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DIRECT CORRELATION BETWEEN THE SCORES OF PANSS/AIMS SCALES AND SOME OXIDATIVE STRESS MARKERS IN TREATED SCHIZOPHRENIC PATIENTS

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Abstract - Oxidative stress is increasingly viewed as potentially important in the pathophysiology of schizophrenia, although most results regarding this subject are contradictory. We previously demonstrated an increased oxidative stress status in schizophrenic patients, regardless of their treatment. In this paper, we were interested in whether there is a correlation between the specific activities of the most important antioxidant enzymes (superoxide dismutase and glutathione peroxidase) and a lipid peroxidation marker (malondialdehyde) and the scores of PANSS/AIMS scales. A direct significant correlation was observed between oxidative stress markers and the aforementioned scales. Our results provide additional evidence regarding the implications of oxidative stress in patients with schizophrenia.

Key words: schizophrenia; oxidative stress; Positive and Negative Syndrome Scale (PANSS); Abnormal Involuntary Movement Scale (AIMS).

INTRODUCTION

In recent years, oxidative stress has drawn increasingly more attention of scientists, and many studies in the medical and biological fields have focused on the mechanisms underlying this process, taking into account the increased significance of oxidative stress in many neuropsychological diseases, including schizophrenia (Halliwell and Gutteridge, 2007). Oxidative stress is a biochemical event, which consists of the disruption of the oxidant/antioxidant balance, the antioxidant component exceeding its defense capacity (Sies, 1997).

Schizophrenia is a debilitating disease characterized by structural and functional changes. However, its pathogenesis is still largely unclear. The involvement of oxidative stress in the pathology of schizophrenia has been speculated by a series of researchers, many studies identifying a change in the balance between pro-oxidant and antioxidant factors in patients with cognitive diseases (Ciobica et al., 2011, Kunz et al. 2008, Martins et al., 2008). Presently, it is thought that, at least in part, the neuropathological changes in this disease may be triggered by the mechanisms associated to oxidative stress (Yao et al., 2001).

Compared to other tissues, the brain has the highest percentage of unsaturated fats, which makes its cells potentially more vulnerable to the attack of free radicals (Ciobica et al., 2012, Padurariu et al., 2013). Moreover, susceptibility to free radicals is amplified by the presence at this level of an increased

number of mitochondria, of neurotransmitter biomolecules rich in electrons, as well as a high level of oxygen (Baloyannis et al., 2006). Most theories regarding the role of oxidative stress in schizophrenia refer to its effect on polyunsaturated fats of the neuronal membrane. Cell membrane, which has a high content of unsaturated fatty acids, plays a protective, anti-inflammatory role and indirectly an antioxidant role, favoring the physiological processes of defense against free radicals, as well as a significant role in cell signaling. In the case of increased oxidative stress, it is possible that an excess of free radicals will alter neural signal transduction and the processing of information with central effect (Herken et al., 2001, Pazvantoglu et al., 2009).

In schizophrenia a reduction of the specific activity of antioxidant enzymes, such as SOD (superoxide dismutase), glutathione peroxidase (GPX) or catalase, but also of nonenzymatic antioxidants (albumin, bilirubin, uric acid) has been observed (Wood et al., 2009, Dadheech et al., 2008), as well as an increase in the markers of lipid peroxidation (malondialdehyde – MDA) (Ciobica et al., 2011). Most studies that have analyzed this theory have identified a reduction in the antioxidant system activity that determines the increase of oxidative stress and which, in its turn, contributes to membrane deficits also observed in persons with this disorder (Mahadik et al., 2003).

We previously showed similar aspects in the case of schizophrenic patients treated with various antipsychotics, reporting a decrease in antioxidant enzyme level, as well as an increase of the level of lipid peroxidation (Padurariu et al., 2010). In the present study, we examined some enzymatic antioxidant factors (SOD and GPX), and an end product of the lipid peroxidation processes (MDA), in order to assess oxidative stress in patients with cognitive disease. Our objective was to study the possible correlation between the scores of specific scales such as PANSS/AIMS and the level of oxidative stress markers.

MATERIALS AND METHODS

The subjects of this study (n=45, among which 39 were patients with schizophrenia and 6 matched-age controls) were selected from the patients of the "Socola" Clinical Hospital of Psychiatry, Iasi. The patients were diagnosed with schizophrenia according to DSM-IV criteria and aged between 18 and 60 years.

The duration of the disease was of at least 5 years, with each patient receiving antipsychotic treatment for at least 2 years. The study complied with the provisions of the Declaration of Helsinki, while the biochemical determinations performed as before (Stefanescu et al., 2012).

In order to study the connections between schizophrenic pathophysiology and oxidative stress, we decided to apply Pearson's Correlation Test between PANSS/AIMS scales and the main markers of determined oxidative stress for all groups of patients (treated with haloperidol, olanzapine, risperidone and quetiapine).

