Oxidative stress in schizophrenia

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الخلاصة

تم تصميم الدراسة الحالية لتقصي التغيرات في حالات الإجهاد التأكسدي عند مرضى الفصام . فقد تم تقدير مستويات (MDA, SOD, GSH and vitamin C) في أمصال المرضى ومجموعة السيطرة . أظهر التحليل الإحصائي باستعمال (student`s t-test) وجد زيادة ملحوظة ($p<0.005$) في مستوى (MDA) مع نقصان ملحوظ ($p<0.005$) في مستويات (GSH, SOD and vitamin C) لدى مرضى الفصام عند مقارنتها مع مثيلاتها في مجموعة السيطرة.

ولتقييم اختلاف الجنس وتأثيره على حالة الإجهاد التأكسدي على مرضى الفصام فقد أظهرت النتائج زيادة ملحوظة ($p<0.025$) في (MDA) و لكن هنالك نقصان ملحوظ ($p<0.005$) في (GSH) و نقصان ملحوظ ($p<0.025$) في (SOD) في الإناث مقارنة بالذكور.

إما بالنسبة لعلاقة الإجهاد التأكسدي بأعراض المرض أظهرت النتائج زيادة ملحوظة ($p<0.05$) في (MDA)، بالنسبة للمرضى (positive symptoms) مقارنة بالمرضى (negative symptoms) بينما هنالك نقصان ملحوظ ($p<0.05$) في (SOD) و(GSH) بالنسبة للمرضى (negative symptoms) مقارنة بالمرضى (positive symptoms) .

النتائج توضح إن هناك دور لمرض الفصام في زيادة حالة الإجهاد التأكسدي. و انه بازدياد حالة الفصام سوء فان متغيرات الجهاد التاكسدي تتغير تبعا لذلك.

Abstract

The present study was conducted to verify the oxidative stress status in schizophrenia. Malondialdehyde, reduce glutathione, superoxide dismutase, and vitamin C levels were measured in sera of seventy schizophrenic patients and thirty healthy individuals. The statistical analysis (student`s t-test) showed a significant ($p<0.005$) increase of malondialdehyde (MDA) while a significant ($p<0.005$) decrease in reduce glutathione (GSH) also a significant ($p<0.005$) decrease in superoxide dismutase and a significant ($p<0.005$) decrease in vitamin C levels in schizophrenic patients when compared with those of the control group. The evaluation of sex differences effect on oxidative stress in schizophrenic patients show a significant ($p<0.025$) increase in MDA but a significant ($p<0.005$) decrease in GSH and a significant ($p<0.025$) decrease in SOD in female in comparison to male groups. According to the symptoms of schizophrenia show there are a significant ($p<0.05$) increase in MDA in positive symptom when compare to negative symptoms while a significant ($p<0.005$) decrease in SOD and GSH in negative symptom when compare to positive symptoms

The results indicate that schizophrenia is associated with oxidative stress. And it appears that when the case gets worse the oxidative stress parameters will dependently changes.

So schizophrenia is a sever psychiatric disorder and since there is an evidence that an excessive free radicals production or oxidative stress may be involved in the pathophysiology of schizophrenic patient. So that the excess quantities of ROS that are produced by schizophrenic patients may overcome the host antioxidant defenses and cause oxidative stress.

Keywords oxidative stress, free radicals, MDA, GSH, SOD, vitamin C, Antioxidants, Schizophrenia.

Introduction

Schizophrenia is defined as a psychotic disorder, one of the most severe mental illnesses. In addition to clinical symptoms, it often causes marked impairments in social, occupational, cognitive and global functioning, with increased mortality and co morbidity. [1] There are currently two main diagnostic systems for diagnosing schizophrenia. These are the American Psychiatric Association's (APA) Diagnostic and Statistical Manual for Mental Disorders (DSM) [2] and the World Health Organization's (WHO) International Classification of Diseases and Causes of Death (ICD). [3] Whether a person is considered to have schizophrenia depends on the diagnostic system used. Each patient suffers from positive or negative symptoms. The positive symptoms, *e.g.*, delusions, hallucinations, grandiosity, excitement, hostility and disorganization are more easily identified, as compared to the negative symptoms. Examples of negative symptoms are apathy, intentional impairment, affective blunting, a sociality, poverty of speech and anhedonis that may be difficult to distinguish from either depression or side effects caused by medication with typical antipsychotic drugs. [4, 5] Approximately half of the schizophrenia patients will experience periods with severe depression during the course of their illness.

