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Evaluation of Platelet Glutamate Dehydrogenase Activity in Late- Life Depressions

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Summary

The aim of the study is to evaluate the activity of platelet glutamate dehydrogenase (GDH) in late-life depression compared to the healthy control group and to reveal possible correlations with clinical data. **Patients and methods:** 42 elderly patients (60–86 years old) with depressive episodes of different nosological categories according to ICD-10 were examined: a single depressive episode (F32.0, F32.1), a depressive episode in recurrent depressive disorder (RDD — F33.0, F33.1) and a depressive episode in bipolar affective disorder (BD — F31.3). The activity of GDH and the severity of depression (using the Hamilton depressive scale, HAMD-17, and the Hamilton scale for assessing anxiety, HARS) were evaluated twice: before the starting the course of antidepressant therapy (day 0) and on the 28th day of the treatment course. **Results:** patients showed a significant decrease in the activity of GDH compared to the control group ($p < 0.0008$). Before the treatment, GDH activity was significantly reduced compared to the control in both RDD and BD ($p < 0.002$ and $p < 0.004$), whereas after the treatment, the decreased GDH activity was observed only in patients with BD ($p < 0.002$). When compared with the control group, male patients showed a significant decrease in GDH activity both before and after the treatment course ($p < 0.017$ and $p < 0.027$), whereas women patients showed the decrease only before the treatment ($p < 0.014$). **Conclusion:** the decreased platelet GDH activity in elderly depressions may indicate an impairment of glutamate metabolism. Gender differences were revealed in the reversal of GDH activity level after the therapy: in men, the level of GDH activity did not recover to control values after the treatment course. An elevation in the level of GDH to control values over a 28-day course of therapy occurred only in patients with RDD, but not in patients with BD.

Keywords: glutamate dehydrogenase, platelets, depressive disorders, late age

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INTRODUCTION

The elderly depression is one of the main problems of geriatric psychiatry due to its high prevalence, difficulties in therapy due to specific factors of aging, and the need for high costs of society for the management of such patients. The heterogeneity of depression in old age is associated not only with differences in early and late manifesting forms of depressive disorders, but also with the interference of age-related changes, cerebral and chronic somatic diseases, as well as many genetic, metabolic, endocrine and neurobiological factors.

Although the emergence of new types of antidepressant medicines increased the therapy safety for elderly depression, it did not solve the problems associated with insufficient effectiveness of therapy, delayed therapeutic response, low quality of outcomes with increased threat of recurrence.

Contemporary neurobiological studies have shown that depression is based not only on a decrease in level of monoamines, but also involves the dysfunction of glutamatergic system [1]. Dysfunction of the glutamatergic system contributes to the pathogenesis of depression, and, therefore, it may serve as a target of antidepressant treatment. In fact, the glutamatergic hypothesis of depression serves as a contemporary concept for the development of fast-acting antidepressants [2–4].

Glutamate dehydrogenase (GDH) is one of the key enzymes metabolizing neurotransmitter glutamate in the brain. GDH catalyzes the reversible conversion of glutamate to α-ketoglutarate [5]. Previous studies [6], including our own [7], have shown the presence of this enzyme in peripheral blood platelets. We have also found that changes in the activity and concentration of GDH detected in platelets in endogenous psychoses can be associated to a

Table 1. Clinical data of the examined groups

Исследуемые показатели/Research parameters	Patients with depression, before treatment (*n* = 42)	Patients with depression, after treatment (*n* = 36)
Depression severity (HAMD-17 total score)	23 [21; 24]	8 [6; 10]
Anxiety (HARS total score)	23 [19; 25]	7 [6; 9]
Cognitive functions (MMSE score)	27 [26; 29]	Non determined

Note. Data are given as Median and quartiles, M [Q25; Q75].

certain extent with psychopathological indicators of the patient condition and the effectiveness of pharmacotherapy [8, 9]. However, platelet GDH activity has never been previously determined in depressive states.

The aim of this work is to assess the platelet GDH activity in elderly depression in comparison with the control group and to identify its possible correlations with clinical data.

