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Original article:

Oxidative stress, MDA, ascorbic acid, and vitamin E in newly diagnosed schizophrenia

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Abstract:

Introduction: Schizophrenia is a heterogenous syndrome characterized by perturbation of language , perception, thinking; social activity, affect and volition. Brain has high rate of oxidative metabolism and white matter of brain has high amount of lipid, therefore, brain is more successful target of free radical damage. This study was undertaken to find out the association of oxidative stress with the antioxidant balance in the newly diagnosed schizophrenia patients and in healthy controls. To support this working sis we measured MDA as the index of lipid peroxidation and individual antioxidants such as vitamin E and vitamin C to evaluate the antioxidant status in newly diagnosed patients and in a control group.

Materials and methods: All the patients and controls were free of any medication at least 2 weeks. Patients with a history of drug abuse or dependence, serious medical illness, severe head injury or seizure disorders were excluded from the study. Also patients with metabolic disorders were excluded from the study. Venous blood samples were collected in plain bulbs and were allowed to clot.

Results: Oxidative stress indicator MDA **was** significantly higher ($p<0.0001$) in newly diagnosed schizophrenia patients than in control population. The individual parameters of antioxidative status tend to decrease in schizophrenia patients. the decrease of Vit E($p<0.0001$) and vitamin C ($p<0.0001$) was significant as compared to control subjects.

Conclusion: In conclusion, oxidant/antioxidant imbalance maybe involved in the pathogenesis of schizophrenia.

Introduction

Schizophrenia is a heterogenous syndrome characterized by perturbation of language , perception, thinking; social activity, affect and volition. The syndrome commonly begins in late adolescence and persists throughout life and affects persons of all social classes. Patients may present with positive symptoms (such as conceptual disorganization, delusion, or hallucination) or negative symptoms(such as loss of function, anhedonia, decreased emotional expression, impaired concentration and diminished social engagement). It has a lifetime prevalence of approximately 1 percent of the population.[1]

Oxidative stress may be defined as a measure of the steady state level of reactive oxygen species of oxygen radical in biological system. The continuous production of reactive oxygen species and its neutralization by antioxidants is characteristics of aerobic life.[2] Free radicals may be generated in cells and tissues through increased radical mediated input by the disruption of internal processes like leukocyte activation and impaired mitochondrial electron transport or as consequence of decreased antioxidant capacity. Antioxidant enzymes like superoxide dismutase (SOD), catalase (CAT), Glutathione peroxidase (GPO) and Glutathione reductase (GR) form the first line of defense against free radicals. Vitamin E, vita-

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min C and vitamin A act as second line of defense. A shift in the balance of the oxidant side may trigger a cascade of reactions leading to formation of highly reactive oxygen metabolites. [3] A growing body of evidence indicates that free radicals can cause metabolic disturbances and cell injury in various ways. The most common and most hazardous reactions encountered as a result of free radical oxidation is lipid peroxidation. In fact, lipid peroxidation is one free radical mediated reaction that is common to vast majority of disorders. [4, 5]

Lipid peroxidation is an autocatalytic free radical mediated destructive process whereby polyunsaturated fatty acids in cell membrane undergo degradation to form lipid peroxides. These later compounds decompose to form a variety of cytotoxic products including malondialdehyde (MDA). This occurs when OH^* is generated close to membrane and attack fatty acid side chains of phospholipids. It prefers to attack fatty acid side chains with several double bonds such as linolenic and arachidonic acid.

Brain has high rate of oxidative metabolism and white matter of brain has high amount of lipid, therefore , brain is more successful target of free radical damage. This study was undertaken to find out the association of oxidative stress with the antioxidant balance in the newly diagnosed schizophrenia patients and in healthy controls. To support this working sis we measured MDA as the index of lipid peroxidation and individual antioxidants such as vitamin E and vitamin C to evaluate the antioxidant status in newly diagnosed patients and in a control group[6].

Materials and methods

The study was conducted at the department of Biochemistry, GRANT MEDICAL COLLEGE AND SIR J.J HOSPITAL, MUMBAI. Total 90 patients with newly diagnosed schizophrenia and age 30 and sex match ed control with an average age of 30.20^{+}. 5.4 years were included in the present study. Diagnosis of schizophrenia was made by Psychiatrists by using Diagnostic and Statistical Manual Of Mental Disorders (DSM-IV) classification (American Psychiatric Association. 1994). [7]

All the patients and controls were free of any medication at least 2 weeks. Patients with a history of drug abuse or dependence, serious medical illness, severe head injury or seizure disorders were excluded from the study. Also patients with metabolic disorders were excluded from the study. Venous blood samples were collected in plain bulbs and were allowed to clot. About one hour the serum was separated by centrifuging at 2500 rpm for 5 min. at room temperature. Serum was free from hemolysis and turbidity.The serum was used for measurement of MDA (as an index of lipid peroxidation), vitamin E and vitamin C (as an index of antioxidant metabolism) in the body. Serum MDA was determined as the measure of Thiobarbituric acid reacting substance (TBARS) by the method of Burgr and Aust [8].serum vitamin E was determined by the method of Baker and Frank [9]. Serum vitamin C (ascorbic acid) levels were estimated by the method of Ayekyaw (10).

