

Serum elevated gamma glutamyltransferase levels may be a marker for oxidative stress in Alzheimer's disease

Burcu Balam Yavuz,¹ Bunyamin Yavuz,² Meltem Halil,¹
Mustafa Cankurtaran,¹ Zekeriya Ulger,¹
Eylem Sahin Cankurtaran,³ Kudret Aytemir⁴
and Servet Ariogul¹

¹Hacettepe University Faculty of Medicine, Department of Internal Medicine, Division of Geriatric Medicine, Ankara, Turkey

²Kecioren Research Hospital, Department of Cardiology, Ankara, Turkey

³Ankara Oncology Hospital, Department of Psychiatry, Ankara, Turkey.

⁴Hacettepe University Faculty of Medicine, Department of Cardiology, Ankara, Turkey

ABSTRACT

Background: Gamma glutamyltransferase (GGT) plays a role in cellular glutathione uptake, which is an important element of antioxidant mechanisms. An increase in serum GGT is thought to be an early and sensitive marker of oxidative stress. Oxidative stress has a role in the pathogenesis of Alzheimer's disease (AD). The aim of this study was to investigate the GGT levels in AD.

Method: In this cross-sectional study, 132 patients with AD (mean age: 74.1 ± 7.4 , female 62.9%) and 158 age- and gender-matched normal controls (mean age: 74.5 ± 6.3 , female 67.1%) were evaluated. For cognitive assessment, MMSE and clock drawing tests were performed; DSM-IV and NINCDS-ADRDA criteria were used. Serum GGT, aspartate aminotransferase, alanine aminotransferase and alkaline phosphatase concentrations were determined.

Results: Median (min-max) GGT levels were 18 (9–70) in AD group and 17 (5–32) in normal controls. Mann-Whitney U test showed that GGT levels were significantly higher in AD patients ($p = 0.012$). Linear regression analysis revealed AD was an independent correlate of elevated GGT levels. Hypertension, diabetes mellitus, total cholesterol, and low density lipoprotein cholesterol were not associated with GGT levels.

Conclusion: GGT levels were increased significantly in AD patients. To evaluate the role of GGT as a marker of oxidative stress in AD, further studies are needed.

Key words: Alzheimer's disease, gamma glutamyltransferase, marker, oxidative stress, vascular risk factor

Correspondence should be addressed to: Dr. Burcu Balam Yavuz, Hacettepe University, Faculty of Medicine, Department of Internal Medicine, Division of Geriatric Medicine, Sıhhiye, 06100, Ankara, Turkey. Phone: +903123053071; Fax: +903123051538. Email: bbyavuz@hacettepe.edu.tr. Received 13 Nov 2007; revision requested 12 Dec 2007; revised version received 17 Dec 2007; accepted 18 Dec 2007.

Introduction

Gamma glutamyltransferase (GGT) plays a role in cellular glutathione uptake and extracellular catabolism of glutathione (Onat *et al.*, 2006; Paolicchi *et al.*, 2006). These mechanisms are important elements of intracellular protective antioxidant mechanisms (Onat *et al.*, 2006). Glutathione is an important element in antioxidant mechanisms, and GGT is therefore thought to have a role in oxidative mechanisms and is regarded as an early and sensitive marker of oxidative stress (Onat *et al.*, 2006). Lim *et al.* have stated that modest increases in serum GGT activity within normal range may be an early marker of cellular oxidative stress (Lim *et al.*, 2004). Oxidative stress is one of the mechanisms which are thought to be involved in the pathogenesis of Alzheimer's disease (AD). Accumulation of free radicals and oxidative stress may have a role in the pathology of AD by leading to lipid peroxidation and neuronal degeneration in the brain (Sano *et al.*, 1997). Therefore, we hypothesized that as GGT is a marker for oxidative stress it may also be a marker for AD.

Gamma glutamyltransferase is also regarded as a cardiovascular risk factor and has been identified as a predictor of cardiovascular mortality (Wannamethee *et al.*, 1995; Emdin *et al.*, 2001; Paolicchi *et al.*, 2006). Elevated GGT was found to be associated with the presence of many cardiovascular risk factors such as hypercholesterolemia, hypertension, diabetes mellitus, myocardial infarction, metabolic syndrome, and obesity (Betro *et al.*, 1973; Nilssen *et al.*, 1990; Wannamethee *et al.*, 1995; Daepfen *et al.*, 1998; Nakanishi *et al.*, 2004; Kim *et al.*, 2005; Onat *et al.*, 2006). Vascular factors have gained importance in the pathogenesis of AD (Launer, 2002; Pansari *et al.*, 2002). It was found that vascular risk factors also increase the risk of AD (Seshadri, 2002; Reitz *et al.*, 2004). Starting from these points, we hypothesized that elevated levels of GGT might be associated with AD as a vascular risk factor.