PATIENTS AND METHODS

The study was carried out in compliance with modern ethical norms and standards of biomedical research, approved by the Helsinki Agreement of the World Medical Association (as amended in 1975/2000) and approved by the Ethics Committee of the "Mental Health Research Centre" (Protocol No 8 dated 02.26.2019).

The clinical-biochemical study (2019–2021) was carried out in the Department of Geriatric Psychiatry and in the Laboratory of Neurochemistry of the MHRC.

The inclusion criterion for the study was the presence of mild or moderate depressive episode (DE) in patients over 60 years of age according to the ICD-10 classification of affective disorders: single DE (F32.0, F32.1), depressive phase within the frame of recurrent depressive disorder (RDR, F33.0, F33.1) or bipolar disorder (BD, F31.3).

Exclusion criteria were the presence of other mental illnesses, primary dementia of various etiologies, brain trauma, drug addiction, severe somatic diseases in the stage of decompensation, as well as a history of allergic reactions or severe multiple hypersensitivity to medications.

Clinical, psychometric, biochemical and statistical research methods were used in the study.

Clinical condition of patients was assessed before the start of the treatment course (day 0) and on the 28th day of treatment using the Hamilton Depressive Scale (HAMD-17) and the Hamilton Anxiety Rating Scale (HARS). The effectiveness of therapy was determined by the difference in the total scores by HAMD-17 and HARS before/after the treatment course. The Mini-Mental State Examination (MMSE) was used for cognitive performance assessment of patients.

The study involved 42 patients with DE, aged from 60 to 86 years (33 women and 9 men, the proportion of men was 21%). Median age and quartiles M [Q25; Q75] were 66 years old [63; 71 years old]. Nosologically, 3 patients (7%) were diagnosed with a single DE, in 28 patients (67%) — DE in RDR, in 11 patients (26%) — DE in BD.

The onset age ranged from 17 to 81 years with a median value of M = 40.5 years [30.0; 55.0 years]. Cases with long course of the disease prevailed (M = 23 years [7; 40 years]).

As judge by the total score by HAMD-17, the majority of patients had moderate depression with M = 23 points [21; 24 points]. 30 patients had moderate and severe depression, 12 patients had mild depression (total HAMD-17 score from 16 to 21 points).

In the majority of cases (34; 81%), the duration of depression before enrollment in the study did not exceed 6 months with M = 3.0 months [2; 5 months], however, 8 (19%) patients had prolonged (⩾ 6 months) depression.

The level of cognitive activity of the patients was not beyond the age norm and, according to the total MMSE score before the start of the study, comprised M = 27 points [26; 29 points]. All examined patients had poly comorbid somatic burden with concomitant diseases with M = 4 diseases [3; 5 diseases].

Clinical data of the examined groups is presented in Table 1.

New generation antidepressants from SSRI and SNRI groups (selective serotonin reuptake inhibitors' group, and selective serotonin and norepinephrine reuptake inhibitors' group, such as venlafaxine, duloxetine), as well as trazodone, from SARI group of serotonin reuptake inhibitor/serotonin antagonist,

Table 2. Platelet glutamate dehydrogenase activity in the control group and in patients with depression before and after the treatment course

Research parameter	Control group	Patients with depression	
	n = 29	before treatment (*n* = 42)	after treatment (*n* = 36)
Activity GDH, U/mg	6.79 [5.76; 7.69]	5.32 [3.71; 6.73]*	5.70 [4.05; 6.83]*

Note. Indices are presented as Median and quartiles, M [Q25; Q75]; * significant changes between the control group and the patient group, $p < 0.001$.

were used for active 28-day therapy of patients. Doses of medicines were standard for this age group.

Blood was sampled to determine the level of GDH activity in patients twice — before the starting the course of pharmacotherapy and on the 28th day of the treatment. Six patients refused the sampling the second blood test.

The control group consisted of 29 people without mental pathology (19 women and 10 men, the proportion of men was 34.5%) aged from 52 to 81 years with M = 58 years [54; 62 years old]. GDH enzymatic activity was determined once in the control group.