Statistical analysis between controls and patients was performed by students‘t’ test using Graph pad prism, version 3.02 software. The data were expressed as mean+-SD, $p < 0.05$ was considered as significant

Results

Analysis between schizophrenic patients and controls were done. Table# 1 shows the comparison of mean of different parameters between cases and control.

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Table#1 - the mean +- SD values of serum MDA, vitamin E and vitamin C in controls and Schizophrenic patients.

PARAMETER	HEATHY CONTROLS	CASES	P VALUES
MDA(nmol/ml)	2.82 $^{+-}$0.46	5.76+-0.58	0.0001
Vit E (mg/Dl)	0.81+-0.24	0.60+-0.11	0.0001
Vit c (mg/Dl)	1.19+-0.14	1.04+-0.14	0.0001

P value <0.05 was considered as significant.

Oxidative stress indicator MDA **was** significantly higher (p<0.0001) in newly diagnosed schizophrenia patients than in control population. The individual parameters of antioxidative status tend to decrease in schizophrenia patients. the decrease of Vit E(p<0.0001) and vitamin C (p<0.0001) was significant as compared to control subjects.

Discussion

The important measure of oxidative stress in our study was the concentration of MDA, which is a product of the free radical process. Our results showed a highly significant increase in the concentration of MDA in serum of the patients with schizophrenia as compared to that in healthy controls. Similar results were obtained by Mahadik et al(2001), Benedicta D Souza et al(2004), Hebben et al (2000), Dasgupta et al(2014) (11,12,13,14). The raised levels of MDA could be due to increased generation of ROS due to the excessive oxidamage generated in these patients.

In present study, our results indicated that the levels of Vitamin E ,Vitamin C were found to be decreased significantly in schizophrenic patients as compared to controls which are supported by many studies.(11,12,14).

This indicates that there was increased generation of free radicals which causes lipid peroxidation as well as there is imbalance between oxidative and antioxidative systems in schizophrenia. Brain has a high rate of oxidative metabolic activity, high oxygen consumption, a high ratio of membrane surface area to cytoplsmic volume and brain cells are composed of greater than 66% phospholipids by mass versus33% in peripheral tissues (15,16). The large amount of fatty acids are present in brain cell membrane as phospholipids.r2 position in phospholipids is occupied by Essential polyunsaturated fatty acids (EPUFAs), which are more susceptible to damage by free radicals. This occur when OH* is generated close to membrane and attacks fatty acid side chains of membrane phospholipids. It prefers to attack fatty acid side chains with several double bonds such as linolenic and arachidonic acid. High lipid content in brain cells made them more vulnerable to the toxic effects of ROS than those in other organs. Arachidonic, linoleic, and linolenic acids are the key PUFA in brain and their metabolism is found to be altered selectively in schizophrenia(17). Phospholipids of cell membranes are required for signal transduction and this process is actively required for neurotransmitters metabolism. Oxidative damage of phospholipids markedly alter the mechanism of neurotransmitters like Dopamine, Norepinephrine in schizophrenia [(18).] An overall result suggests the disturbance in antioxidant balance in schizophrenia which may be involved in the pathogenesis of schizophrenia. Majority of studies also confirm that oxidative stress and oxidative damage is present in schizophrenia, in never medicated and early stage of disease [(19, 20, 21)].

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Conclusion

In conclusion, oxidant/antioxidant imbalance maybe involved in the pathogenesis of schizophrenia. The present study has clearly shown higher MDA level and reduced total antioxidant capacity which supports the hypothesis of oxidative damage in schizophrenia. This oxidative damage can be prevented by antioxidant and PUFA supplementation. Vitamin E and vitamin C are well known antioxidants that are postulated to protect against damage to biological membranes by their ability to scavange free radicals. Since antioxidant alone may stop ongoing oxidative damage and PUFA have the potential to restore the cellular structure, their combined use may be necessary for optimal treatment of oxidative cell damage.

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