RESULTS

The Pearson's test determined the achievement of high statistical significations such as: SOD *vs.* PANSS ($r = 0.463$, $p = 0.005$) (Fig. 1), GPX vs. PANSS ($r = 0.59$, $p = 0.0001$) (Fig. 2) and MDA vs. PANSS ($r = -0.496$ – inversely proportional correlation, $p = 0{,}002$) (Fig. 3).

In the case of the AIMS correlation with the specific activity of SOD ($r = -0.624$, we observed an inversely proportional correlation, $p = 0.0001$) (Fig. 4), GPX ($r = -0.507$ – inversely proportional correlation, $p = 0.002$) (Fig. 5), and with the level of MDA ($r = 0.368$, $p = 0.03$) (Fig. 6).

DISCUSSION

The correlations between the parameters of oxidative stress status (SOD, GPX and MDA) and the psychometric scales PANSS and AIMS point to a connection between the psychopathology of schizophrenia and the central oxidative stress status.

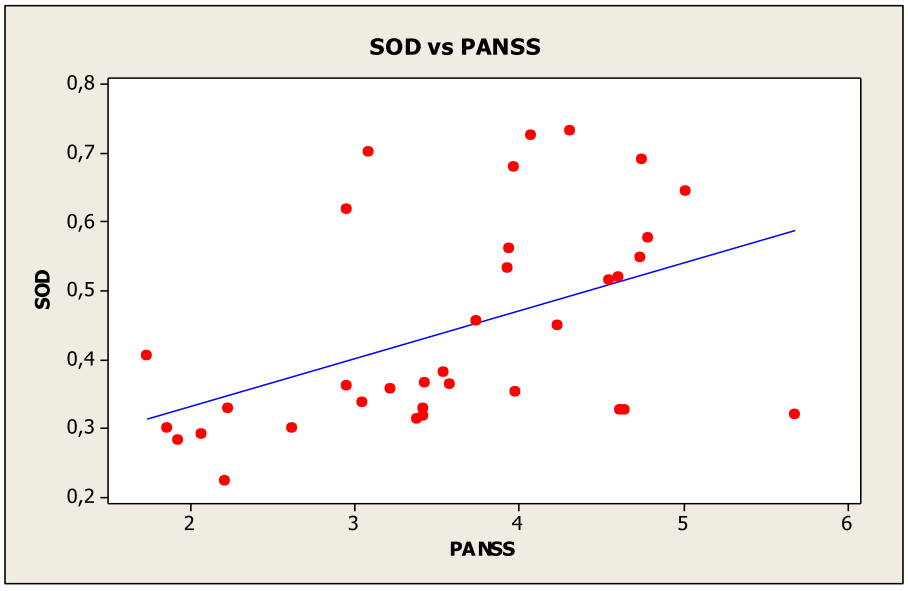

Fig. 1. Comparison between the dynamics of the PANSS score and the specific activity of SOD, studied by means of Pearson's correlations.

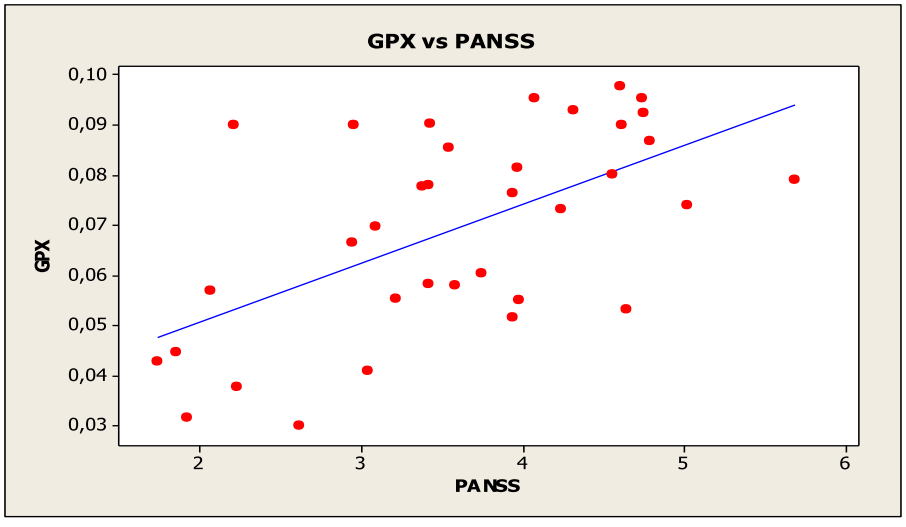

Fig. 2. Comparison between the dynamics of the PANSS score and the specific activity of GPX, studied by means of Pearson's correlations.