The aim of this study was to investigate the GGT levels in AD and control groups as a possible marker of oxidative stress and as a vascular risk factor.

Methods

Subjects and Cognitive Assessment

In this cross-sectional study, following comprehensive geriatric assessment and cognitive assessment, 132 AD patients and 158 control patients with normal cognitive status aged 65 years and over admitted to our geriatric medicine outpatient clinic for routine medical care were enrolled in this study. For cognitive assessment, Mini-mental State Examination (MMSE) (Folstein *et al.*, 1975) and clock drawing tests (Stahelin *et al.*, 1997) were performed. The diagnosis of AD was made according to DSM-IV (American Psychiatric Association, 1994) and NINCDS-ADRDA (McKhann *et al.*, 1984) criteria after cognitive assessment and neuroimaging performed using magnetic resonance (MR). Clinical Dementia Rating Scale (CDR) scores of the patients with AD were 1 and over (Hughes *et al.*, 1982). Age- and gender-matched patients without memory complaint, with normal neuropsychiatric test results (MMSE and clock

drawing tests), who did not meet the criteria for dementia (American Psychiatric Association, 1994) or mild cognitive impairment (Petersen *et al.*, 1999), and whose CDR scores were 0 were enrolled in a normal cognitive status control group. In addition, information from a knowledgeable informant was obtained to ensure there was no change in cognitive function for the normal cognitive status group.

Exclusion criteria were: alcohol consumption; GGT levels over 100 U/L; serum aspartate aminotransferase (AST) and serum alanine aminotransferase (ALT) levels over 40 U/L; and alkaline phosphatase (ALP) concentrations greater than three times the upper limit of the reference range. Hepatitis C virus antibody (antiHCV) and hepatitis B virus surface antigen (HBs Ag) were measured and patients with positive results were also excluded.

Blood pressure was measured in the left arm twice by a standardized mercury sphygmomanometer following approximately five minutes of seated rest. Patients with blood pressure exceeding 140/90 mm Hg were diagnosed with hypertension.

The study protocol was consistent with the Declaration of Helsinki and informed consent was obtained prior to enrollment.

Laboratory tests

Following an overnight fast, blood samples were obtained by antecubital venipuncture and analyzed immediately. Serum ALP, ALT and AST concentrations were determined using enzymatic methods. Serum GGT levels were assayed by the kinetic procedure using gamma-glutamyl-p-nitroanilide as substrate and glycylglycine as acceptor with a Roche/Hitachi analyzer. Plasma concentrations of total cholesterol (TC), triglyceride (TG), and low density lipoprotein cholesterol (LDL-C) were determined by the enzymatic chemistry.

Statistical analysis

Categorical variables are given as percentages, normal distributed continuous variables as mean \pm SD, and skew distributed continuous variables as median (minimum-maximum). In order to make comparisons between the AD and control groups, the t-test was used for normally distributed continuous variables, the Mann-Whitney U-test for skew distributed continuous variables, and the χ^2 test for comparing categorical variables. A correlation analysis to examine the correlation between GGT concentrations and MMSE scores in the AD group was performed by Spearman correlation test. In order to find the independent correlation between GGT levels and AD, linear regression analysis was performed with the variables AD, age, gender, hypertension, diabetes mellitus, TC, LDL, TG, ALP, ALT and AST levels. A p value < 0.05 was considered to be statistically significant. The statistical package SPSS 10.0 for Windows was used to perform the statistical analysis.

Results

One hundred and thirty-two patients with AD (mean age: 74.1 ± 7.4 , female 62.9%) and 158 normal controls (mean age: 74.5 ± 6.3 , female 67.1%) were evaluated. Mean age and gender were similar between groups. The demographic properties and general characteristics of the study population are depicted in Table 1.

Median (min-max) GGT levels were 18 (9–70) in AD group, 17 (5–32) in normal controls. The Mann-Whitney U test showed that GGT levels were significantly higher in AD patients ($p = 0.012$). The laboratory test results are given in Table 1. Correlation between MMSE scores and GGT levels were analyzed in the AD group and no significant correlation was determined ($r = 0.08$, $p = 0.39$).

Fifty-five patients were found to have diabetes mellitus. Serum GGT levels of the patients with and without diabetes mellitus were compared and the Mann-Whitney U test revealed no difference ($p = 0.28$). GGT levels of the patients with and without hypertension were also compared and no significant difference was detected ($p = 0.59$, Mann-Whitney U test).

