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Malondialdehyde plasma concentration correlates with declarative and working memory in patients with recurrent depressive disorder

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Abstract Oxidative stress has been implicated in the cognitive decline, especially in memory impairment. The purpose of this study was to determine the concentration of malondialdehyde (MDA) in patients with recurrent depressive disorders (rDD) and to define relationship between plasma levels of MDA and the cognitive performance. The study comprised 46 patients meeting criteria for rDD. Cognitive function assessment was based on: The Trail Making Test , The Stroop Test, Verbal Fluency Test and Auditory-Verbal Learning Test. The severity of depression symptoms was assessed using the Hamilton Depression Rating Scale (HDRS). Statistically significant differences were found in the intensity of depression symptoms, measured by the HDRS on therapy onset versus the examination results after 8 weeks of treatment ($P < 0.001$). Considering the 8-week pharmacotherapy period, rDD patients presented better outcomes in cognitive function tests. There was no statistically significant correlation between plasma MDA levels, and the age, disease duration, number of previous depressive episodes and the results in HDRS applied on admission and on discharge. Elevated levels of MDA adversely affected the efficiency of visual-spatial and auditory-verbal working memory, short-term declarative memory and the delayed recall declarative memory. 1. Higher concentration of plasma MDA in rDD patients is associated with the severity of depressive symptoms, both at the beginning of antidepressants pharmacotherapy, and after 8 weeks of its duration. 2. Elevated levels of plasma MDA are related to the impairment of visual-spatial and auditory-verbal working memory and short-term and delayed declarative memory.

Keywords Oxidative stress · MDA · Depressive disorders · Cognitive functions

Introduction

The most evident symptoms of recurrent depressive disorders (rDD) are related to the emotional functioning of affected patient. However, depression also disturbs the cognitive functions of affected patients [1]. Cognitive function impairment in patients, who suffer from depressive disorders, can differ in scope and severity (varying from selective, specific and mild deficits to generalized and pronounced changes) [2].

Emotional stress can be viewed as a cause of adverse conditions that induces a induce a variety of biochemical and behavioural changes. Oxidative stress is a critical route of damage in various psychological stress-induced disorders such as recurrent depressive disorders [3, 4]. The most recent findings in neurobiological research provided an

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increasing evidence that inflammatory and neuroprogressive processes play a significant role in depression [5]. Preclinical and clinical studies on depression highlighted an increased production of inflammatory markers, such as interleukin (IL)-1, IL-6, tumor necrosis factor-α and interferon- α and γ. In animal models, acute and chronic administration of cytokines or cytokine inducers trigger depressive symptoms. There is now evidence that oxidative stress plays an important role in depression, i.e. increased lipid peroxidation, damage to DNA and functional proteins, and decreased levels of antioxidants, such as glutathione, zinc, vitamin E and coenzyme Q10, and antioxidant enzymes, such as glutathione peroxidase [6, 7]. The activation of the inflammatory and neuroprogressive pathways may induce the brain damage observed in depression through both reduced neurogenesis and increased neurodegeneration [7, 8].

Malondialdehyde (MDA) is a product of lipid peroxidation and also a sensitive indicator of cell membrane damage. MDA, a marker of the severity of lipid peroxidation processes, reflects the degree of cellular damage. Increased MDA is a biomarker of antioxidant defense systems capacity and oxidative damage caused by reactive oxygen species (ROS) [9]. Oxidative stress plays a role in the pathogenesis of a number of diseases, including many diseases of central nervous system (i.e. ischemic stroke, Alzheimer's disease—AD, Parkinson's disease—PD, amyotrophic lateral sclerosis—ALS, multiple sclerosis—MS) [10] and psychiatric diseases [11]. In patients with social phobia augmented antioxidant enzymes activity (catalase—CAT, superoxide dismutases—SOD, glutathione peroxidases—GPx) and MDA were observed [12]. Increased levels of antioxidant enzymes were also found in patients with schizophrenia [13], bipolar disorder [14] and obsessive–compulsive disorder (OCD) [15]. Moreover, oxidative stress has been implicated in the cognitive decline, especially in memory impairment [16, 17].

The purpose of this study was to determine the concentration of MDA in patients with recurrent depressive disorder and to define relationship between plasma levels of MDA and the cognitive performance.

Materials and methods

Patients

The study comprised 46 patients meeting criteria for recurrent depressive disorders (women $n = 26$, 56.52%), aged 20–62 ($M = 48.06$ years, SD = 10.86). All the patients were native Poles, inhabitants of the central Poland and unrelated. 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 Łódź (No RNN/603/08/KB).

