

Thiol protein groups correlate with cognitive impairment in patients with recurrent depressive disorder

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Abstract

BACKGROUND: Depressive disorders are multifactorial diseases in which cognitive impairments are one of typical features. Thiol protein groups (TPGs) are elements of chemical structure of compounds having antioxidative properties (glutathione peroxidase, metallothioneins) and their oxidation reflects the loss of compensatory capacity of antioxidative mechanisms. The purpose of this study was to determine the level of TPGs in patients with recurrent depressive disorder (rDD) and to define relationship between plasma levels of TPGs and the cognitive performance.

MATERIAL AND METHODS: The study comprised 76 subjects: patients with rDD ($n=43$) and healthy subjects (comparison group, CG – $n=33$). Cognitive function assessment was based on the following 4 tests: the Trail Making Test (TMT), the Stroop Test, Verbal Fluency Test (VFT) and Auditory Verbal Learning Test (AVLT).

RESULTS: The level of TPGs was higher in patients with rDD. In rDD group, the elevated concentration of TPGs in plasma was associated with a decrease in efficiency of declarative-memory, working memory and verbal fluency. The higher was the concentration of plasma TPGs, the greater was the severity of depressive symptoms measured by 21-item Hamilton Depression Rating Scale (HDRS), before and after pharmacotherapy. In CG group, the elevated TPGs levels were associated with worse cognitive test performance (AVLT and VFT tests).

CONCLUSIONS: 1) Our study confirms previous results showing increased TPGs level in depression. 2) Our data suggest relation between increased plasma TPGs level in depression and cognitive impairment. 3) The elevated levels of plasma TPGs are related to impairment of the short-term and delayed declarative memory, verbal fluency and working memory.

INTRODUCTION

Depression and the severity of depressive symptoms are both important and independent risk factors of the development and progression of cognitive impairment (Talarowska *et al.* 2010; Tanaka *et al.* 2012). Chronic inflammatory processes have been investigated as candidate pathways that subsequently link cognitive deficits and depression. Oxidative stress, mitochondrial dysfunction, inflammatory response, altered cell signaling and gene expressions are some of the key features of depressive disorders that lead to morphological and ultrastructural changes in the brain and to cognitive decline (Maes *et al.* 2010).

Social stress, which is the cause of depression, may induce both oxidative stress and cognitive impairments (Kupper *et al.* 2009; Rothman & Mattson 2010; Talarowska *et al.* 2012). Oxidative stress is an imbalance between reactive oxygen species (ROS) and the antioxidant defense system. It is involved in the majority of pathological conditions and many diseases. ROS and other oxidants can cause oxidation of lipids, proteins, carbohydrates and DNA, with the following tissue damage. Toxic products of oxidation proceed cytostatic effects causing membrane damage and lead into cell death *via* apoptosis or necrosis. ROS are engaged in cellular damage, resulting from metabolic disturbances, epileptic conditions, various neurodegenerative diseases, such as Alzheimer disease, parkinsonism, amyotrophic lateral sclerosis and also in mental illnesses (e.g. depressive disorders) (Hepp *et al.* 2005).

In order to protect against adverse effects of free radicals and their derivatives to human body, there is a group of antioxidants, divided into enzymatic and non-enzymatic substances. Enzymatic antioxidants are represented mainly by enzymes such as: copper-zinc superoxide dismutase (CuZnSOD), catalase (CAT), glutathione peroxidase (GPx) and glutathione reductase (GR). Glutathione (GSH), thioredoxin (Trx), vitamins, melatonin, polyphenols, trace elements, albumins act as non-enzymatic free radicals scavengers. Glutathione is the most important thiol non-enzymatic antioxidant (γ -glutamylcysteinylglycine), which participates in first line of defense. The characteristic feature of glutathione are thiol groups which determine its antioxidative characteristics. Estimation of thiol groups is considered to be better antioxidant stress indicator than measurement of total antioxidative capacity (TAC) (Balcerczyk & Bartosz 2003). The role of glutathione in protection against effects of oxidative stress is its function as tripeptide as a cofactor of such enzymes as glutathione peroxidase and glutathione S-transferase which detoxicate products of oxidative stress. Glutathione takes also part in a direct removing of hydroxyl radical and singlet oxygen (Holmgren 2000). This peptide is responsible for amino acids transport through the cell membrane. Another important function of glutathione is keeping in balance of peptide thiol groups. Glutathi-

