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## **BLOOD LEVELS OF GLUTAMATE OXALOACETATE TRANSAMINASE ARE STRONGER ASSOCIATED WITH GOOD OUTCOME IN ACUTE ISCHEMIC STROKE THAN GLUTAMATE PYRUVATE TRANSAMINASE.**

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**ABSTRACT**

Ischemic stroke is associated with an excessive release of glutamate in brain. Glutamate-oxaloacetate transaminase (GOT) and glutamate-pyruvate transaminase (GPT) are two enzymes that are able to metabolize blood glutamate facilitating the lowering of extracellular levels of brain glutamate. Our aim was to study the association between blood levels of both enzymes and stroke outcome in the patients with acute ischemic stroke.

We prospectively studied 365 patients with first ischemic stroke <12 hours. Glutamate, GOT and GPT levels were determined in blood samples obtained at admission. We considered functional outcome at 3 months (good outcome: mRS  $\leq 2$ ; poor outcome mRS  $> 2$ ), early neurological deterioration (END) in the first 72 h (Increment  $\geq 4$  points in NIHSS) and infarct volume (CT at 36-72h) as end-points.

We have found an inverse correlation between GOT and GPT levels and blood glutamate levels. Patients with poor outcome showed lower levels of GOT ( $11.9 \pm 8.2$  vs.  $22.7 \pm 10.2$  mU/mL,  $p < 0.0001$ ) and GPT ( $19.5 \pm 14.3$  vs.  $24.7 \pm 20.3$  mU/mL,  $p = 0.004$ ). A negative correlation has been found between GOT (Pearson coefficient =  $-0.477$ ,  $p < 0.0001$ ) and GPT (Pearson coefficient =  $-0.116$ ,  $p = 0.027$ ) levels and infarct volume. Patients with END showed higher levels of blood glutamate ( $381.7 \pm 97.9$  vs.  $237.6 \pm 114.0$   $\mu\text{mol/L}$ ,  $p < 0.0001$ ) and lower levels of GOT ( $10.8 \pm 6.7$  vs.  $18.1 \pm 10.8$  mU/mL,  $p < 0.0001$ ).

This clinical study shows an association between high blood GOT and GPT levels with good outcome in ischemic stroke patients, being this association stronger for GOT than GPT levels.

## INTRODUCTION

Ischemic stroke is a leading cause of death and disability in developed countries. Thrombolytic therapy with recombinant tissue plasminogen activator (rtPA) remains as the only pharmacological treatment that has demonstrated to be effective in acute ischemic stroke [1]. However, the administration of rtPA is linked to severe side effects and only a small percentage of patients currently benefit from this therapy [2]. Therefore, it is mandatory to develop new and effective therapies that can improve outcome after ischemic stroke.

It is well established that during ischemia glutamate acts as an important mediator of neuronal degeneration, being released in large amounts from neurons and astrocytes, causing cellular overload of calcium, mainly through its action on calcium-permeable NMDA receptors [3]. This overload of calcium leads to necrosis and breakdown of cellular structures including proteins, DNA and membrane phospholipids [3]. In fact, previous studies by our group have demonstrated that neurological deterioration of patients with acute ischemic stroke is associated with higher glutamate levels in blood and cerebrospinal fluid [4, 5].

Since ischemic stroke is associated with an excessive release of glutamate in brain, a decrease of blood glutamate levels could lead to a larger glutamate gradient between brain and blood, facilitating the lowering of extracellular levels of brain glutamate with neuroprotective effects [6].

According to this the blood enzymes, glutamate-oxaloacetate transaminase (GOT) and glutamate-pyruvate transaminase (GPT), are able to metabolize glutamate in peripheral blood, leading to a decrease of the levels of this amino acid [6].

Studies in animal models of traumatic brain injury have reported that treatment with recombinant GOT [7] or recombinant GPT [8] causes a decrease of blood glutamate levels inducing neuroprotective effect. However, there have been no human clinical trials demonstrating the benefit of these two enzymes yet. Our aim was to study the association between the levels of these enzymes in blood and the stroke outcome in the patients.