In spite of a significant number of articles referring to the implications of oxidative stress in psychiatric deficiencies, schizophrenia is one psychiatric disease about which very little is known with regards to the implications of oxidative stress. including differences between treated and untreated patients, and the effects of treatment with typical vs. atypical antipsychotics on oxidative stress. These aspects might be due to different analyzed areas (for example tissue or blood), the different type of treatment or disease duration (Parikh et al., 2003, Raffa et al., 2009, Miljevic et al., 2010). The results of this study reveal

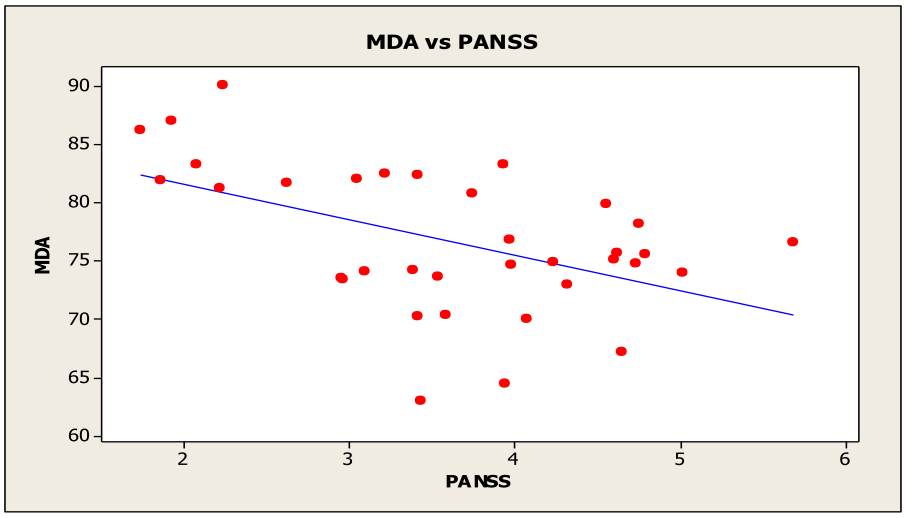

Fig. 3. Comparison between the dynamics of the PANSS score and the MDA concentration, studied by means of Pearson's correlations.

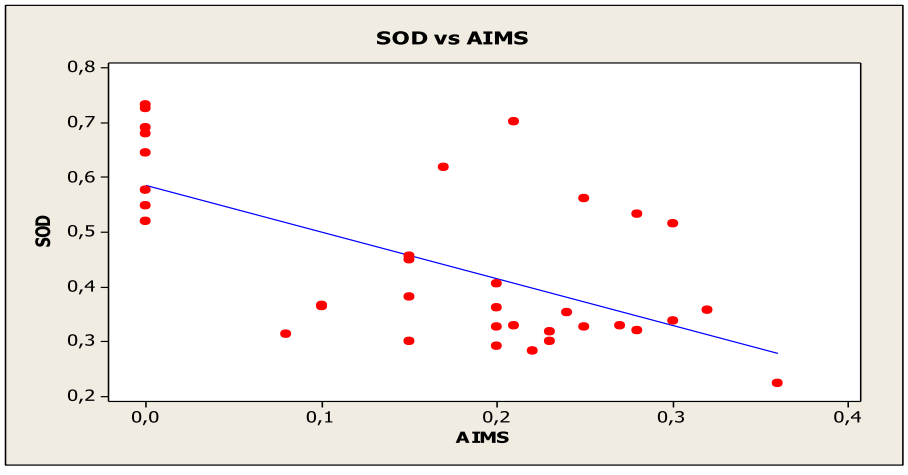

Fig. 4. Comparison between the dynamics of the AIMS score and the specific activity of SOD, studied by means of Pearson correlations.

a direct connection between the level of the markers of oxidative stress and the scores of a specific scale applied to these patients.

Considering the presented aspects, some authors suggested the use of antioxidants for the amelioration of schizophrenic symptomatology. Zhang et al. (2001a) proved in two different studies that application of a *Ginkgo biloba* extract along with the classical treatment with haloperidol augmented the efficiency of antipsychotics and reduced some extrapyramidal side effects. Moreover, the supplementation with *Gingko biloba* led to an improvement of Scale results for the negative and positive symptoms, also generating a decrease in the activity specific to SOD (Zhang et al., 2001b).