Isolation of platelets, determination of GDH activity

Blood from the cubital vein of the subjects was collected in vacutainers with sodium citrate and processed within no more than 2 hours after blood sampling. Platelets were isolated from blood samples, 50% of glycerol was added to the suspension and stored at –20 °C; platelet extracts were prepared as described earlier before the determining the GDH activity [10].

GDH activity was determined by spectrophotometric kinetic method using xMark plate spectrophotometer (Bio-Rad) by the rate of the decrease in NADH absorption at 340 nm according to the method [11], with modifications as described earlier [8]. Protein concentration was determined by the Lowry method using Bio-Rad DC Protein Assay (USA) and bovine serum albumin (Sigma-Aldrich, USA) as a protein standard. After determining the protein concentration, the GDH specific activity (U/mg) was calculated.

STATISTICAL ANALYSIS

The hypothesis of GDH activity normal distribution in the examined groups was tested using the Shapiro–Wilk test. The Mann–Whitney U-test and calculation of Spearman rank correlation coefficients (R) were used to assess the significance of differences, changes in parameters and relationships between them. Differences and correlations were considered significant at $p < 0.05$.

RESULTS

Both in the control group and in the patient group, the data on GDH activity were not normally distributed, that was confirmed by checking for normal distribution by the Shapiro–Wilk test ($p < 0.01$); therefore, nonparametric research methods were used.

Although there was a between-group difference in age between controls and patients with depression, no significant correlation was found between platelet GDH activity with age in the controls or in patients, when determining Spearman rank correlation coefficients (R = 0.07, $p = 0.73$ and R = 0.08, $p = 0.63$, respectively), which made it possible to compare these groups.

Comparison of GDH activity revealed significant differences between the control group and patients before and after the course of therapy (Mann–Whitney U-test, $p < 0.0008$ and $p < 0.007$, respectively) (Table 2).

When comparing the activity of platelet GDH in men and women within the control group and within the group of patients as a whole, there were no significant differences in GDH activity between the representatives of different genders ($p > 0.1$). However, whereas the GDH activity in women was significantly lower than the control values ($p = 0.014$) before the treatment, it became indistinguishable from the control after the treatment course ($p = 0.085$). Men showed a significant decrease in GDH activity both before and after treatment ($p = 0.017$ and $p = 0.027$, respectively) compared with the control group (Fig. 1).

GDH activity was analyzed in patients with different affective disorders (BD, RDR, DE subgroups).

Mann–Whitney U-test showed a significant decrease in GDH activity in patients with RDR and BD before their treatment ($p < 0.002$ and $p < 0.004$ in comparison with the controls, respectively). As for GDH activity after the treatment course, decreased

GDH activity was observed only in patients with BD ($p < 0.002$), while the GDH activity in patients with RDR approached the values in the control group (Fig. 2). Patients with a single DE were excluded from this analysis and the values of GDH activity for them are not shown in Fig. 2 due to the small size of the subgroup.

The subgroups of patients with BD and RDR diagnoses didn't differ in terms of the gender ratio: 18% of men in patients with BD, 21% of men in patients with RDR. Comparison of GDH activity in men and women within the RDR subgroup, as well as in BD subgroup did not reveal significant differences. Comparison of GDH activity in women from the subgroups of RDR, BD and DE by the Kruskal–Wallis test showed no significant differences.

Comparison of activity between men with BD, RDR, DE diagnoses was not carried out due to the small number of men in all subgroups.

As a result of therapy, patients in general showed a significant decrease in the total scores by HAMD-17 and HARS (Wilcoxon test, $p < 0.01$), but no significant correlations of the GDH activity baseline level with general clinical assessments of the patient's condition both before and after therapy has been revealed.