## PATIENTS AND METHODS

Ischemic stroke patients from two University Hospitals in Spain were prospectively included in this study. We initially included 453 consecutively patients with first episode of ischemic stroke, with clinically suspected hemispheric location, evaluated within the first 12 hours from stroke onset, with functional independence prior to stroke defined as modified Rankin Scale (mRS) score  $\leq 1$ . Patients who were included in clinical trials (n=50) or had previous liver failure (n=20) or severe systemic disease (n=18) were excluded, so a total of 365 patients were finally included in this study.

All patients were treated according to the recommendations of the Cerebrovascular Disease Study Group of the Spanish Neurological Society (GEECV-SEN). Demographic data (age, sex), previous history of high blood pressure, diabetes and heart disease, alcohol consumption and smoking habit were recorded at admission. Blood samples were collected at admission for the determination of biochemistry analysis, glutamate, GOT and GPT levels.

Diffusion-weighted magnetic resonance imaging (DWI-MRI) was also obtained at admission. Computed tomography (CT) was performed in case of early neurological deterioration (END) and in all patients between 36 and 72 hours from stroke onset to calculate infarct volume by using the formula  $0.5 \times a \times b \times c$  (where  $a$  is the maximal longitudinal diameter,  $b$  is the maximal transverse diameter perpendicular to  $a$ , and  $c$  is the number of 10-mm slices containing infarct) [9]. Stroke subtype was classified according to TOAST criteria [10], once carotid and transcranial ultrasound study and echocardiogram were performed. The National Institutes of Health Stroke Scale (NIHSS) was used to evaluate stroke severity and quantified every two hours during the first 24 hours and every 8 hours during the rest of the hospitalization period. All patients were clinically reevaluated at 3 months  $\pm$  7 days.

We considered the following end-points: a) functional outcome at 3 months assessed by mRS and categorized as good outcome (mRS  $\leq$ 2) and poor outcome (mRS  $>$ 2); b) infarct volume determined in the neuroimaging performed between 36-72 hours; and c) the presence of END, defined as an increase  $\geq$ 4 points in NIHSS from basal to any other determination performed within the first 72 hours.

The Local Ethical Committees approved the clinical protocol and the patients or relatives gave signed informed consent.

### Statistical analysis

Results are expressed as percentages for categorical variables and as mean (SD) or median [quartiles] for the continuous variables, depending on the normal or non-normal distribution of data. Proportions were compared using the chi-square test, and the Student's  $t$  test or the Mann-Whitney test to compare continuous variables between groups. Pearson analysis was used for bivariate correlations.

The influence of GOT, GPT and glutamate levels on functional outcome was assessed by logistic regression analysis, after adjusting for the main baseline variables related to outcome in the univariate analyses (enter approach and probability of entry  $p < 0.05$ ). Results were expressed as adjusted odds ratios (OR) with the corresponding 95% confidence intervals (95% CI). OR values for GOT and GPT were analyzed by quartiles, chosen lowest concentration as reference range for the analysis. The influence of GOT, GPT and glutamate levels on infarct volumes was evaluated by general linear models after adjusting for variables associated in the bivariate comparisons. Statistical analyses were conducted using SPSS 16.0 for Windows XP.

### RESULTS

We studied 365 patients (70.5  $\pm$  11.4 years, 57.5% male). Average time from stroke onset to inclusion in the study was 3.0  $\pm$  2.1 hours. One hundred and thirty patients (35.6%) received thrombolytic therapy with rtPA within the first 3 hours from stroke onset following SITS-MOST criteria.

