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HEMOSTASIS MEASURES, PLATELET ENZYMATIC ACTIVITIES AND CLINICAL RESPONSE TO PSYCHOPHARMACOTHERAPY IN FEMALE PATIENTS WITH PSYCHOTIC DEPRESSION

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Abstract

The **objective** was to reveal links between hemostasis measures, platelet enzymatic activities and the clinical response to psychopharmacotherapy (PPT) in female patients with psychotic depression.

Methods. Hemostatic parameters and platelet enzymatic activities were measured before the start of PPT, and the PANSS and HDRS scores were monitored in a course of comprehensive PPT. **Results**. Blood biochemical measures were significantly linked to PANSS and HDRS scores after a course of PPT, as well as with score reductions on these scales. **Conclusion**. Revealing associations between blood parameters and the clinical response to PPT in female patients will facilitate individualized prognosis of PPT efficacy.

INTRODUCTION

Psychotic depression is a complex problem affecting women's mental health. It develops in various psychopathologies and negatively impacts patients' mental status and their quality of life [1]. Psychopharmacotherapeutic (PPT) correction of depressive states is complex due to unpredictable course, variety of exacerbations and response to PPT [2, 3]. Previously, we

discovered blood hypercoagulation in such female patients [4, 5]. Platelets play a role beyond regulating hemostasis. Their metabolism is flexible, and proteome is similar to that of neurons [6] in that they contain glutamate metabolism enzymes, such as phosphate-activated glutaminase (PAG) and glutamate dehydrogenase (GDH), antioxidant enzymes, including glutathione-dependent enzymes [7, 8], and mitochondrial respiratory enzymes [9]. Studies on the relationship between the platelet proteome, hemostasis parameters, and response to PPT are particularly relevant for clinical psychiatry, since, in future, the information could be applied in practice for individual choice of PPT and prognosis of its quality. We previously found that response to PPT was associated with activity levels of platelet enzymes [7], but it was unknown whether it was linked to hemostasis parameters. It also remained unclear how precisely proteomic composition of platelets is regulated in health and in mental illness, that is, how changes in metabolism during platelet activation, associated with their participation in hemostasis, relate to changes in levels of other proteins and enzymes, in particular those listed above and of interest from the point of view of psychopathology.

The aim of the study was to reveal links of hemostasis parameters and platelet enzymatic activity levels with the clinical response to PPT in female patients with psychotic depression.

Materials and Methods

The study was retrospective, observational, in-patient, approved by the Ethics Committee of the RMHRC (Protocol No. 926 dated March 27, 2025, Professor Igor V. Kolykhalov, the Head), it adhered to principles of the Helsinki Declaration of the World Medical Association, as amended in 1975-2024, all patients and control group volunteers signed Informed Consent to participate in the study, which was conducted with due regard for the protection of personal data.

Severity of condition and symptoms were assessed by PANSS and its subscales and by the HDRS [10-12] before the start of PPT course and upon its completion; biomarkers were assessed once before the start of the PPT course. Post-treatment PANSS or HDRS total scores are designated as PANSS2 and HDRS2. Quality of clinical response was defined as the absolute difference (Del) in PANSS and HDRS scores before and after the course of PPT and as the relative reduction (Red) in PANSS and HDRS scores over the course of PPT.

Forty examined female patients aged 17–58 years (median, M=28.0 [20.5; 37.0]) with psychotic depressive-delusional states in schizophrenia, schizoaffective or bipolar disorder (F20.02; F25.1; F31.5 by ICD-10) and a disease duration of 1 to 20 years underwent a course of comprehensive complex antipsychotic therapy with typical and atypical antipsychotics of the second and third generations and SSRIs or AARIs, as well as anticonvulsants with normothymic activity in the inpatient department of the RMHRC in accordance with clinical practice standards.

Exclusion criteria: acute stage of somatic or infectious diseases; substance abuse; antiplatelet therapy.

The control group included 41 healthy women aged 18–56 years (M=33.0 [25.0; 46.0]).

Hemostasis and biochemical platelet measures

Platelet-free plasma was isolated from blood samples (5.4 ml, with 3.2% sodium citrate). We monitored the formation of thrombi (clots) and fibrinolysis in plasma samples by video capture and its digital processing by original methods of Fibrinodynamics (FD) and Thrombodynamics (TD) [4, 5], (HemaCore LLC, Russia).

The TD and FD methods provide the following measures: Tlag (min) – delay time of clot formation onset; Tsp (min) – onset time of spontaneous clots; V (μm/min) – clot growth rate; Vi (μm/min) – initial clot growth rate; CS (μm) – size of fibrin clot 30 min after start of the test; D (arbitrary units, AU) – clot density; CoMaxVal (AU) – coagulation maximum value; LyMax (min) – duration of maximum clot brightness; LL (min) – duration of clot lysis; OCP (AU) – Overall Coagulation Potential; OHP (AU) – Overall Hemostatic Potential (characterizes the hemostasis system balance); OFP (AU) – Overall Fibrinolysis Potential; OFP=OCP-OHP; and OFP% where $OFP\% = \frac{OCP-OHP}{OCP} \times 100\%$.