one thiol groups participate in removing electrophilic xenobiotics. Moreover, glutathione presents ability to regenerate such antioxidants as vitamin E, which is due to reduction of tocopheryl radical. Another thiol antioxidant is thioredoxin system (TRX), which maintains thiol peptide groups and prevents ROS effects of protein oxidation (Baty *et al.* 2002; Dickinson & Forman 2002).

The purpose of this study was to determine the level of thiol protein groups (TPGs) in patients with recurrent depressive disorder (rDD) and to define relationship between plasma levels of TPGs and the cognitive performance. We hypothesized that patients with rDD may have a changed level of the TPGs compared to that of healthy controls and that level of TPGs might affect cognitive function in patients with rDD.

MATERIAL AND METHODS

Patients

The study was carried out in a group of 76 subjects: women, $n=52$, 68.42%, range of age 22–57 years (mean age – 40.29 ± 11.71 , $x \pm SD$); men $n=24$, 31.53%, range of age 20–62 years (mean age – 45.46 ± 13.66 , $x \pm SD$). The study participants were divided into 2 groups: patients with rDD ($n=43$) and healthy subjects (a comparison group, CG, $n=33$). All the patients were native Polish, inhabitants of the central Poland and were unrelated (Table 1). An informed, written consent for participation in the study was obtained from each subject, according to the protocol, approved by the Bioethical Committee of the Medical University of Lodz (No RNN/603/08/KB).

Experimental procedure

Patients were selected for the study according to the inclusion criteria of ICD-10 (F32.0-F32.2, F33.0–F33.8) (ICD-10 Classification of Mental & Behavioural Disorders 1993). They were selected from the group of 58 patients in whom rDD was diagnosed. All the subjects were examined during the course of their hospitalisation. The presence of axis I and II disorders, other than depressive episode, and the diagnosis of somatic diseases and injuries of the central nervous system (CNS), which could have affected the cognitive performance, were regarded as exclusion criteria. Other exclusion criteria were: inflammatory or autoimmune disorders, neurological disorders, substance abuse or dependence and unwilling to give informed consent. Patients who were taking non-steroidal anti-inflammatory drugs were excluded from the study.

In all the included subjects, case history was obtained prior to main study procedure, using the standardized Composite International Diagnostic Interview (CIDI) (Patten 1997). Additionally, the number of depression episodes and the disease duration periods were recorded in each patient. During hospitalization all the patients received antidepressant pharmacotherapy.

Tab. 1. Demographic characteristics of the group with rDD vs. the CG group and the data concerning the course of disease.

Characteristics		rDD* (n=43)			CG** (n=33)		
		n	%	(±SD)	n	%	(±SD)
Gender	Female	25	58.14	-	27	81.82	-
	Male	18	41.86	-	6	18.18	-
Age (yrs)		-	-	47.03 (±10.96)	-	-	39.67 (±10.47)
Education level	Primary	13	30.23	-	-	-	-
	Secondary	24	55.81	-	7	21.21	-
	High	6	13.95	-	26	78.79	-
rDD	Disease duration yrs	-	-	8.23 (±7.91)	-	-	-
	Number of depression episodes	-	-	6.31 (±6.75)	-	-	-

* rDD - recurrent depressive disorders; ** - CG-control group.