One hundred ninety-seven patients (54.0%) showed poor outcome at 3 months. Patients with poor outcome were older and had more frequently

female sex, cardioembolic stroke, lower tobacco consumption, larger history of atrial fibrillation, higher initial stroke severity, higher percentage of END, higher glucose, fibrinogen and blood glutamate levels and lower GOT and GPT levels at admission (Table 1). We found an inverse correlation between GOT and GPT levels with blood glutamate levels at admission. This correlation was higher for GOT levels (Pearson coefficient = - 0.426,  $p < 0.0001$ ) than for GPT levels (Pearson coefficient = - 0.174,  $p = 0.001$ ) (Figure 1). To analyze whether transaminases or blood glutamate were independently associated with functional outcome we performed a logistic regression model using poor outcome as independent variable (Table 2). Levels of GOT and GPT at admission were divided in quartiles. For GOT levels, 1<sup>o</sup> quartile was 0 and 10 mU/mL, 2<sup>o</sup> quartile 10 – 14 mU/mL, 3<sup>o</sup> quartile 14 – 21,85 mU/mL and 4<sup>o</sup> quartile >21.85 mU/mL, in case of GPT levels, the interval of quartiles were, 1<sup>o</sup> quartile: 0 – 12,90 mU/mL, 2<sup>o</sup> quartile: 12,90 – 18 mU/mL, 3<sup>o</sup> quartile: 18 – 25 mU/mL and 4<sup>o</sup> quartile > 25 mU/mL). In the first model, including only GOT, we found that both GOT and blood glutamate levels were associated with functional outcome after adjustment by age, sex, stroke subtype, smoke habit, atrial fibrillation, NIHSS, END, infarct volume and glucose and fibrinogen levels. OR values were more significant for the higher levels of GOT. In the second model, including only GPT, we found that only blood glutamate levels were independently associated with poor outcome.

Regarding infarct volume, we found an inverse correlation with GOT (Pearson coefficient = -0.477,  $p < 0.0001$ ) and GPT (Pearson coefficient = -0.116,  $p = 0.027$ ) levels (Figure 2), whereas a positive correlation was found for glutamate levels (Pearson coefficient = 0.426,  $p < 0.0001$ ). Other variables associated with infarct volume were a previous history of high blood pressure, systolic blood pressure at admission, glucose levels, leukocyte count, NIHSS and the presence of END. (all  $p < 0.05$ ) We performed a multiple linear regression model adjusted by significant variables in the univariate analysis (Table 3). In a first multiple linear regression model including only GOT levels, we found that GOT, but not blood glutamate levels, was independently associated with infarct volume. In the second model, including only GPT, we found that GPT loses its independence and only blood glutamate levels were independently associated with infarct volume.

Finally, we analyzed those factors associated with END, which was presented in fifty-eight patients (15.9%). In the univariate model, older age, higher levels of blood glutamate and lower levels of GOT were associated with END (Table 4). In the logistic regression model, we found that both GOT (OR: 0.93, CI 95%: 0.88 – 0.98;  $p = 0.010$ ) and blood glutamate levels (OR: 1.09, CI 95% 1.06 – 1.13;  $p < 0.0001$ ) were independently associated with the presence of END.

## DISCUSSION

In this study, we have found that higher GOT and GPT levels were associated with lower levels of blood glutamate, and better functional outcome, reduced infarct volume and lower percentage of END, being this association stronger for GOT than GPT levels.

Previous studies have shown that high glutamate levels in blood and in cerebrospinal fluid are associated with large infarct volume and greater stroke severity [4], higher frequency of END [5], and infarct growth [11], which leads to poor functional outcome. Since glutamate plays a central role in the ischemic cascade, this neurotransmitter represents a good target in the search for neuroprotective agents in ischemic stroke. However, clinical trials have failed to demonstrate the neuroprotective effect of glutamate antagonists [12-17], probably due to the narrow therapeutic window [18].

Under normal physiological conditions, glutamate is released in the synaptic cleft and quickly removed by the excitatory amino acid transporters (EAATs), located on astrocytes and neurons [19]. Besides astrocytes and neurons, the presence of EAATs has also been observed in endothelial cells of brain vasculature, which supports the important role of these cells in the maintenance of glutamate levels in the extracellular medium [20]. In fact, it has been described that endothelial cells have facilitative carriers for glutamate in the luminal membranes, and EAATs in the abluminal membrane. This localization allows a diffusion of glutamate from brain to the blood torrent following a gradient of concentration. Therefore, the decrease of blood glutamate levels leads to facilitate the lowering of extracellular levels of brain glutamate [6, 20, 21].