A multivariate linear regression analysis was performed in order to assess the independent effect of AD on GGT levels. AD, age, gender, hypertension, diabetes mellitus, ALT, AST, ALP, TC, TG and LDL-C levels were put

Table 1. General characteristics and laboratory results of the study population

	ALZHEIMER'S DISEASE (N = 132)	CONTROL (N = 158)	P
Age	74.1 ± 7.4	74.5 ± 6.3	0.35
Gender (M/F)	49/83	52/106	0.45
MMSE score	22.9 ± 6.5	26.6 ± 3.6	<0.001
SBP (mmHg)	140 ± 24	148 ± 20	0.003
DBP (mmHg)	82 ± 12	87 ± 13	0.002
GGT (U/L)	18 (9; 70)	17 (5; 32)	0.012
ALP (U/L)	149.7 ± 66.2	135.5 ± 76.9	0.08
ALT (U/L)	18.1 ± 6.9	17.5 ± 6.9	0.67
AST (U/L)	19.5 ± 6.4	20.9 ± 6.1	0.05
Diabetes mellitus	19 (14.4%)	36 (22.8%)	0.07
Hypertension	75 (56.8%)	122 (77.7%)	<0.001
TC (mg/dL)	208.5 (97.0; 337.0)	205.5 (7.7; 377.0)	0.18
TG (mg/dL)	121.0 (43.0; 501.0)	111.0 (19.0; 448.0)	0.026
LDL (mg/dL)	125.0 (40.4; 265.0)	125.6 (33.4; 240.0)	0.42

Categorical variable age is given as n, normal distributed continuous variables are demonstrated as mean \pm SD, and skew distributed continuous variables as median (minimum-maximum).

P values were derived by t-test for normally distributed continuous variables, by Mann-Whitney U test for skew distributed continuous variables, and by χ^2 test for categorical variables.

M/F = male/female; MMSE = Mini-mental State Examination; SBP = systolic blood pressure; DBP = diastolic blood pressure; GGT = gamma glutamyltransferase; ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; TC = total cholesterol; TG = triglyceride; LDL = low density lipoprotein.

Table 2. Results of regression analysis – the effects of the parameters on elevated GGT levels

	BETA	t	P
Alzheimer's disease	0.202	3.782	<0.001
Age	-0.017	-0.299	0.77
Gender (M/F)	-0.206	-3.833	<0.001
DM	-0.010	-0.185	0.85
HT	-0.018	-0.327	0.74
AST	0.001	0.020	0.98
ALT	0.330	6.233	<0.001
ALP	0.059	1.098	0.27
TC	0.044	0.770	0.44
TG	0.125	2.307	0.022
LDL-C	-0.098	-1.112	0.27

DM = diabetes mellitus; HT = hypertension; AST = aspartate aminotransferase; ALT = alanine aminotransferase; ALP = alkaline phosphatase; TC = total cholesterol; TG = triglyceride; LDL-C = low density lipoprotein cholesterol.

into the equation to establish the independent correlates of GGT. Linear regression analysis revealed that AD was significantly correlated with GGT levels (beta: 0.2, t: 3.8, $p < 0.001$, 95%CI: 1.822; 5.776). Other significant independent covariates of serum GGT were gender (beta: -0.2, t: -3.8, $p < 0.001$, 95%CI = -6.090; -1.957), ALT levels (beta: 0.3, t: 6.2, $p < 0.001$, 95%CI: 0.310; 0.595), and TG levels (beta = 0.1, t: 2.3, $p = 0.022$, 95%CI: 0.002; 0.029). Table 2 demonstrates results of linear regression analysis. This analysis showed that gender, serum ALT and TG levels were significantly correlated with GGT as well as AD.

Discussion

The present study is the first to examine whether GGT levels, as an early marker of oxidative stress, are related to AD. It was found that serum GGT concentrations are significantly increased in AD patients. This increment may be a marker of oxidative stress in AD.