Oxidative stress is defined as an imbalance between pro-oxidants (free radical species) and the body's antioxidants. [6] It may be due to either increased production of reactive oxygen species (ROS) or decreased levels of antioxidants (enzymatic and non-enzymatic) or both. [7]

Free radical is any atom (e.g. oxygen, nitrogen) or group of atoms with at least one unpaired electron in the outermost shell. [8] So that there is increasing evidence that free radical-mediated CNS neuronal dysfunction is involved in the pathophysiology of schizophrenia. [9, 10] Free radicals (oxyradicals, such as superoxide, hydroxyl ions, and nitric oxide) cause cell injury when they are generated in excess or the antioxidant defense is impaired. Both of these processes seem to be affected in schizophrenia. So that the supplementation with of antioxidants (vitamin C & E) is effective in improving psychopathology with chronic-medicated schizophrenic patient. [11]

Materials and Methods

- In this study 70 schizophrenic patients and 30 healthy subjects (control group) were enrolled. The demographic characteristics of the study subjects are shown in Table 1. The enrolled patients (N = 70) were consecutive admissions to outpatient psychiatric units of Al- Hakeem general hospitals in al Najaf, Iraq. Diagnosis of schizophrenia was derived from a structured clinical according to DSM IV (American Psychiatric Association, 1994).

Table 1: Demographic table show the details of control and patients groups:-

	Schizophrenia (70)	**control (30)**
Sex, M/F	**43/27**	**16/14**
Age (years)	**18-65**	**15-60**
Positive Symptoms	**35**	**-------**
Negative symptoms	**35**	**-------**

- From each individual, 5 ml of blood were withdrawn, samples were allowed to clot at 37 C° for 15 min. then it was centrifuged at 5000 xg for 15 min. Sera were removed, divided into aliquots and stored, frozen at -17 C° until analysis.

- **Malodialdehyde**

Lipid peroxidation levels were monitored by determining MDA by thiobarbituric acid (TBA) method procedure described by (Guidet B.and Shah S.V., 1989).[12]

- **Superoxide dismutase**

The activity of this enzyme was measured by using Super oxide dismutase Assay kit in ELISA**.** [13]

- **Reduced glutathione**

The principle of GSH levels measurement is relay on 5,5-dithiobis (2-nitrobenzoic acid) (DTNB) which is a disulfide chromogen that is readily reduced by sulfahydryl group of GSH to an intensely yellow compound. The absorbance of the reduced chromogen is measured by spectrophotometry at 412 nm which is directly proportional to the GSH concentration.[14]:

- **Vitamin C**

The levels of vitamin C were measured by using the standard curve after measuring the absorbance at 520 nm. [14]

Statistical analysis

The statistical analysis included all subjects, and the comparative of significance using (students-T-test), mean, and standard deviation was used.

Results

Malondialdehyde, reduce glutathione, superoxide dismutase, and vitamin C levels were measured in sera of seventy schizophrenic patients and thirty healthy individuals. There were a significant ($P < 0.005$) elevation in sera MDA of schizophrenic patients in comparison with the control group as showed in table 2

In contrast, GSH, SOD, and VIT C values show a significant ($P < 0.005$) decrease in sera of schizophrenic patients when compared with those of the control group as in the same table

Table 2: Level of Malondialdehyde (MDA), reduced glutathione (GSH), Superoxide dismutase (SOD), and vitamin (C), in sera of Schizophrenic patients and the control group:-

