

Twenty three patients entered the study. In 2 cases the 72 hour sample could not be taken due to discharge from hospital or death. Seventeen of the 23 patients were male, 4 asian, 3 black, and 16 white. The median age of the patients was 69 years (range 42 to 83 years). Seven patients gave a history of hypertension and 5 a history of diabetes mellitus. The reported alcohol status was; heavy drinker: 9%, light drinker: 22%, and non-drinker: 69%.

None of the stroke cases presented with a history suggestive of cerebral haemorrhage and none required lumbar puncture. It is, therefore, most likely that the patients all suffered a cerebral infarction, although in only 3 cases was this confirmed by computerized tomography. A further 3 patients presented in atrial fibrillation, suggesting a probable embolic aetiology.

The proportion of patients with elevated GGT levels at the three times of sampling is shown in Table I. Figure 1 shows that there were no clear differences between the GGT results in drinkers compared with non-drinkers. An acute rise and fall in GGT was seen in a minority of patients. Amongst those not reporting any regular alcohol consumption 31% (5/16) had elevated GGT levels 36 hours following their stroke.

Figure 2 illustrates the change in GGT between the first and second sample. There was a tendency for the level to rise rather than to fall and for the rises to be larger than the falls. In one patient the serum GGT rose sharply by 239 IU/l between the first and second samples, a level which was subsequently not sustained. These results were checked by repeating the assay on stored samples within a week of being taken and similar results were obtained.

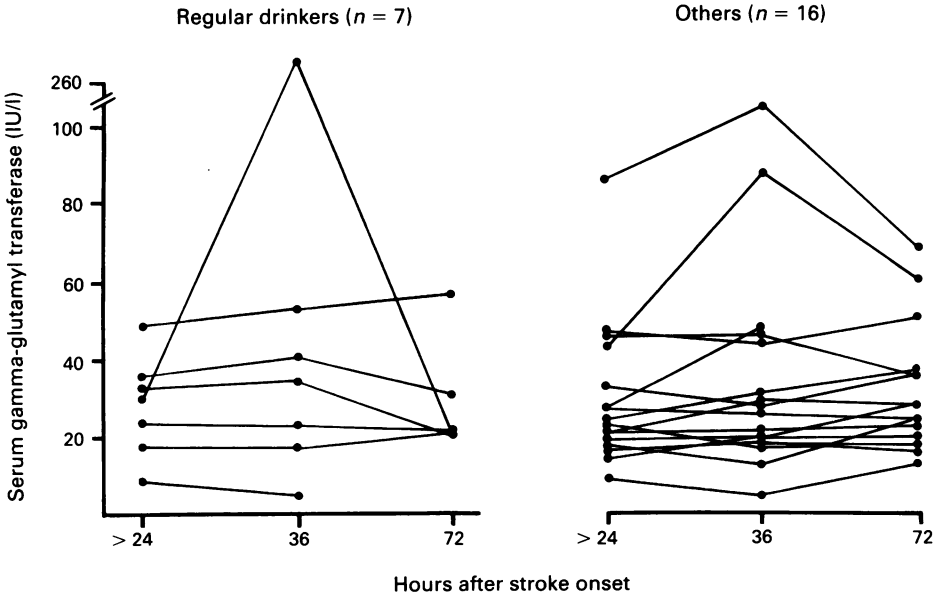

Figure 1 Serial serum GGT profile in 23 acute stroke patients.

Table I Serial assessment of GGT levels after acute stroke

Time of sample after stroke (hours)	*Percent elevated (actual number)*	*(95 percent confidence interval)*
12	13 (3)	(3 to 34)
36	30 (7)	(13 to 53)
72	24 (5)	(8 to 47)

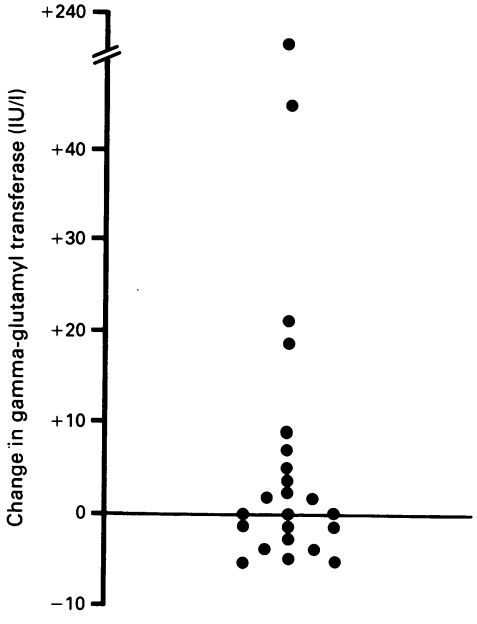

Figure 2 Change in serum GGT between initial and second (36 hour) samples in acute stroke patients.