Serum GGT is proposed as an early and sensitive marker for oxidative stress (Lee *et al.*, 2004; Paolicchi *et al.*, 2006; Onat *et al.*, 2006). It has an important role in maintaining intracellular glutathione transport into cells, thus mediating intracellular protective antioxidant mechanisms (Kugelman *et al.*, 1994; Takahashi *et al.*, 1997; Karp *et al.*, 2001; Onat *et al.*, 2006). As it has a role in increasing glutathione transport into the cell, an increase in GGT levels was thought to be a response to oxidative stress (Kim *et al.*, 2005). Increased levels of oxidative stress have been demonstrated in the brain of AD patients (Zhu *et al.*, 2004; 2005), and markers for oxidative stress such as advanced glycation end products (AGE), glycoxidative end products and

lipid peroxidation adduction products were detected in neurofibrillary tangles, amyloid plaques, and neurons of patients with AD (Rottkamp *et al.*, 2000; Zhu *et al.*, 2007). As well as these cerebral changes, a systemic increase in oxidative stress markers may also occur in AD. A decrease in antioxidant levels and alterations in antioxidant enzyme activities are reported in AD (Rottkamp *et al.*, 2000; Bourdel-Marchasson *et al.*, 2001; Rinaldi *et al.*, 2003). These changes suggest a systemic imbalance in oxidative defense mechanism in AD patients (Zhu *et al.*, 2007). Markers of oxidative damage such as heme oxygenase-1 and 8-hydroxyguanosine were found to be increased in the AD brain (Rottkamp *et al.*, 2000). Based on this evidence it can be argued that GGT may serve as a simple and feasible marker for oxidative stress in AD.

Oxidative stress can also play a role in the pathophysiology of cardiovascular diseases. The vascular endothelium regulates the passage of macromolecules and circulating cells from blood to tissue. It is thus a major target of oxidative stress and plays a critical role in the pathophysiology of several vascular diseases (Zhu *et al.*, 2007). Atherosclerosis may be a consequence of oxidative stress and inflammation (Libby, 2002; Stocker and Keane Jr, 2004; Yamada *et al.*, 2006). Yamada *et al.* identified ALT and GGT as independent markers of cardiovascular risk associated with systemic inflammation and oxidative stress (Yamada *et al.*, 2006). Both cardiovascular factors and oxidative stress are the possible mechanisms in the pathogenesis of AD. Therefore, it can be hypothesized that increased levels of GGT, thought to have a role in both of these phenomena, may be a link between these two important mechanisms in the pathogenesis of AD.

Another additional point deserving discussion is that GGT has been proposed as a cardiovascular risk factor. Some studies have suggested that elevations of these serum liver enzymes (ALT, GGT) are simple markers of cardiovascular risk (Yamada *et al.*, 2006). Kim *et al.* stated that an increase in serum GGT levels is found together with diabetes, dyslipidemia, obesity and metabolic syndrome (Kim *et al.*, 2005). Serum GGT concentration was found to have a strong association with many cardiovascular risk factors in different studies (Nilssen and Førde, 1994; Kim *et al.*, 2005). Some prospective studies have shown that GGT is an independent risk marker for cardiovascular and cerebrovascular diseases (Wannamethee *et al.*, 1995; Jousilahti *et al.*, 2000). Onat *et al.* (2006) also stated that GGT may contribute actively to atherothrombogenesis. Much epidemiological and clinical data suggest that cardiovascular risk factors are involved in the pathogenesis of AD (Zulli *et al.*, 2005). As well as the vascular changes detected in brains of people with AD and the close association of AD with cardiovascular risk factors (Buee *et al.*, 1997; Launer *et al.*, 2000; de la Torre, 2000; Reitz *et al.*, 2004), endothelial dysfunction – an early marker for atherosclerosis – was detected in AD patients (Dede *et al.*, 2007). When this range of evidence regarding the role of cardiovascular risk factors in AD pathogenesis is considered, the role of GGT in AD, as a possible cardiovascular risk factor, gains importance.

Some limitations of this study should be mentioned. First, the study itself was not prospective. Secondly, measurement of direct oxidative stress markers was lacking. Further studies comparing direct oxidative stress markers and GGT may help to clarify the role of GGT as an oxidative stress marker in AD.

In conclusion, we believe that our data suggest that the serum GGT concentration may be a marker for oxidative stress in AD. To the best of our knowledge this is the first study to demonstrate an association between AD and GGT as a marker of oxidative stress and vascular risk. However, as this is a cross-sectional study, causality cannot be determined. Further prospective studies are warranted to evaluate this relationship and find out whether elevated serum GGT may be an independent predictor of AD.

Conflict of interest

None.

Description of authors' roles

B. B. Yavuz designed the study, supervised the data collection, carried out the statistical analysis and wrote the paper. B. Yavuz designed the study and carried out the statistical analysis. M. Halil collected data and assisted with writing the paper. M. Cankurtaran and E. S. Cankurtaran assisted with writing the paper. Z. Ulger collected data. K. Aytemir supervised the study design. S. Ariogul designed the study, supervised the data collection and assisted with writing the paper.

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