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ROLE OF ANTIOXIDANTS IN SCHIZOPHRENIA

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ABSTRACT

Schizophrenia is a clinical syndrome of variable, but profoundly disruptive psychopathology that involves cognition, emotion, perception and other aspects of behavior. There is increasing evidence that oxidative injury contributes to pathophysiology of Schizophrenia. Hence, identification of various oxidants and antioxidants may help to determine their possible role in the etiology and treatment of the disease. The present study assessed the oxidative stress in patients with schizophrenia by measuring serum Malonaldehyde levels and their antioxidant status by measuring blood levels of Vitamin E, Vitamin C, Reduced Glutathione and β- Carotene in a group of sixty patients. The study was conducted over a period of 18 months in the Goa Medical College and the Institute of Psychiatry and Human Behaviour. Diagnosis of Schizophrenia was made using the ICD-10 classification. A control group of sixty healthy subjects was recruited. As compared to matched controls, the acutely admitted patients suffering from Schizophrenia exhibited significantly increased lipid peroxidation products and decreased antioxidants namely Vitamin C, Vitamin E, Reduced Glutathione and β-Carotene suggesting that the oxidative damage that occurs in Schizophrenic patients exhausts the antioxidant defense of the body leading to low levels of antioxidants.

KEYWORDS: Schizophrenia, Oxidative stress, Antioxidants.

INTRODUCTION

Schizophrenia is a mental disorder characterized by disintegration of thought processes and of emotional responsiveness. It most commonly manifests itself as auditory hallucinations,

paranoid or bizarre delusions or disorganized speech or thinking and it is accompanied by significant social or occupational dysfunction.[1] Schizophrenia affects around 0.3–0.7% of people at some point in their life, or 24 million people worldwide as of 2011. It strikes without regard to gender, race, social class or culture. According to DSM-IV-TR, the annual incidence of schizophrenia ranges from 0.5 to 5.0/10,000, with some geographic variation. Although it affects men and women with equal frequency, schizophrenia most often appears in men in their late teens or early twenties, while it appears in women in their late twenties or early thirties. Finding the causes for schizophrenia proves to be difficult as the cause and course of the illness is unique for each person.[2-5] Interfering with a person's ability to think clearly, manage emotions, make decisions and relate to others, schizophrenia impairs a person's ability to function to their potential when it is not treated. Unfortunately, no single, simple course of treatment exists. Research has linked schizophrenia to a multitude of possible causes, including aspects of brain chemistry and structure, as well as environmental causes. Finding the causes for schizophrenia proves to be difficult as the cause and course of the illness is unique for each person.[6] One of the factors which has been known to contribute to the pathogenesis of schizophrenia is 'Free Radical Damage'. The brain and nervous system are particularly prone to free radical damage since the membrane lipids are very rich in polyunsaturated fatty acids.[7] Free radicals, primarily the reactive oxygen species, superoxide and hydroxyl radicals which are highly reactive having an unpaired electron in an atomic or molecular orbit are generated under physiological conditions during aerobic metabolism. Antioxidant defense mechanism is a protective mechanism of the cell that serves to minimize the toxic effects of free radicals. Chemical compounds and reactions capable of generating potential toxic oxygen species can be referred to as pro-oxidants. In a normal cell, there is an appropriate pro-oxidant: antioxidant balance. However, this balance can be shifted towards the pro-oxidants when production of ROS (reactive oxygen species) is greatly increased or when levels of antioxidants are diminished. This state is called "oxidative stress" and can result in serious cell damage if the stress is massive or prolonged.[8] There is increasing evidence that oxidative injury contributes to pathophysiology of schizophrenia. Hence, this study aimed to identify the various oxidants and antioxidants to determine their possible role in the etiology and treatment of Schizophrenia.

MATERIALS AND METHODS

The study was conducted in the department of Biochemistry and Psychiatry, Goa Medical College which includes the Institute of Psychiatry and Human Behaviour. The study was

carried out on sixty healthy Schizophrenic patients and sixty age and sex matched normal subjects. Diagnosis of Schizophrenia was based on the World Health Organization's International Statistical Classification of Diseases and Related Health Problems, the ICD-10. These criteria use the self-reported experiences of the person and reported abnormalities in behavior, followed by a clinical assessment by a mental health professional. Subjects met the following inclusion\exclusion criteria: age between fifteen to fifty years, Schizophrenia was the primary diagnosis. Subjects with current affective disorder including manic episode, concomitant substance abuse, mental retardation and severe medical illness were excluded. Informed consent was taken from the subjects and an Institutional Ethics Committee clearance was obtained. Fasting venous blood samples were collected from the subjects and were subjected to the following biochemical parameters: Ascorbic acid, β- Carotene, Whole blood Glutathione (GSH), Lipid peroxide in terms of Malondialdehyde (MDA) and Tocopherol