GOT and GPT are two enzymes that metabolize glutamate levels in the peripheral blood [6]. GOT, using oxaloacetate as co-substrate, is able to transform glutamate to 2-ketoglutarate and aspartate. GPT converts glutamate to 2-ketoglutarate and alanine, using pyruvate as co-substrate. Therefore, the properties of these enzymes to metabolize glutamate in blood show that they could be used as new neuroprotective tools against excitotoxic neuronal injury after ischemic stroke [6, 22].

We have also observed in our laboratory that oxaloacetate-mediated GOT activation in animal model of cerebral ischemia induces a decrease of blood and cerebral glutamate levels reflecting a reduction of infarct size, edema volume, and sensorimotor deficits [23]. Therefore, the inverse correlation observed between GOT and GPT levels with blood glutamate levels, together with the association between GOT and GPT levels with good functional outcome could be explained by the capacity of these enzymes to reduce the neurotoxic effect of elevated glutamate levels in the brain following ischemic stroke. In view of the stronger association of GOT than GPT with respect to good outcome and infarct reduction, it is also tentative to postulate that future clinical trials with both blood enzymes should be driven preferably in the use of GOT better than GPT.

In conclusion, this study shows a good association between high blood GOT and GPT levels with good outcome in ischemic stroke patients, being this association stronger for GOT than GPT levels, although further studies are necessary to demonstrate if these blood enzymes really can be used as therapeutic tools for ischemic stroke.

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**Table 1.** Basal characteristics of patients with good and poor outcome.

	<b>Good outcome n = 168</b>	<b>Poor outcome n = 197</b>	<b>p</b>
Age, years	67.3 ± 12.7	73.2 ± 9.5	<0.0001
Male sex, %	67.3	49.2	0.001
Time from onset, h	3.1 ± 2.2	2.9 ± 2.1	0.435
Etiology (TOAST criteria)			<0.0001
- Atherothrombotic, %	11.3	18.8	
- Cardioembolic, %	45.8	52.3	
- Lacunar, %	8.3	0.5	
- Undetermined, %	34.5	28.4	
History of hypertension %	58.3	66.5	0.128
History of diabetes, %	18.5	18.8	0.523
History of hypercholesterolemia, %	28.0	31.5	0.270
Smoke habit, %	38.1	27.4	0.033
Alcohol consumption, %	7.7	4.1	0.176
Coronary heart disease, %	16.1	14.7	0.772
Atrial fibrillation, %	24.3	39.0	0.008
Systolic blood pressure, mm Hg	156.3 ± 27.5	157.9 ± 27.9	0.573
Diastolic blood pressure, mm Hg	84.0 ± 14.4	84.2 ± 16.2	0.927
Body temperature, °C	36.3 ± 0.4	36.4 ± 1.6	0.694
Glucose level, mg/dL	124.7 ± 46.1	139.8 ± 55.3	0.005
Leukocyte count, x 10 <sup>3</sup> /mL	8.9 ± 2.9	9.2 ± 2.9	0.541
Platelets, x 10 <sup>3</sup> /mL	236.4 ± 81.9	233.7 ± 70.9	0.736
Fibrinogen, mg/dL	426.0 ± 119.9	452.9 ± 120.8	0.034
NIHSS	7 [5, 12]	17 [12, 19]	<0.0001
Thrombolytic therapy (SITS-MOST), %	35.7	35.5	0.929
Early neurological deterioration, %	2.4	27.4	<0.0001
Volumen de la lesión, mL	13.3 ± 25.1	98.6 ± 79.1	<0.0001
Blood glutamate, µmol/L	191.2 ± 102.3	319.6 ± 108.2	<0.0001
GOT, mU/mL	22.7 ± 10.2	11.9 ± 8.2	<0.0001
GPT, mU/mL	24.7 ± 20.3	19.5 ± 14.3	0.004

**Table 2.** Logistic regression model for GOT (Model 1) and GPT (Model 2) using poor outcome as dependent variable, after adjustment by age, sex, etiology, smoke habit, atrial fibrillation, NIHSS, END, infarct volume and glucose and fibrinogen levels.