The CG consisted of 33 healthy subjects with family history negative for psychiatric disorders. The healthy controls included community volunteers, enrolled into the study on the criteria of the psychiatric CIDI interview (Patten 1997). Controls with other psychiatric diagnoses, concerning axis I and II disorders, neurological disorders, substance abuse or dependence were excluded from the study.

On the basis of medical records and anamnesis, it was established that none of the participants had been diagnosed with mental disability or any of the analyzed intellectual deficits.

All subjects were free of medical illness, including infections and inflammatory or allergic reactions. None of the control subjects or depressed patients were treated with drugs known to influence lipid metabolism, immune response, or endocrine function. The control subjects were free of all medication for at least 2 months prior to blood sampling. None of the control subjects were drinkers, heavy smokers or had ever taken psychotropic drugs.

Cognitive functions assessment

Cognitive function assessment was based on the following 4 tests: the Trail Making Test (TMT), Stroop Test, Auditory-Verbal Learning Test (AVLT) and Verbal Fluency Test (VFT).

Part A of TMT was applied for evaluation of psychomotor speed, while part B was used for assessment of spatio-visual performance, working memory and executive functions (Sánchez-Cubillo *et al.* 2009).

The Stroop Test was performed with the use of paper cards. The test is used for working memory and attention processes evaluations. The Stroop Test consists of two parts: RCNb (reading colour names in black), where the tested subject has to read as quickly as possible 10 rows of written text with 5 words in each row, the words being the names of colours, printed in black ink on a white paper sheet) and NCWd (naming colour of word-different), where the tested subject has to name as quickly as he/she can the ink colours of particular

words, while the ink colour of a given word does not correspond to the colour which the word designates (Audenaert *et al.* 2001).

For evaluating auditory-verbal memory, both direct and delayed one, and the effectiveness of learning processes, a Polish equivalent of the Rey Auditory-Verbal Learning Test, the, so-called, Auditory-Verbal Learning Test (AVLT) was applied. Participants were given a list of 10 nouns repeated over five subsequent trials. After 30 minutes, another trial was undertaken to repeat the words presented before (Łuria 1976).

Verbal Fluency Test (VFT) evaluates the ability to form and fluently utter words compatible with given criteria. The test consists of three parts: names of animals, names of sharp objects, words beginning with the letter 'k' (McDowd *et al.* 2011).

Severity of depression

The severity of depression was assessed by the 21-item Hamilton Depression Rating Scale (HDRS) (Demyttenaere & De Fruyt 2003; Hamilton 1960).

Regarding the patients with rDD, HDRS, the Stroop Test, TMT, AVLT and VFT were applied at the therapy onset. All the patients were examined on admission, i.e., at the symptomatic phase, before or shortly after previous antidepressant drug regime modification. In the CG group, neuropsychological tests were performed in single examination. Examination of patients by the above-mentioned tests was done by the same person in each particular case: the same psychologist examined the patients with neuropsychological tests, including an evaluation of obtained results, while the HDRS test was performed by the same physician-psychiatrist.

Measurement of the plasma TPGs

Blood samples were collected in 5 ml EDTA-containing tubes after overnight fasting on the initial test day. The blood samples were centrifuged at 4000 rpm for 10 min at 4°C to remove plasma. Plasma samples for TP determinations were kept at -70°C until they were analyzed.

Protein oxidation was determined as described by Rice-Evans *et al.* (1991) by plasma thiol groups (SH) with help of Ellman reagent. The principle of the method is the reaction between 5,5'-dithiobis(2-nitrobenzoic) acid (DTNB) and protein thiol groups, which results in releasing 5-thio-2-nitrobenzoic anion, having an intensive yellow color. Two parallel samples have to be prepared, each containing 300 μ l of plasma, 300 μ l 10% dodecyl sulphate (SDS) and 2.5 ml 10 mmol phosphate buffer (pH=8.0). The absorbance of samples was measured at wavelength of 412 nm (A0). 300 μ l of DTNB was added and incubated at temperature of 37 °C for 1 hour. To the control sample, 300 μ l of phosphate buffer was added. Once again the absorbance was measured at wavelength of 412 nm (A1). The difference between absorbances A1-A0 (after subtraction analogous value received for the control group) is the measure of the SH groups content. The concentration of SH groups was read from calibration curve for glutathione. The results were expressed in Trolox equivalents (μ mol/l).