Parameters	groups	N.	Mean ±SD	C.S
MDA (µM)	Control	30	3.99±0.15	P<0.005
	Patients	70	11.81±2.60	
GSH (µM)	Control	30	76.56±6.23	P<0.005
	Patients	70	36.0±11.78	
SOD (U/L)	Control	30	85.85±7.32	P<0.005
	Patients	70	56.1±11.9	
VIT.C (mg/dl)	Control	30	3.41±0.83	P<0.005
	Patients	70	1.75±1.01	

The effect of gender on oxidative stress in schizophrenic patients are showed in table 3, there is a significant ($P < 0.025$) increase in serum MDA concentration, while there is a significant ($P < 0.005$) decrease in serum GSH, and a significant ($P < 0.025$) decrease in serum SOD level but there was no significant difference in VIT C level in male patients when compared with those of female patients.

Table 3: Level of MDA, SOD, GSH and VIT C in sera of Schizophrenic patients in relation to gender:-

Parameters	group	NO	Mean ± SD	p value
MDA (µM)	malle	43	11.34±2.79	P<0.025
	Female	27	12.57±2.11	
GSH (µM)	males	43	40.18±11.52	P<0.005
	Female	27	30.77±9.99	
SOD (U/L)	males	43	58.67±11.7	P<0.025
	Female	27	52.14±11.36	
VIT. C (mg/dl)	males	43	1.75±1.05	N.S
	Female	27	1.65±0.94	

Concerning symptoms, the results in table 4 show that there is a significant ($p<0.05$) increase in MDA of schizophrenic patients with positive symptoms when compare to patients with negative symptoms while a significant ($p<0.005$) decreases of GSH and a significant ($p<0.005$) decrease for SOD whereas vitamin C shows no significant changes in the two groups of patients. The positive symptom group with negative symptom group where compared in the table below.

Table 4:- Level of MDA, SOD, GSH and VIT C in sera of Schizophrenic patients and control groups in relation to symptoms:-

Parameters	means±S.D (+ve)	means±S.D (-ve)	C.S
MDA (µM)	12.37±2.62	11.26±2.49	p<0.05
GSH (µM)	41.54±11.17	31.25±10	p<0.005
SOD (U/L)	61.94±10.99	50.37±9.97	p<0.005
VIT. C (mg/dl)	1.87±1.03	1.55±0.97	N.S

The results in table 2 indicate a high oxidative stress in the schizophrenic patients group and this may be the promoter of many pathophysiological changes in those patients. The raise of MDA levels in those patients is tightly correlated with the alteration of oxidative stress parameters. The raise in MDA level attributable to the raise in the generation of ROS owing to the high rate of oxidative damage processes occur in those patients. The oxygen species in turn have the ability to oxidize many important biomolecules including brain cell membrane lipids. Similar reports show that MDA level was elevated in patients with schizophrenia. [15, 16]

On the other hand, GSH, SOD, and Vitamin C activities were found to decrease in schizophrenic patients in respect to control group. These results are in consistence with the hypothesis which suggests that there is a deficiency in the amount of antioxidant in patients with schizophrenia which was put forward by Zhang et al 2006. [17]

The results in table 3 indicate that the oxidative stress in female is higher than that in male the cause of this difference between male and female may belong to the negative relationship between prolactin and SOD that the putative enhancement of prolactin in schizophrenic females may lead to decrease SOD activity. Depending on this attribution the raises in oxidative stress in females may be related to the hormonal alteration. [18]

The result in table 4 indicate that the oxidative stress in positive symptom is higher than of negative symptom due to the fact that those patients with positive symptom have higher levels of long chain unsaturated fatty acid that is more susceptible to peroxidation by free radicals and lower levels of saturated fatty acid that is less affected by oxidative damage The patients with negative symptom show the opposites events, high levels of saturated fatty acid with low levels of long chain poly unsaturated fatty acid. [19]

Conclusion

- Schizophrenia is associated with an increase in oxidative stress**.**
- The gender of patients is significantly related to the oxidative stress status and it is more in female in comparison with male.
- Schizophrenic patients with positive symptoms suffer from oxidative damage more than the patients with negative symptoms.
- Schizophrenic patients need for more attention by physician to correct their oxidative stress and relief their oxidative stress accumulations using the suitable treatments.

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