DISCUSSION

Despite the accumulated data, the pathogenesis of depression remains largely unclear. There are articles in literature describing the relationship between metabolic changes in glutamate system in the brain and psychological and behavioral changes — both in patients with depression and in the laboratory animal models simulating behavior resembling depression. So, depressive-like behavior is observed in animals with knock-outed gene encoding the subunit GluD1-KO of the δ-type ionotropic glutamate receptor [12]. In addition, the antidepressant effects of ketamine, an NMDA-type glutamate receptor antagonist, are widely known. Alterations in the glutamate uptake rate by

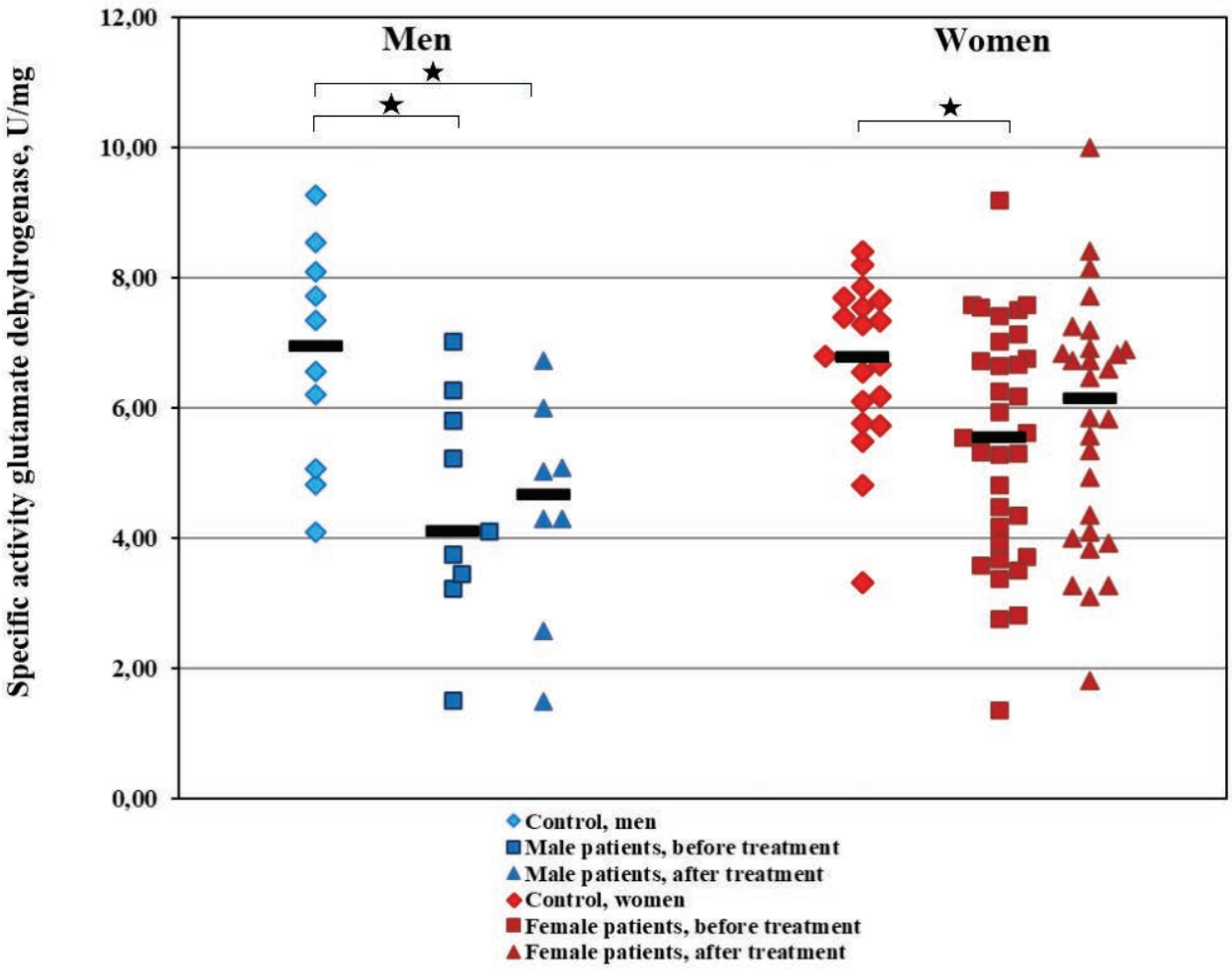

Fig. 1. Glutamate dehydrogenase (GDH) activity in men and women in the control group (rhombuses), in the group of patients before the treatment course (squares), after the treatment course (triangles); horizontal black lines — medians for the groups. On the ordinate axis — the specific activity of GDH (U/mg). * Significant differences between the control group and the patient group, $p < 0.05$