Drop-outs

58 (100%) patients started treatment at the initial day of the study, but only 45 (75%) of them were in remission from depression after 8 weeks of therapy and completed the study, according to our project guidelines. Of the 15 dropouts, 9 were due to pharmacological side effects (headache, sleep disturbances, nausea), 6 were due to lack of improvement in depression symptoms after 6 weeks of treatment. No serious adverse events were reported and no abnormalities in laboratory tests were found during the trial period.

Statistical analysis

Statistical analysis of the collected material utilized descriptive methods, as well as a statistical conclusion. In order to describe the studied group of patients and CG group, structural indexes were calculated in the qualitative analysis of characteristics. In order to estimate the average values for the quantitative characteristics, arithmetic means were calculated. Standard deviation (SD) was adopted as the measure of scatter.

The Lilliefors (Kolmogorov-Smirnov) test for normality was used to evaluate distribution normality of the studied variables. The test values turned out to be statistically insignificant, thus providing no foundations to reject the distribution normality hypothesis.

The t-test for dependent groups was used to evaluate differences in the degree of depressive disorders in the group of rDD patients, both on admission (rDD-I) and after 8 weeks of the therapy continuation (rDD-II). Differences in the TPGs levels were assessed between the rDD groups and the CG, using the t test for independent samples. The relationships between neuropsychological tests with the TPGs levels were expressed as Spearman's correlation coefficients. In all the statistical methods, the p value for statistical significance was: $p < 0.05$.

RESULTS

On admission, 8 subjects met the HDRS score criteria for moderate and 35 – for severe depression episode. On the day of discharge, 26 subjects did not meet the HDRS criteria for depressive disorder, 10 – met the HDRS criteria for mild depression and 7 – for moderate depression. Statistically significant differences were found in the intensity of depression symptoms, measured by the HDRS in rDD group on therapy onset (rDD-I) vs. the examination results after 8 weeks of treatment (rDD-II) ($p < 0.001$; Figure 1).

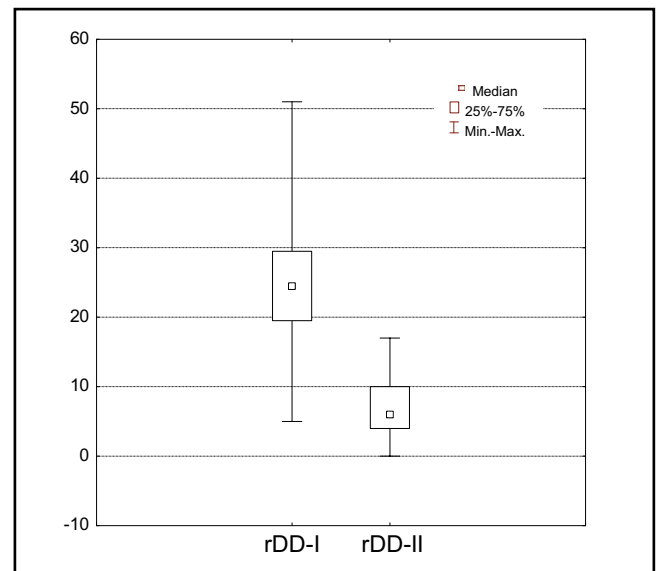


Fig. 1. Differences in the degree of depressive disorders in rDD group. rDD - recurrent depressive disorders; HDRS - Hamilton Depression Rating Scale; rDD-I – HDRS on admission; rDD-II - HDRS after 8 weeks of the therapy continuation.