The use of essential polyunsaturated fatty acids has also been suggested, having in mind the disorders of the membrane phospholipid metabolism that occur in schizophrenic patients (Mahadik et al., 2001). The decrease of the levels of some essen-

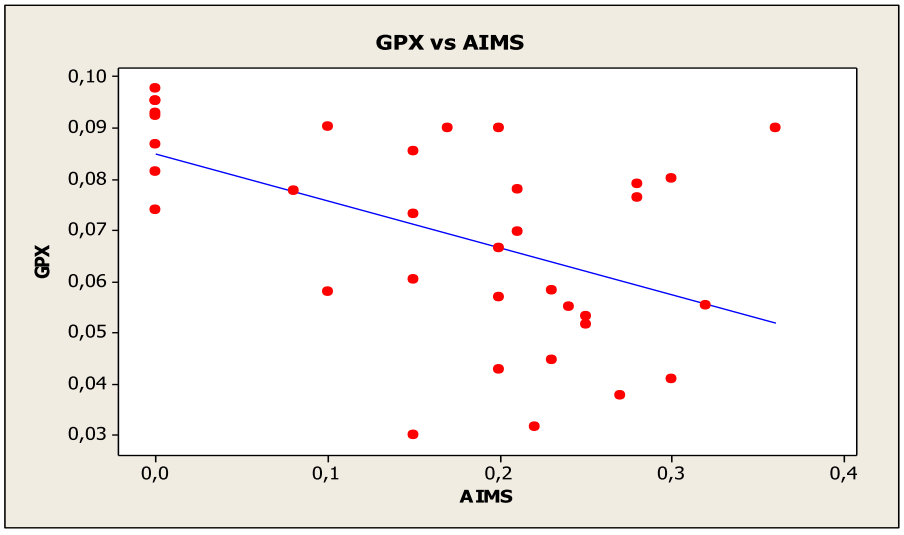

Fig. 5. Comparison between the dynamics of the AIMS score and the specific activity of GPX, studied by means of Pearson correlations.

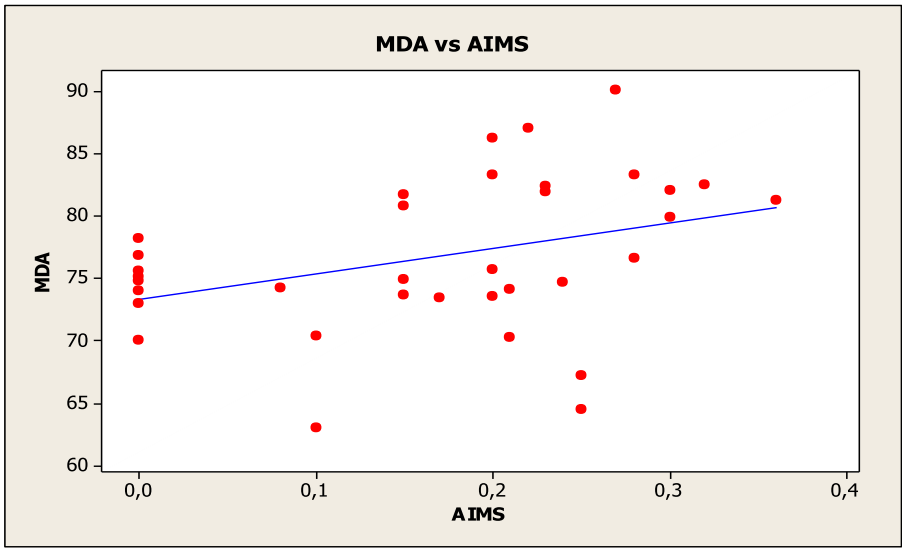

Fig. 6. Comparison between the dynamics of the AIMS score and the MDA concentration, studied by means of Pearson correlations.

tial polyunsaturated fatty acids, such as arachidonic acid, eicosapentaenoic acid, docosapentaenoic acid, docosahexaenoic acid, and their association with different psychopathological aspects has been reported both in patients who received antipsychotic medication and those who have never been treated, immediately after the occurrence of the first psychotic episode (Arvindakshan et al., 2003). It seems that these composites would have special importance at the central level and in behavioral progress. At the same time, there are theories that claim that this deficiency might have existed before the occurrence of the psychotic episode, even since the embryonic stages of growth. Taking into consideration the crucial role of membrane phospholipids in the transmission of the signal from neurotransmitters or growth factors

through the receiver, one may also speak of their implication in information processing of schizophrenic patients.

Some authors reported a significant correlation between the severity of symptoms and the levels of arachidonic and docosahexaenoic acids in schizophrenia (Bitanihirwe et al., 2011). These levels are influenced at turn by and patient's lifestyle and diet. Moreover, it was revealed that a combination of eicosapentaenoic/docosahexaenoic acid and vitamins C and E led to a significant reduction in schizophrenic psychopathology, suggesting possible use of these supplements in long-term management of schizophrenia (Arvindakshan et al., 2003). In addition, the use of alpha-tocopherol was mentioned in some studies, especially for the treatment of tardive dyskinesia that might appear as a side effect of long-term treatment with antipsychotics (Berger et al., 2007).

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