Table 1 Demographic characteristics of the group with rDD and the data concerning the course of disease

Characteristics	rDD $n = 46$		
	n	%	(±SD)
Gender			
Female	26	56.52	–
Male	20	43.48	–
Age in years			
–	–	–	48.06 (±10.87)
Education level			
Primary	14	30.43	–
Secondary	26	56.52	–
High	6	13.04	–
Education period in years			
–	–	–	11.61 (±2.58)
Disease			
Disease duration in years	–	–	8.31 (±8.17)
Number of depression episodes	–	–	5.98 (±6.64)

rDD recurrent depressive disorders, *n* numbers of patients; % percentage, ±*SD* standard deviation

Education was measured by the number of school years completed. The education period ≤9 years was considered primary, 10–12 years—secondary and >12 years—higher education (according to the Polish educational system). Demographic characteristics and clinical course data are presented in Table 1.

Patients were selected for the study according to the inclusion criteria of ICD-10 (F 32.0–7.32.2, F 33.0–F 33.8) [18]. All the subjects were examined during the course of their hospitalisation. The study group included subjects, hospitalised for the first time for depressive episode and depression treatment-naïve, as well as those, treated for many years before and with multiple hospitalisation episodes in history, the latter admitted for various degrees of health deterioration. 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. In all the included subjects, case history was obtained prior to main study procedure, using the standardized Composite International Diagnostic Interview (CIDI) [19]. Additionally, the number of depression episodes and the disease duration periods were recorded in each patient. During hospitalization

all the patients received antidepressant pharmacotherapy, including the selective serotonin reuptake inhibitors (SSRI, $n = 19$), 5-HT2A/C receptor antagonists ($n = 4$), combined serotonin-norepinephrine reuptake inhibitors (SNRI, $n = 4$), serotonin antagonist and reuptake inhibitors (SARI, $n = 5$), SSRIs in combination with receptor antagonists ($n = 5$), SSRIs in combination with a new generation of antidepressants ($n = 4$), melatoninergic agonists ($n = 1$), and tricyclic antidepressants (TCA, $n = 1$). The specified agents were administered in therapeutic doses, defined by Taylor et al. [20].

No evaluations of the intellectual functions of the enrolled patients were carried out prior to the psychological examination. However, 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. None of the examined subjects smoked cigarettes.

Methods

Cognitive function assessment was based on: The Trail Making Test (TMT), The Stroop Test, Auditory-Verbal Learning Test (AVLT) and Verbal Fluency Test (VFT). Different versions of the AVLT and VFT were performed in the second examination (after 8 weeks of pharmacotherapy) in order to eliminate the learning effect. In case of Stroop Test and TMT the learning effect has little impact on the performance [21–25].

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. Regarding the Trail Making Test, time periods, required to complete each part, were estimated. The authors based their analysis on raw results [21, 22].

The Stroop Test (Colour-Word Interference Test) was performed with the use of paper cards. We used a Polish version based on the original Stroop Test cards. The test is used for working memory evaluations. The level of the test performance depends on the efficiency of attention functions (i.e. concentration, selectivity). The test provides data, concerning cognitive flexibility and the inhibition of impulsive, automatic response (because of its requirement to counteract an automatic, interfering response). 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. The test evaluation is based on the time, obtained during the first part and the second part of the test and the number of perseverance errors, made during the second part. The NCWd Part of the Stroop Test measures effectiveness of verbal working memory, executive functions, and attention processes. In the reported study, the dependent variables were: the number of errors made in the NCWd part, and the duration of each test part performance [23–25].

For evaluating auditory-verbal memory, both direct and delayed, and the effectiveness of learning processes, a Polish equivalent of the Rey AVLT, the, so-called, AVLT was applied. Participants were given a list of 10 nouns (notebook, tree, duck, train, candle, hammer, radio, doll, butter, river—in the first examination; needle, fish, chair, bicycle, mirror, lollipop, ball, apple, tie, glass ball—after 8 weeks of pharmacotherapy) presented in a repeating five-trial sequence. The researcher read words from a list, then, the person repeated all the words, memorised during each learning trial. After 30 min, another trial was undertaken to repeat the words presented before [26, 27]. AVLT is a clinical trial with no Polish adaptation (neither accuracy and reliability/integrity coefficients nor Polish standards have been developed).

Verbal Fluency Test evaluates the ability to form and fluently utter words compatible with given criteria. The test consists of three parts. The first two parts consist in listing in 60 s as many as possible words that belong to a given semantic category (usually names of objects). In the third part the objective is to list in 60 s as many as possible words that belong to a given phonetic category—words beginning with a given letter. In the presented study these categories were: names of animals (category 1); names of sharp objects (category 2) and words beginning with the letter 'k' (category 3) (examination on admission) and names of plants (category 1), names of round objects (category 2), words beginning with the letter 'm' (category 3) (examination after 8 weeks of pharmacotherapy). The result of the test is the number of correct words listed for each of categories [28].