platelets [13] and changes in the concentration of glutamate in the blood serum were also found in BD [14]. All these data indicate the participation of the glutamate system in the pathogenesis of depression.

In our work we have found significantly reduced activity of platelet GDH in elderly patients with depression before and after treatment with antidepressants, when compared with individuals in the control group. This fact confirms the impairment of glutamate metabolism in depression. It should be noted that a decrease in the activity of platelet GDH was also revealed in schizophrenia when compared with controls [8], this fact indicates the general pathogenetic features of these diseases.

The effectiveness of antidepressant treatment with selected antidepressants in present study was high in depressive elderly patients. The search for relationships between the effectiveness of therapy and GDH activity did not reveal significant correlations. On the other hand, we have found that the course of 28-day antidepressant therapy had a different effect on the activity of platelet GDH in different subgroups of patients. Thus, before the treatment course, women and men showed a decreased activity of GDH in comparison with the controls. After the treatment, GDH activity became undistinguished from the control values in women, while in men there were significant differences still from the control. That is, gender differences were revealed in changes in the GDH level under antidepressant therapy with a longer preservation of the anomalous GDH activity levels in men. The

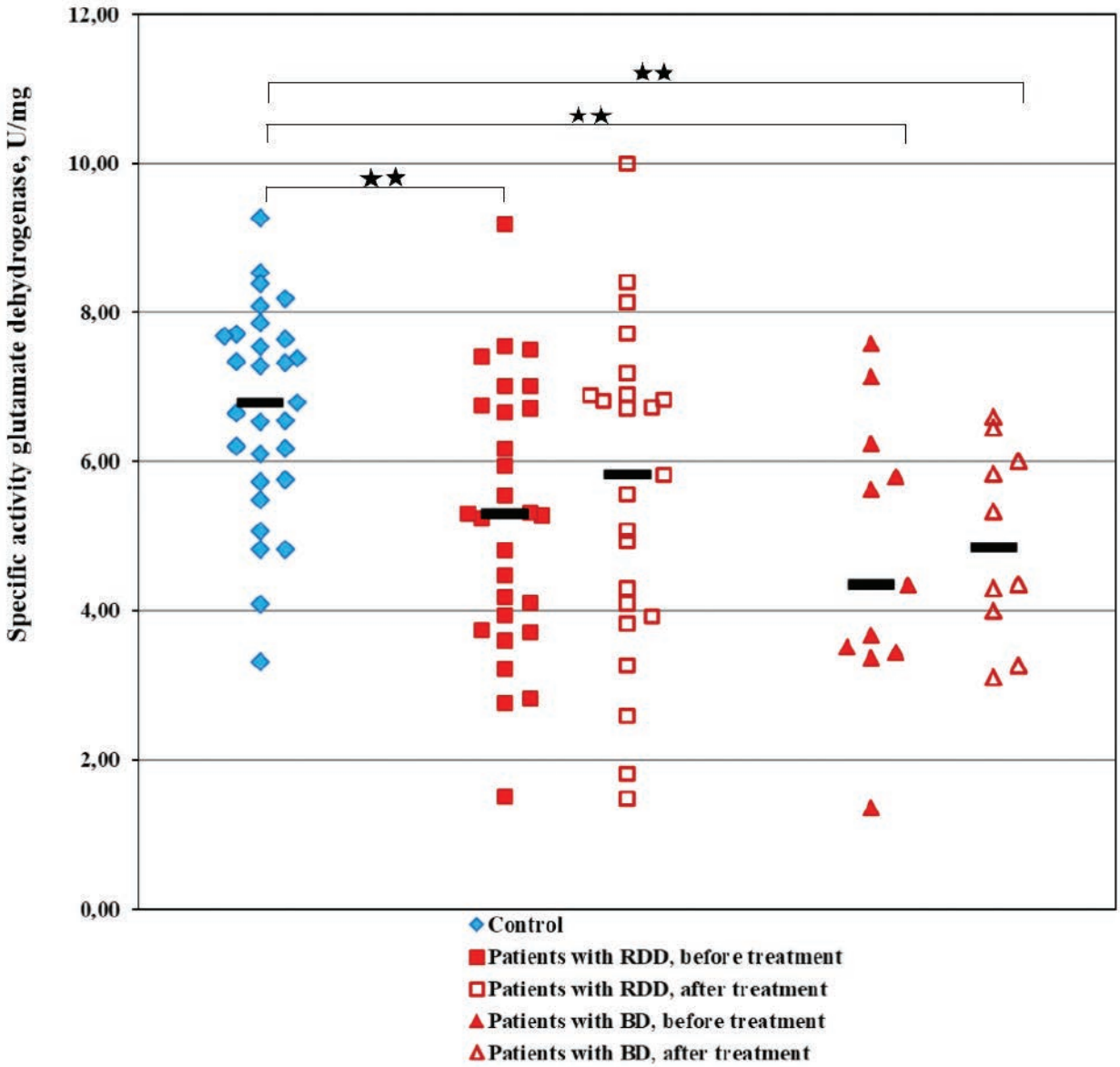

Fig. 2. Glutamate dehydrogenase (GDH) activity in the control group (rhombuses) and in subgroups of patients with RDD (squares) and BD (triangles); the horizontal black lines are the medians for the groups. On the ordinate axis — specific activity of GDH (U/mg). **Significant differences between the control group and the patient group, $p < 0.01$

obtained results agree with the literature data on gender dimorphism of both glutamate metabolism and the course of depression [15, 16].

We have shown that the decreased platelet GDH activity was observed before the treatment course in depressed patients with BD and RDR. Due to the small number of men in the subgroups with BD, RDR, and DE the statistical between-group comparison was impossible, therefore, in the future, it is of interest to study expanded subgroups of patients — both men and women — with depression with different nosological units.