A. Determination of Ascorbic acid in blood

Method: 2, 6-Dichlorophenolindophenol titration

Principle: Titration with 2,6-Dichlorophenolindophenol in acid solution. This blue coloured compound is red acid solution and on titration with ascorbic acid oxidized to D-L-ascorbic acid. If a mixture of ascorbic acid and D-L- ascorbic acid is present, only former reacts with the dye. D-L-ascorbic acid can be reduced back to ascorbic acid in acid solution by hydrogen sulphide so that titration measures all biologically active substance present. Hence, fresh sample of blood is to be used.

B. Determination of Carotenes in serum

Method: Carr Price Reaction (Kimble, 1938-1939; Kaser and Stekol, 1943)

Principle: Proteins are precipitated with ethanol and the retinol and carotenes extracted into light petroleum. After reading the intensity of the yellow colour due to carotenes, the light petroleum is evaporated off and the residue dissolved in chloroform. Carr-Price reagent is added and the amount of blue colour produced read. Since carotenes also give some colour, a correction for this is made in order to obtain that due to retinol present.

C. Determination of Whole blood Glutathione

Method: Beutler's Method, 1963

Principle: Glutathione (GSH) in the whole blood or red blood cells is maintained in reduced state through reduced nicotinamide adenine dinucleotide phosphate and glutathione

reductase. The functions of reduced glutathione seem to keep sulphydryl groups in their active reduced state and through glutathione peroxidase to remove hydrogen peroxide.

D. Determination of Serum Lipid Peroxide

Method: Kei Satoh's method, 1978

Principle: Lipoproteins are precipitated from serum by addition of trichloroacetic acid. Then the precipitate is washed with sulphuric acid and thiobarbituric acid. The mixture is heated in boiling water bath for half an hour. Pink coloured form is extracted with butanol and butanol layer read against 530nm using colorimeter. The determined values are expressed in terms of Malondialdehyde (nmol/ml) used as reference standard.

E. Determination of Serum Tocopherol

Method: Quaife et al., 1949; Baker and Frank, 1968

Principle: A simple method for determining plasma tocopherol is available using the Emmerie-Engel reaction which is based on the reduction by tocopherols of ferric to ferrous ions which then form a red complex with α,α'-Dipyridyl. Tocopherols and carotenes are first extracted into xylene and the extinction read at 460nm to measure the carotenes. A correction is made for these after adding ferric chloride and reading at 520nm.

RESULTS

A total of sixty patients suffering from first episode of Schizophrenia and sixty age and sex matched healthy normal subjects were evaluated.

Table 1: Comparison of mean levels of Serum Malondialdehyde (MDA), Ascorbic acid (Vitamin C), Tocopherol (Vitamin E), Whole blood Glutathione (GSH) and β- Carotene in Test (Schizophrenia) and Control patients.

PARAMETER	GROUP	NO. OF SAMPLES (N)	MEAN±SD	MIN.	MAX.
Serum MDA (nmol/ml)	Schizophrenia	60	10.55 ± 2.89	5.3	18.3
	Control	60	1.39 ± 0.69	0.5	3.0
Serum Vitamin C (mg/l)	Schizophrenia	60	8.15 ± 2.64	4.5	15.0
	Control	60	9.71 ± 1.47	6.4	13.3
Serum Vitamin E (mg/l)	Schizophrenia	60	7.21 ± 2.87	2.0	12.0
	Control	60	10.66 ± 1.40	8.0	14.0
Whole blood Glutathione (mg%)	Schizophrenia	60	36.56 ± 15.25	10.0	70.0
	Control	60	51.23 ± 15.83	22.0	90.0
Serum β- Carotene (mg/l)	Schizophrenia	60	1.13 ± 0.75	0.16	4.60
	Control	60	1.57 ± 0.81	0.20	3.70