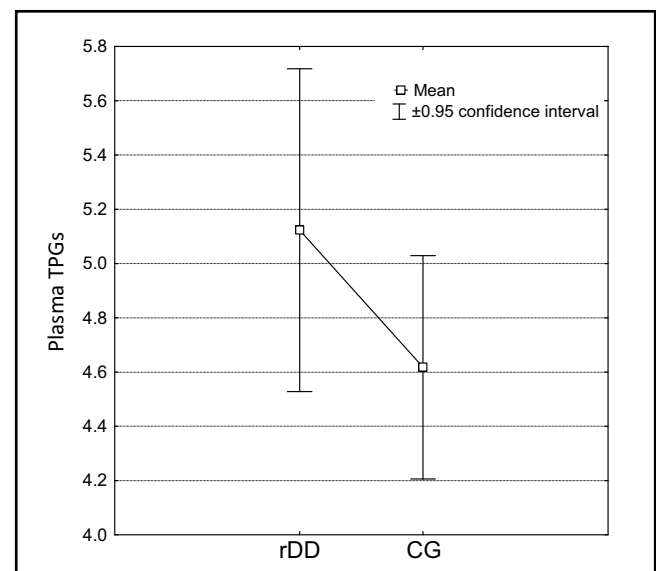


Fig. 2. Comparison of control and study group on TPGs. TPGs - thiol protein groups; rDD - recurrent depressive disorders; CG - control group.

Tab. 2. Spearman's rank correlation coefficients (Rs) for the variables tested – rDD group (n=43).

Variable	Rs
Plasma TPG*s&HDRS** on the day of admission to the hospital	0.149
Plasma TPGs &HDRS after 8 weeks of pharmacotherapy	0.086
Plasma TPGs &Stroop Test/RCNb*** time(s)	-0.008
Plasma TPGs &Stroop Test/NCWd# time(s)	-0.127
Plasma TPGs &Stroop Test/NCWd (errors)	-0.019
Plasma TPGs &TMT##/A time(s)	-0.094
Plasma TPGs &TMT/B time(s)	0.136
Plasma TPGs &AVLT### 1 trial	-0.328*
Plasma TPGs &AVLT after 30 minutes	-0.111
Plasma TPGs &VFT ¹ /animals	-0.263
Plasma TPGs &VFT/sharp objects	-0.052
Plasma TPGs &VFT / letter „k”	-0.028

*TPGs - thiol protein groups; ** - HDRS-Hamilton Depression Rating Scale; *** - RCNb-reading colour names in black; # - NCWd-naming colour of word-different; ## - TMT-Trail Making Test; ### - AVLT-Auditory Verbal Learning Test; 1 - VFT Verbal Fluency Test; *p<0.005.

Tab. 3. Spearman's rank correlation coefficients (Rs) for the variables tested – CG group (n=33).

Variable	Rs
Plasma TPGs* &Stroop Test/RCNb** time(s)	-0.098
Plasma TPGs &Stroop Test/NCWd# time(s)	-0.005
Plasma TPGs &Stroop Test/NCWd(errors)	-0.019
Plasma TPGs &TMT##/A time(s)	-0.159
Plasma TPGs &TMT/B time(s)	-0.044
Plasma TPGs &AVLT### 1 trial	0.059
Plasma TPGs &AVLT after 30 minutes	-0.004
Plasma TPGs &VFT ¹ /animals	-0.011
Plasma TPGs &VFT/sharp objects	-0.121
Plasma TPGs &VFT/letter „k”	-0.018

*TPGs - thiol protein groups; ** - RCNb-reading colour names in black; # - NCWd-naming colour of word-different; ## - TMT-Trail Making Test; ### - AVLT-Auditory Verbal Learning Test; 1 - VFT-Verbal Fluency Test; *p<0.005.

The mean value of TPGs in the study group was $4.91 \pm 1.65 \mu\text{mol/l}$ ($x \pm \text{SD}$). There were no significant differences in plasma TPGs level ($\mu\text{mol/l}$) between patients with rDD and controls ($p=0.18$; Figure 2). The level of TPGs was higher in patients with rDD.