After treatment, an increase in GDH activity to the control range registered only in the subgroup of patients with RDR, while it remained reduced in patients with BD. This observation may indicate different mechanisms of platelet GDH activity control in different subgroups of patients with depression and requires further study.

Comorbid somatic diseases are the most important well-known factors affecting the etiology, pathogenesis and course of depressions in late age. Almost all depressive patients included in our study had a poly comorbid somatic burden of somatic diseases with number M = 4 diseases [3; 5 diseases]. In this regard one could assume that not only depressive disorder, but also multiple somatic pathology likely influences the platelet GDH activity. Our analysis did not reveal statistically significant relationships between the platelet GDH activity and the number of concomitant somatic diseases or the presence of their decompensation in the current depression. This is probably due to the small size of the sample of depressed patients (42 people), as well as to the difficulties in selecting a comparison group with comparable somatic burden in the pilot study. Nevertheless, the possibility of the potential effect of poly comorbid somatic pathology on the activity of platelet GDH in elderly depressed patients remains open and requires further study.

CONCLUSION

The observed fact of a decrease in platelet GDH activity in elderly depressions confirms the data available in the literature on the impairment of glutamate metabolism in depression. Active 4-week therapy with antidepressants of the SSRI, SARI and SNRI groups effectively reduced depressive symptoms, but no relationship between GDH activity and the effectiveness of patients' therapy was found. At the same time, the level of GDH activity did not increase to the control values in men after a course of therapy, in contrast to women.

We have found that the GDH activity after the course of therapy changed and reached the level of control values in the subgroup of patients with RDR, while the GDH activity did not reach the control values in the subgroup of patients with BD. These data may be a sign of the persisting instability of therapeutic remission in the depressive phase of BD, requiring additional therapy, directed at the glutamate system.

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