The severity of depression was assessed by the 21-item Hamilton Depression Rating Scale (HDRS) [29, 30]. Depressive symptom intensity levels were classified by the grades, specified in the study by Demyttenaere and De Fruyt [31]. The HDRS scale was also used for clinical improvement evaluations after applied pharmacotherapy, with HDRS scores after 8 weeks of therapy as improvement indicators versus depression levels (in HDRS scale). The psychic status improvement and the efficacy of applied therapy were evaluated in two aspects: the response to therapy and disease remission. A response to therapy was defined as $\geq 50\%$ depression symptom reduction versus the base level, while HDRS score <7 was regarded remission.

In the whole group the blood was collected at the same period of the day. MDA plasma concentrations was determined according to the method of Placer et al. [32]. HDRS, The Stroop Test, TMT, AVLT and VFT were applied at the therapy onset (on admission) and after 8 weeks of its continuation. All the patients were examined on admission, i.e., at the symptomatic phase, before or shortly after previous antidepressant drug regime modification. In the control group, neuropsychological tests were performed in single examination. Examination of patients with 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.

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 structural indexes were calculated in the qualitative analysis of characteristics. In order to estimate the mean values of the quantitative characteristics, arithmetic means (M) 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 and of the neuropsychological tests performance levels in the group of rDD patients, both on admission (rDD-I) and after 8 weeks of the therapy continuation (rDD-II). The relationships between neuropsychological tests with the MDA 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, 2 subjects met the HDRS score criteria for mild, 8 for moderate and 36 for severe depression episode. On the day of discharge, 29 subjects did not meet the HDRS criteria for depressive disorder, 13 met the HDRS criteria for mild depression and 4 for moderate depression (see Fig. 1).

Statistically significant differences were found in the intensity of depression symptoms, measured by the HDRS in rDD group on therapy onset (rDD-I) versus the examination

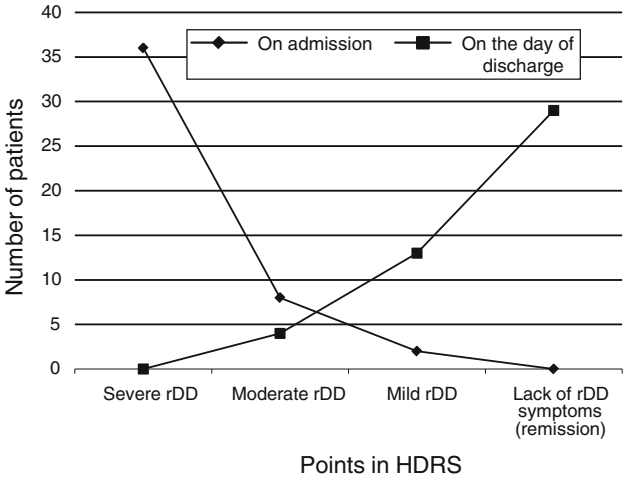

Fig. 1 Enhancement of depression symptoms in the study group ($n = 46$) on admission and on the day of discharge (measured by HDRS). *rDD* recurrent depressive disorders, *HDRS* Hamilton Depression Rating Scale

results after 8 weeks of treatment (rDD-II) ($P < 0.001$) (see Table 2).

Considering the 8-week pharmacotherapy period, rDD patients presented better outcomes in cognitive function tests versus the results on therapy onset (see Table 2): RCNb/time ($P = 0.009$), NCWd/time ($P = 0.03$), NCWd/errors ($P = 0.849$, *ns*), TMT part A/time ($P = 0.01$), TMT part B/time ($P = 0.04$), VFT/animals ($P = 0.13$, ns), VFT/'k' letter ($P = 1.00$, *ns*), VFT/sharp objects ($P = 0.92$, *ns*).

The mean value of plasma MDA in the study group was $M = 5.931$ (± 1.095). Table 3 presents the relationship between selected variables associated with the course of the disease, and MDA plasma concentration.

There was no statistically significant correlation between plasma MDA levels (mmol/l), and the age of subjects, duration of illness, number of episodes of depression, and the results in HDRS applied on admission and discharge.

Table 4 presents the correlation between the plasma level of MDA, and the cognitive test results. Although the link was not statistically significant, it was observed, that elevated levels of MDA in blood plasma adversely affected the efficiency of visual-spatial (TMT) and auditory-verbal working memory (The Stroop Test, VFT/'k' letter), short-term declarative memory (AVLT—trial 1) as well as the delayed recall declarative memory (AVLT after 30 min).