Specific activities of enzymes of energy- (cytochrome *c*-oxidase, COX, creatine phosphokinase, CPK), glutamate- (GDH and phosphate-activated glutaminase, PAG), and glutathione metabolism (glutathione reductase, GR, glutathione-S-transferase, GST) [7] were determined, and concentrations of SOD isoenzymes were measured by ELISA ("Cytokine"LTD, Russia) in the extracts of isolated platelets.

MedCalc 17.4.1 (MedCalc Software Ltd) was used for statistical processing of data. The normality of data distribution was tested using the Shapiro-Wilk test. Differences and correlations were considered significant at $p < 0.05$. Bonferroni correction for multiple comparisons was applied.

RESULTS

The studied parameters were compared between the patient and control groups. CoMaxVal, OCP and OFP did not differ significantly. This indicates that clot density does not differ between patients and controls. On the other hand, LyMax, LL and OHP are significantly lower in patients than in controls (p=0.006), while OFP% significantly exceeds control values (p=0.005). Thus, the patients exhibit an imbalanced hemostasis system.

COX and GDH activities in patients are significantly reduced relative to the control group (p=0.002), while PAG is increased (p=0.003). COX is involved in energy metabolism, and decreased COX activity and respiratory rate lead to a decrease in energy metabolism. Changes in activities of two glutamate-metabolizing enzymes (GDH, breaking down glutamate, and PAG, synthesizing glutamate) are observed in opposite directions relative to control values. This likely indicates dysregulation of glutamate metabolism associated with psychotic depression in patients (at least before PPT course). However, all three enzymes (COX, GDH, and PAG) are of mitochondrial localization, and changes in activity levels of these enzymes indicate altered platelet mitochondrial processes in the patients.

Even more pronounced intergroup differences between patients and controls are revealed when comparing correlations between hemostasis parameters, as well as correlations between hemostasis measures and platelet enzymatic activity levels (Table 1).

Table 1. Correlations between hemostasis characteristics and blood biochemical parameters in the control group (A) and patients (B).

A

	CoMaxVal	LyMax	LL	OCP	OHP	OFP	OFP%	COX	CPK	GDH	GR	SOD	GST	D	CS	Tlag	Vi	V	Vst	D	Tsp
CoMaxVal				0,82	0,64	0,63							0,46	0,8							
LyMax				0,59	0,86		-0,76					-0,73		0,36	0,33				0,39		
LL				0,43		0,7	0,38										-0,4				
OCP					0,84	0,72				0,33		-0,4	0,55		0,33			0,34		0,67	
OHP							-0,72					-0,64	0,41		0,35			0,37	0,33	0,53	
OFP							0,41	0,38		0,41				0,46							0,72
OFP%												0,6				-0,47					
COX										0,63	0,4	0,39	0,44								
CPK																					
GDH													0,55								
GR																					
SOD															-0,47			-0,46	-0,46		
GST																					
D																					
CS																	0,88	0,94	0,94		
Tlag																					
Vi																		0,8	0,78		
V																					
Vst																					
D																					
Tsp																					

B

	CoMaxVal	LyMax	LL	OCP	OHP	OFP	OFP%	COX	CPK	GDH	GR	SOD	GST	D	CS	Tlag	Vi	V	Vst	D	Tsp
CoMaxVal				0,59	0,49	0,45								0,93	0,53			0,48	0,58	0,93	
LyMax				0,62	0,81		-0,71		-0,4									0,38			
LL						0,52	0,43								-0,76		-0,6	-0,73	-0,71		
OCP					0,8	0,63			-0,3					0,66						0,66	
OHP							-0,72		-0,4	0,39				0,5						0,5	
OFP							0,58							0,55						0,55	
OFP%										-0,45					-0,33			-0,32	-0,33		
COX										0,43						-0,38					
CPK													0,34								
GDH											-0,43										
GR													0,42								
SOD																					
GST																					
D															0,35						
CS																-0,41	0,9	0,94	0,94	0,35	
Tlag																	-0,4	-0,31	-0,34		
Vi																		0,73	0,8		
V																				0,32	
Vst																				0,41	
D																					
Tsp																					

The obvious between-group differences in correlation patterns may indicate the presence of regulatory links between coagulation and platelet antioxidant defense systems in normal conditions, which disappear in the pathology.

On the other hand, appearance of new correlations in the patient group, as compared with norma, apparently indicate arising compensatory links shifting metabolism to pathological state.

In order to understand whether the studied measures are related to clinical response of patients to PPT, an assessment was made of relationships between studied parameters of hemostasis and platelet enzymes with clinical measures of patients after PPT course.

Spearman correlation coefficients (R) were determined between the biochemical measures and PANSS2 and HDRS2 (only significant links were regarded). SOD, GDH and OHP measures were directly correlated with PANSS2 and HDRS2 scores (R=0.37÷0.40). Therefore, it can be said that the higher are the values of these biomarkers in patients, the less favorable is the prognosis for their condition after PPT course (in relation to both psychotic and depressive symptoms). Conversely, PAG and OFP% are inversely correlated with PANSS-Neg2 and HDRS2 scores (R = -0.34 ÷ -0.44), hence, the higher their values in patient, the more favorable the prognosis for the patient' condition after PPT course. However, after Bonferroni correction, only the association between OFP% and HDRS2 remains significant (R = -0.44, p = 0.008).