Five of the 23 patients had a prior history of diabetes mellitus (4 males, one of whom was a heavy drinker). The initial GGT was elevated in 2 (40%), both non-drinkers, compared to one (6%) of those without a history of diabetes mellitus. The mean level of the initial GGT was 21 IU/l (95% confidence interval 6 to 36) higher in the diabetics compared with non-diabetics.

Discussion

Our data suggest that GGT is transiently elevated in some patients with acute stroke independently of other factors. This is consistent with a report of elevated levels in the CSF and serum of stroke patients.[4] This early study, however, did not investigate a possible initial rise, only a gradual decline which could have been due to discontinuing alcohol consumption, although alcohol habits were not recorded in that study.

It is known that in its role of carrying amino-acids across cell membranes, GGT is found in the endothelial cytoplasm of capillary loops in the choroid plexus, where it participates in the formation of cerebro-spinal fluid.[4] It is found elsewhere in the central nervous system including ganglion cells, cells of the central canal of the spinal cord and in the intima and adventitia of atherosclerotic cerebral arteries.[2] Both anoxic damage to the brain with disruption to the blood–brain barrier and induction of GGT to aid post-traumatic protein catabolism could account for elevated levels in the serum of stroke patients. The observed elevation is, however, unlikely to be due to immobility causing release from skeletal muscle, as in muscle wasting diseases, an elevation of GGT is not found.[2]

A similar rise and fall in serum GGT levels has previously been reported in patients following an acute myocardial infarction.[5] There are several isoenzymes of GGT[6] which may in future clarify whether the source is cerebral, cardiac or hepatic.

Interpretation of GGT levels after a stroke is further complicated by our finding that diabetics appear to have raised GGT levels. This is consistent with previous work indicating an elevated GGT in 20% of cases of uncomplicated diabetes mellitus.[2] Recently, Robinson has indicated that overweight is also commonly associated with an elevated GGT.[7] As diabetes and overweight are probable risk factors for stroke, it would be surprising if they were not reflected in an excess of elevated GGT results in stroke patients.

We have not demonstrated consistent rises in serum GGT following a stroke in all patients but the elevations noted in some patients need further evaluation. A considerably larger study would be needed to confirm and enlarge our findings. In the meantime, however, physicians should be wary of attributing all unexplained high GGT levels in stroke patients to excessive alcohol consumption.

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References

1. Gill, J.S., Shipley, M.J., Hornby, R.H., Gill, S.K. & Beevers, D.G. A community case-control study of alcohol consumption in stroke. *Int J Epidemiol* 1987, **17:** 542–547.
2. Rosalki, S.R. Gamma-glutamyl transpeptidase. *Adv Clin Chem* 1975, **17:** 53–107.
3. Hatano, S. Experience from a multicentre stroke register, a preliminary report. *Bull WHO* 1976, **54:** 541–553.
4. Nand, N., Gupta, S., Sharma, M., Khosla, S.N., Saini, A.S. & Lal, H. Evaluation of enzymes in serum and cerebrospinal fluid in cases of cerebrovascular accidents. *Angiology* 1987, **38:** 750–755.
5. Agostoni, A., Ideo, G. & Stabilini, R. Serum G-glutamyl transpeptidase activity in myocardial infarction. *Br Heart J* 1965, **27:** 688–690.
6. Wenham, P.R., Horn, D.B. & Smith, A.F. Multiple forms of gamma-glutamyltransferase: a clinical study. *Clin Chem* 1985, **31:** 569–573.
7. Robinson, D. & Whitehead, T.P. Effect of body mass and other factors on serum liver enzyme levels in men attending for well population screening. *Ann Clin Biochem* 1989, **26:** 393–400.