Discussion

The results of numerous studies demonstrate the imbalance in oxidant-antioxidant system in patients with recurrent depressive disorder [33]. In the present study higher levels of plasma MDA in rDD patients was correlated with more

Table 2 Cognitive tests performance on admission and after 8 weeks of therapy

Variable	rDD-I M (±SD)	rDD-II M (±SD)	*t*	*P*
HDRS	24.37 (±7.69)	6.89 (±3.97)	15.16	<0.001*
Stroop Test/RCNb time (*s*)	38.83 (±19.16)	32.61 (±11.62)	2.77	0.009*
Stroop Test/NCWd time (*s*)	81.01 (±47.77)	69.25 (±35.89)	2.18	0.03*
Stroop Test/NCWd (errors)	5.01 (±6.53)	4.51 (±14.81)	−0.19	0.849
TMT/A time (*s*)	56.01 (±39.11)	45.73 (±24.94)	2.51	0.01*
TMT B time (*s*)	121.53 (±91.59)	95.83 (±43.56)	2.08	0.04*
AVLT 1 trial	5.29 (±1.35)	5.29 (±1.35)	0.01	1
AVLT after 30 min	5.96 (±2.51)	6.55 (±2.23)	−1.24	0.22
VFT/category 1	18.19 (±5.52)	16.81 (±4.35)	1.53	0.13
VFT/category 2	8.93 (±2.85)	8.87 (±3.37)	0.09	0.92
VFT/category 3	13.97 (±5.03)	13.91 (±4.27)	0.01	1.00

HDRS Hamilton Depression Rating Scale, *TMT* Trail Making Test, *AVLT* Auditory Verbal Learning Test, *VFT* Verbal Fluency Test, *rDD-I* patients with recurrent depressive disorders, examined on therapy onset, *rDD-II* RDD patients after 8-week therapy, ±*SD* standard deviation, *P** statistically significant, $P < 0.05$

Table 3 Spearman's rank correlation coefficients (Rs) for the variables tested

Variable	Plasma MDA µMol/l	
	Pearson's *r*	*P*
Age ($n = 46$)	−0.026	0.818
Disease duration ($n = 46$)	0.009	0.951
Number of depressive episodes ($n = 46$)	−0.005	0.976
HDRS on the day of admission to the hospital ($n = 46$)	0.182	0.235
HDRS on the day of discharge ($n = 46$)	0.166	0.286

MDA Malondialdehyde, *HDRS* Hamilton Depression Rating Scale, *n* number of patients

severe depressive symptoms, both at the pharmacotherapy onset, and after 8 weeks of therapy admission. Kuloglu et al. [34] found a higher concentration of MDA in blood

Table 4 Spearman's rank correlation coefficients (Rs) for the variables tested

Variable	*n*	*R*	*t*	*P*
Plasma MDA & Stroop Test/RCNb time (*s*)	46	0.155	1.042	0.302
Plasma MDA & Stroop Test/ NCWd time (*s*)	46	0.198	1.341	0.186
Plasma MDA & Stroop Test/ NCWd (errors)	46	0.108	0.721	0.474
Plasma MDA & TMT/A time (*s*)	46	0.151	1.005	0.321
Plasma MDA & TMT/B time (*s*)	46	0.055	0.364	0.716
Plasma MDA & AVLT 1 trial	46	−0.117	−0.784	0.437
Plasma MDA & AVLT after 30 min	46	−0.045	0.305	0.761
Plasma MDA & VFT/Animals	46	0.027	0.181	0.856
Plasma MDA & VFT/sharp objects	46	0.322	2.259	0.028*
Plasma MDA & VFT/letter 'k'	46	−0.036	−0.241	0.811

TMT Trail Making Test, *AVLT* Auditory Verbal Learning Test, *VFT* Verbal Fluency Test, *MDA* Malondialdehyde, *P** statistically significant, $P < 0.05$

plasma of patients with OCD and concomitant depressive disorders (OCD + DD) compared to patients with OCD (OCD − DD). These authors also found a positive correlation between the plasma MDA concentration and the intensity of depressive symptoms measured by HDRS in the group of OCD + DD patients. The results point to the conclusion that the concentration of MDA in blood plasma may be associated with the severity of depressive disorders [35].