In addition to correlations with PANSS2 and HDRS2 scores, significant links were also found of biomarkers with scores obtained on individual HDRS items after PPT course. Table 2 shows the Spearmen correlation coefficients. These correlations are interesting because they allow us to identify biomarkers that not only predict the overall condition of patients after a course of PPT, but also identify specific features of the patient's clinical response to PPT. The relationships between LyMax, OFP, OFP%, GDH, and suicidal tendencies in patients at the end of PPT course seem relevant.

Table 2. Correlations (Spearman coefficients R and significance levels p) of hemostasis parameters, platelet enzymatic activity levels with scores for individual PANSS and HDRS items after PPT course and their changes during PPT course (Red, Del).

Biochemical measures	Clinical assessments	R	P-value
Scores by individual items HDRS2			
LyMax	HDRS 1 (low mood)	0.48	0.004
	HDRS 3 (suicidal tendencies)	0.45	0.007
OHP	HDRS 1 (low mood)	0.49	0.003
OFP	HDRS 3 (suicidal tendencies)	-0.47	0.005
	HDRS 11 (somatic anxiety (physiological signs))	-0.52	0.001
OFP%	HDRS 1 (low mood)	-0.59	0.0002

	HDRS 3 (suicidal tendencies)	-0.55	0.0009
GDH	HDRS 3 (suicidal tendencies)	0.44	0.009
	HDRS 21 (obsessive-compulsive disorders)	0.53	0.001
Delta (Del) or reduction (Red) of PANSS scores			
LyMax	PANSS-Neg Del	-0.44	0.005
	PANSS-Neg Red	-0.45	0.004
	PANSS-Psy Del	-0.45	0.004
	PANSS-Psy Red	-0.45	0.005
	PANSS Del	-0.48	0.002
	PANSS Red	-0.49	0.002
LyMaxVal	PANSS-Neg Del	-0.35	0.03
	PANSS-Neg Red	-0.40	0.01
	PANSS-Psy Del	-0.43	0.007
	PANSS-Psy Red	-0.46	0.003
	PANSS Del	-0.43	0.007
	PANSS Red	-0.49	0.002
OCP	PANSS-Neg Red	-0.34	0.03
	PANSS-Psy Del	-0.37	0.02
	PANSS-Psy Red	-0.36	0.02
	PANSS Del	-0.40	0.01
	PANSS Red	-0.38	0.01
OHP	PANSS-Neg Del	-0.36	0.02
	PANSS-Neg Red	-0.39	0.01
	PANSS-Pos Del	-0.35	0.03
	PANSS-Psy Del	-0.44	0.005
	PANSS-Psy Red	-0.44	0.005
	PANSS Del	-0.45	0.005
	PANSS Red	-0.46	0.003
OFP%	PANSS-Psy Del	0.39	0.01
	PANSS-Psy Red	0.41	0.01
	PANSS Del	0.37	0.02
	PANSS Red	0.42	0.009
GST	PANSS-Pos Del	0.36	0.02
	PANSS-Pos Del	0.36	0.02
GDH	PANSS-Psy Del	-0.45	0.005
	PANSS-Psy Red	-0.39	0.01
CPK	PANSS-Neg Del	0.37	0.02
	PANSS-Neg Red	0.36	0.02
	PANSS-Pos Del	0.49	0.002
	PANSS-Pos Red	0.39	0.01
COX	PANSS-Pos Del	0.37	0.02

SOD	PANSS-Pos Red	-0.39	0.01

The most practically important relationships are those between the biochemical parameters and the change (both Del and Red) by PANSS and HDRS, which are presented in Table 2.

Table 2 shows that associations were found between a number of hemostasis measures and platelet enzymatic activity levels and the clinical characteristics of patients' responses to PPT. However, only three associations withstood the Bonferroni correction for multiple comparisons.

Thus, we had never previously studied the relationship between hemostasis measures (fibrinolytic activity) and the quality and characteristics of the clinical response to PPT. This study revealed such a relationship for the first time. Indeed, both methods—TD and FD—were used in this study based on encouraging previous research findings in the field of female psychopathology [4, 5]. However, despite the close correlations between the TD and FD measures, the parameters of TD turned out to be less closely related (sensitive) to changes in indicators (scores) on psychometric scales changing under the influence of PPT.

Limitations of the study: It was impossible to evaluate all the studied parameters after a course of PPT and explore whether PPT affects these parameters. Also, due to the small and heterogeneous nature of the female patient group, some of the associations found here likely do not withstand the Bonferroni correction.

Conclusion

The data of our study evidence that the platelet proteomic composition of healthy women and female patients has different relationships with the hemostasis system. This is indicated by different correlations in norma and pathology between hemostatic parameters and the levels of the enzymes studied, which are not directly involved in hemostatic processes.

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