	OR (CI 95%)	p
<b><i>Model 1</i></b>		
<b>GOT (2<sup>o</sup> quartile)</b>	0.61 (0.18 – 2.11)	0.436
<b>GOT (3<sup>o</sup> quartile)</b>	0.16 (0.05 – 0.53)	0.003
<b>GOT (4<sup>o</sup> quartile)</b>	0.09 (0.02 – 0.36)	0.001
<b>Glutamate</b>	1.09 (1.06 – 1.13)	<0.0001
<b><i>Model 2</i></b>		
<b>GPT (2<sup>o</sup> quartile)</b>	1.10 (0.38 – 3.17)	0.852
<b>GPT (3<sup>o</sup> quartile)</b>	1.00 (0.35 – 2.82)	0.658
<b>GPT (4<sup>o</sup> quartile)</b>	0.61 (0.21 – 1.77)	0.361
<b>Glutamate</b>	1.01 (1.00 – 1.01)	0.004

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**Table 3.** Multiple linear regression model for GOT (Model 1) and GPT (Model 2) using infarct volume as dependent variable, after adjustment by previous history of high blood pressure, systolic blood pressure at admission, glucose levels, leukocyte count, NIHSS and the presence of END.

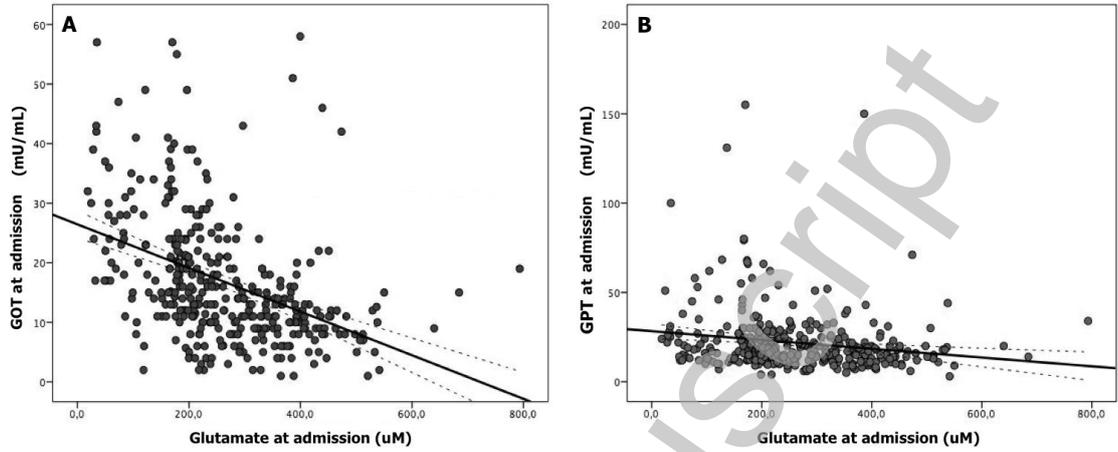
	<b>B (CI 95%)</b>	<b>p</b>
<b><i>Model 1</i></b>		
<b>GOT</b>	-1.95 (-2.53 to -1.37)	<0.0001
<b>Glutamate</b>	0.32 (-0.23 to 0.87)	0.252
<b><i>Model 2</i></b>		
<b>GPT</b>	0.34 (-0.67 to 0)	0.051
<b>Glutamate</b>	0.08 (0.02 to 0.13)	0.005

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**Table 4.** Basal characteristics of patients with early neurological deterioration (END).