Table 2 presents the correlation between the level of TPGs, and the cognitive test results for patients with rDD before pharmacotherapy ($n=43$). There were no statistically significant relationship between the assessed variables, however elevated concentration

Tab. 4. Spearman's rank correlation coefficients (Rs) for the variables tested (n=73).

Variable	Rs
Plasma TPGs* &Stroop Test/RCNb*** time(s)	0.057
Plasma TPGs &Stroop Test/NCWd# time(s)	-0.009
Plasma TPGs &Stroop Test/NCWd(errors)	0.023
Plasma TPGs &TMT##/A time(s)	0.006
Plasma TPGs &TMT/B time(s)	0.151
Plasma TPGs &AVLT ###1 trial	-0.214
Plasma TPGs &AVLT after 30 minutes	-0.131
Plasma TPGs &VFT ¹ /animals	-0.212
Plasma TPGs &VFT/sharp objects	-0.093
Plasma TPGs &VFT/letter „k”	-0.087

*TPGs - thiol protein groups; ** - RCNb-reading colour names in black; # - NCWd-naming colour of word-different; ## - TMT-Trail Making Test; ### - AVLT-Auditory Verbal Learning Test; 1 - VFT-Verbal Fluency Test; *p<0.005.

of TPGs in plasma was associated with a decrease in efficiency of short-term declarative memory (AVLT-trial1), long-term declarative-memory (AVLT after 30 minutes), visual-spatial working memory (TMT part B) and verbal fluency (VFT). There was no such relation in the case of Stroop Test and TMT part A. There was no statistically correlation between TPGs level and the results in HDRS on the day of admission to the hospital. However, the higher was the concentration of plasma TPGs, the greater was the severity of depressive symptoms measured by HDRS (Table 2).

Table 3 presents the correlation between the level of TPGs, and the cognitive test results for CG patients ($n=33$). Elevated TPGs levels were associated with worse cognitive test performance: AVLT-trial 1 (short-term declarative memory) and VFT (verbal fluency) (Table 3).

Table 4 presents the correlation between the level of TPGs, and the cognitive test results for all examined subjects ($n=76$). Elevated TPGs levels were associated with worse cognitive test performance: AVLT-trial 1 (short-term declarative memory), AVLT after 30 minutes (long-term declarative-memory), VFT (verbal fluency), TMT and Stroop Test (visual-spatial and verbal working memory) (Table 4).

DISCUSSION

The present results demonstrate that plasma level of TPGs is higher in patients with rDD than in controls. SH-groups are components of compounds having antioxidative properties (glutathione peroxidase, metallothionein, albumin) and their oxidation to disulfidebridges reflects the lost of compensatory capacity of antioxidative mechanisms. The increase of this parameter at those suffering from depression in comparison

with healthy ones indicates the more intensive course of antioxidative processes at those with depression.

The higher activities of TPGs might be a compensatory mechanism to excessive production of ROS in depressed patients. Results are in line with data obtained by Gałeczki *et al.* (2009). In the mentioned work, patients with depressive disorder have statistically higher activities of antioxidant enzymes, such as CuZnSOD and CAT in erythrocytes before treatment as compared to healthy controls.

In the animal model, Claeysen *et al.* (2008) confirm that after trauma, the SH groups decrease which suggesting an enhanced protein oxidation. According to Ansari and Scheff (2010), decline in antioxidants occurs early in the progression of the dementia. The free radical burden continues to increase with a decline in cognitive status. It seems that the course of depressive disorders is important. In the case of acute conditions, the plasma level of SH groups is reduced, while in chronic depression it is increased. In the course of chronic diseases (e.g., depressive disorders), we observe the compensatory increase in activity and/or expression of antioxidant processes (Maes *et al.* 2009).