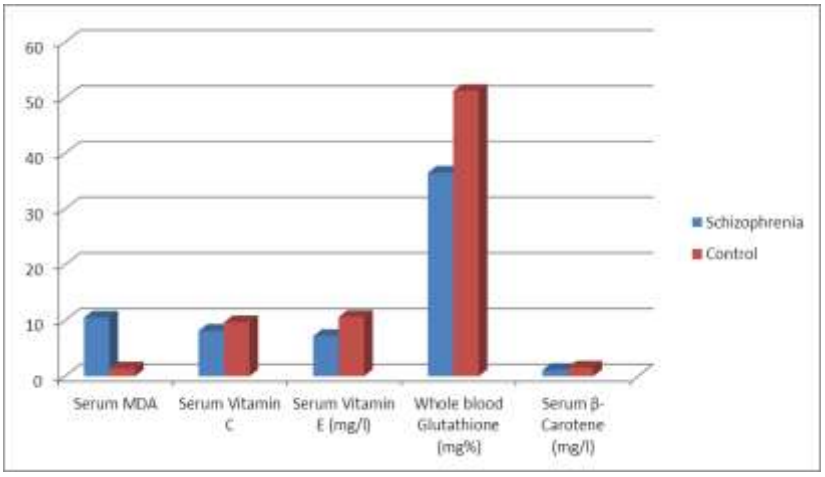

Figure 1: Diagramatic representation of the comparison of mean values of Serum Malondialdehyde (MDA), Ascorbic acid (Vitamin C), Tocopherol (Vitamin E), Whole blood Glutathione (GSH) and β- Carotene in Test (Schizophrenia) and Controls.

Table 2: Correlation of Antioxidants (Vitamin C, Vitamin E, Reduced Glutathione and β-Carotene) with Oxidative Stress (MDA).

		Malondialdehyde (MDA)
Vitamin C	Pearson Correlation	-0.271**
	Sig. (2-tailed)	0.003
	N	120
Vitamin E	Pearson Correlation	-0.561**
	Sig. (2-tailed)	0.001
	N	120
Reduced Glutathione	Pearson Correlation	-0.436**
	Sig. (2-tailed)	0.001
	N	120
β- Carotene	Pearson Correlation	-0.224*
	Sig. (2-tailed)	0.014
	N	120

**Correlation is significant at the 0.01level (2-tailed)

* Correlation is significant at the 0.05level (2-tailed)

DISCUSSION

Schizophrenia is a group of psychotic disorders characterized by disturbances in perception, behavior, and communication. A person with schizophrenia has deteriorated occupational, interpersonal, and self-supportive abilities.[9] The chemical nature of a schizophrenic brain is not completely understood. The brain and nervous system are particularly prone to free radical damage since the membrane lipids are very rich in polyunsaturated fatty acids and areas of human brain are very rich in iron, which plays an essential role in generating free

radical species.[7] There is abundant evidence that free radicals are involved in membrane pathology in the central nervous system and may play a role in neuropsychiatric disorders including Schizophrenia.[7,10] The present study included 120 subjects, 60 healthy schizophrenic patients and 60 age and sex matched normal subjects and evaluated the following parameters: one of the markers of oxidative stress, Malondialdehyde; and the antioxidants Vitamin C, Vitamin E, β-Carotene and Glutathione. The present study showed increased level of mean Malondoaldehyde (MDA) as compared to control groups. The mean MDA level of the schizophrenic group was 10.55 ± 2.89 nmol/ml and of the control was 1.39 ± 0.69nmol/ml. This observation suggests the increased oxidative stress in Schizophrenia as compared to controls. Also the mean serum levels of vitamin C, vitamin E, Glutathione and β-Carotene were decreased in patients with Schizophrenia as compared to controls. The mean vitamin C, vitamin E, Glutathione and β- Carotene level of the schizophrenic group was 8.15 ± 2.64mg/l, 7.21± 2.87mg/l, 36.56 ± 15.25 mg% and1.13± 0.75mg/l respectively and of the control was 9.71 ± 1.47mg/l, was10.66 ± 1.40mg/l, 51.23 ± 15.83mg% and 1.57 ± 0.81mg/l respectively. The brain has certain attributes that make it exceptionally vulnerable to free radical attack. It has highly oxygenated structures responsible for almost one- fifth of the body's total oxygen. In addition, there is disruption of brain energy metabolism mediated by antioxidant perturbation. Intense oxidative stress and decreased antioxidants may contribute to neuronal death and alter the information processing in Schizophrenia.[10]

CONCLUSION

From the present study of 120 subjects which comprised of 60 patients with Schizophrenia and 60 healthy controls, we concluded that:

Oxidative injury contributes to pathophysiology of Schizophrenia, which is indicated by the increased lipid peroxidation products and a decrease in antioxidants namely vitamin C, vitamin E, whole blood Glutathione and β-Carotene. The oxidative damage that occurs in schizophrenic patients exhausts the antioxidant defense of the body leading to low levels of antioxidants. Intense oxidative stress and decreased antioxidants in Schizophrenia can be recognised as a modifiable risk factor and in turn new modalities can be formed to decrease the severity of the disease by dietary intervention and lifestyle modification.

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