	<b>END NO n = 307</b>	<b>END YES n = 58</b>	<b>p</b>
Age, years	69.9 ± 11.7	73.8 ± 9.3	0.017
Male sex, %	58.6	51.7	0.385
Time from onset, h	2.9 ± 2.1	3.3 ± 2.4	0.189
Etiology (TOAST criteria)			0.073
- Atherothrombotic, %	13.7	24.1	
- Cardioembolic, %	49.2	50.0	
- Lacunar, %	4.9	0	
- Undetermined, %	32.2	25.9	
History of hypertension %	60.6	74.1	0.055
History of diabetes, %	18.2	20.7	0.713
History of hypercholesterolemia, %	31.3	22.4	0.212
Smoke habit, %	32.2	31.0	0.879
Alcohol consumption, %	6.5	1.7	0.221
Coronary heart disease, %	15.6	13.8	0.844
Atrial fibrillation, %	32.6	44.8	0.097
Systolic blood pressure, mm Hg	156.3 ± 27.7	162.3 ± 27.7	0.131
Diastolic blood pressure, mm Hg	83.7 ± 15.5	86.2 ± 14.8	0.270
Body temperature, °C	36.4 ± 0.5	36.1 ± 2.7	0.075
Glucose level, mg/dL	130.9 ± 50.7	142.7 ± 56.7	0.113
Leukocyte count, x 10 <sup>3</sup> /mL	8.9 ± 2.8	9.5 ± 3.2	0.205
Platelets, x 10 <sup>3</sup> /mL	236.6 ± 77.4	226.5 ± 69.0	0.356
Fibrinogen, mg/dL	441.7 ± 122.6	434.3 ± 112.7	0.669
NIHSS	12 [6, 18]	14 [8, 19]	0.084
Thrombolytic therapy (SITS-MOST), %	37.5	25.9	0.101
Blood glutamate, µmol/L	237.6 ± 114.0	381.7 ± 97.9	<0.0001
GOT, mU/mL	18.1 ± 10.8	10.8 ± 6.7	<0.0001
GPT, mU/mL	22.3 ± 18.5	19.6 ± 9.6	0.101

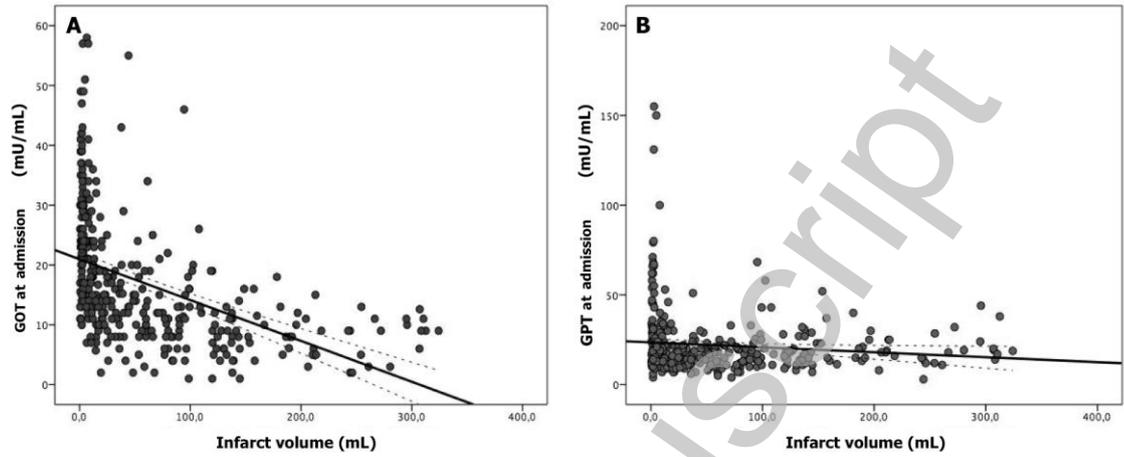
**Figure 1.** Correlation between GOT levels at admission (A) and GPT levels at admission (B) with glutamate levels at admission.



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**Figure 2.** Correlation between GOT levels at admission (A) and GPT levels at admission (B) with infarct volume.



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