Another finding of our study is a link between cognitive impairment in rDD patients and increased level of TPGs. To our knowledge, this is the first study investigating relation between cognitive function and level of TPGs in depression. In the group of patients with depression the increased level of TPGs is related to decreased efficiency of those cognitive functions which are related to hippocampus area-short-term and delayed declarative memory, as well as verbal fluency (Table 2). For the whole examined group, apart from already mentioned, efficiency of operating memory (visual-spatial and verbal) was also decreased. Results are in line with data obtained by Ansari and Scheff (2010). They observed that individuals with lower MMSE (Mini-Mental State Examination) scores had lower GSH/GSSR (oxidized GSH) ratios (Ansari & Scheff 2010). Moreover, a decrease in GSH levels and subsequent GSSG production has been linked to neuronal loss in AD (Benzi & Moretti 1995).

Depressive disorders are associated with neurodegeneration and a reduced neurogenesis in the brain (Meas *et al.* 2009). After trauma or stress, imbalance between oxygen species production and free radicals scavengers determine the outcome of local and distant tissue damage, and further organ failure. The results of our research indicate that – in case of depression – the region of hippocampus and prefrontal cortex is particularly sensitive area to oxidative stress. It turns out that in hippocampal neurons, various ion channels and receptors have been shown to be sensitive to redox modulation (Evola *et al.* 2010). At those suffering from depression the changes observed in hippocampus are similar to the ones associated with the aging process. Numerous anatomical and physiological alterations have been characterized in the hippocampus with aging

that may contribute to cognitive decline (decreased hippocampal volume, vascular rarefaction, decreased trophic support, increased oxidative stress and inflammation, decreased metabolism and glucose utilization, dysregulation of protein synthesis, folding, and accumulation, and impaired neurotransmitter synthesis and release) (Vanguilder & Freeman 2011). Furthermore, lipid peroxidation is significantly much higher in hippocampus and inferior parietal lobe of elderly individuals who exhibit mild cognitive impairment (MCI) (Butterfield *et al.* 2006; Vanguilder & Freeman 2011). Moreover, the hippocampal CA1 region and dentate gyrus are more prone to damage by oxidative stress (Uysal *et al.* 2012). Taking the above results into account, we may suggest that there is a connection between oxidative stress and memory or learning processes. An oxidative stress pathway starts in the CA3 sector progresses to CA1 and, then, continues to other hippocampal and cortical areas building a pathological pathway for AD progression (Cruz-Sánchez *et al.* 2010).

Frontal lobes and especially prefrontal cortex is the second brain area vulnerable to damages being the consequence of oxidative stress (Cruz-Sánchez *et al.* 2010; Mandal *et al.* 2012). A variety of studies suggest that major depression involves abnormalities of corticolimbic structures, including prefrontal cortex (Gruber *et al.* 2011; Hammar & Ardal 2009; Tavares *et al.* 2007). According to Fraquas *et al.* (2012), lower baseline GSH levels is significantly associated with greater volume decrease in left frontal gray matter in children and adolescents with first-episode psychosis.

Our present study reports the data to support a link between oxidative stress, depressive disorders and cognitive decline. It should be emphasized that the mechanisms mediating these effects are unclear. Correlations between the oxidative stress marker and cognitive impairment indicate that oxidative stress should be considered as a risk factor in the development of cognitive disorders. The results obtained by us seem to partially confirm the inflammatory/oxidative stress theory of depression. According to our data, plasma TP level needs further confirmation and investigation but it might possibly be another peripheral marker of cognitive disturbances in depressive disorders.

The smaller number of patients with rDD in our study group may be a limitation of our study. The results of our preliminary study require further validation in subsequent research.

CONCLUSIONS

1. Our study confirms previous results showing increased TPGs level in depression.
2. Our data suggest relation between increased plasma TPGs level in depression and cognitive impairment.
3. Elevated levels of plasma TPGs are related to impairment of short-term and delayed declarative memory, verbal fluency and working memory.

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