Interestingly, we found no significant inverse relationship between age and plasma MDA. There is a hypothesis that MDA is involved in the aging process. Reacting with proteins, MDA generates production of lipofuscin that accumulates intracellularly. Lipofuscin accumulation is a symptom of aging and can be regarded as a marker of biological age [36, 37]. Delibas et al. study [38] also proved no statistically significant relationship between patients age and the concentration of MDA in plasma. The fact that antidepressants act as an antioxidative agent should be taken into consideration [6, 39].

The influence of oxidative stress on cognitive performance has been repeatedly confirmed [40–42]. Some studies have demonstrated an accumulation of products of free radical damage in the CNS and in the peripheral tissues of patients with AD or mild cognitive impairment (MCI) [43]. Ambali et al. [44], in a study based on animal models have shown that increased concentrations of MDA in the brain of rats were associated with decreased efficiency of eye-hand coordination, memory and learning abilities. Among patients with AD, Delibas et al. [38] observed an inverse correlation between the concentration of MDA in plasma and the results in

Mini-Mental State Examination (MMSE), which is the most commonly administered psychometric screening assessment of cognitive functioning. Correspondingly, Torres et al. [42] observed elevated levels of MDA, not only among patients with AD, but also in patients with a diagnosis of MCI. MDA plasma concentration correlated negatively with the results of the MMSE. According to the authors, the level of plasma MDA can be considered as a biomarker of MCI and AD. Analogous results were found in a study by Umur et al. [45]. It should be noted, however, that in most cited papers, the assessment of cognitive functioning was based on MMSE which is not a very sensitive diagnostic tool. In our study, we used sensitive psychological methods allowing a more accurate assessment of the effectiveness of selected cognitive functions. The analysis revealed that increased level of MDA in patients with rDD is related to the impairment of visual-spatial and auditory-verbal working memory, short-term and delayed declarative memory.

Recent neurobiological findings suggest that depressive disorders are associated with structural and functional changes in the brain structures which are critical for declarative and working memory functioning [1]. The most frequent changes in the brain structure of patients with depressive disorders, include reduced volumes of: the frontal lobes, the orbital prefrontal cortex, the anterior part of the cingulate gyrus, the hippocampus and the amygdala [46]. In studies on animal models, neurodegenerative changes of the hippocampal structures were observed, as well as neurogenesis inhibition in the dentate gyrus of the hippocampus and reduction of the length and number of apical dendrites in pyramidal cells of the hippocampal CA3 region [47]. According to Cai et al. [48], oxidative stress is a well established mechanism of cellular injury in mammals. Brain tissue contains a large amount of polyunsaturated fatty acids, which are highly susceptible to oxidative reactions. Oxidative stress and increased gliosis have been associated with aging related behavioral impairments on spatial learning tasks in the rodent, and similar increases in gliosis in the cortex and hippocampal CA1 region have been observed in the rat after exposure to oxidative stress.

It is worth mentioning, that sources of oxidative stress include numerous exogenous factors, such as alcohol consumption, cold, drugs intake (i.e. steroids), viral and bacterial infections, trauma, electromagnetic radiation, toxins, strenuous or excessive exercise, stress, poor diet, cigarette smoking [49]. Studies by Sarandol et al. [50] (6-week therapy) and Gałecki et al. [51] (12-week therapy) did not confirm the beneficial effects of antidepressant pharmacotherapy on optimal oxidant/antioxidant balance. Nevertheless, Kotan et al. [39] found decreased MDA levels following a 24-week antidepressant treatment. Therefore, the length of treatment appears to be an important variable to consider. Using an animal model, Novio et al. [4] confirmed the high efficacy of fluoxetine in reducing negative effects of oxidative stress. Gałecki et al. argue [35], that adding acetylsalicylic acid (ASA) to the treatment of DD diminishes the negative effects of oxidative stress and increases the effectiveness of treatment. The study provided evidence that combined therapy with fluoxetine and ASA is characterized by the same efficacy and clinical safety as fluoxetine monotherapy, additionally resulting in improvement of oxidative stress parameters in the patients treated for DD.

Undoubtedly, further studies are necessary before a firm conclusion how exactly oxidative stress impact cognitive functioning in patient with rDD can be reached.

The smaller number of patients with rDD in our study may be a limitation of this research. Furthermore, sample size might possibly affect the statistical significance of the results. Taking into account the above-mentioned limitation, the results should be interpreted with caution. The results of our preliminary study require further validation in subsequent research.

Conclusions

1. Higher concentration of plasma MDA in rDD patients is associated with the severity of depressive symptoms, both at the beginning of antidepressants pharmacotherapy, and after 8 weeks of its duration.
2. Elevated levels of plasma MDA are related to impairment of visual-spatial and auditory-verbal working memory and short-term and delayed declarative memory.

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