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Age and Gender Related Changes in Free Radical Pathology and Antioxidant Defense in Schizophrenia

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Abstract: The aim of the present study was to estimate the effect of age and gender on the levels of primary and secondary antioxidants and Malondialdehyde in red blood cells of the selected Schizophrenia patients. In our present study, the activities of six free radical scavenging enzymes (super oxide dismutase (SOD), catalase (CAT)), glutathione peroxidase (GSH-Px), glutathione Transferase (GST), glucose-6-phosphate dehydrogenase (G6PD), Caeruloplasmin ferroxidase (Cp) and the level of thiobarbituric acid-reactive substances (TBARS) as an index of lipid per oxidation were analyzed in the different age groups of schizophrenia patients. Role of gender was also analyzed in both schizophrenia and control subjects. It was observed from the results that there was a significant increase in erythrocyte MDA levels and activity of SOD and a significant decrease in erythrocyte CAT,GSH- Px, Cp-ferroxidase and G6PD levels in patients with schizophrenia, when compared to controls ($p<0.01$). The results have also shown that among different age groups, highly significant oxygen free radical production, evidenced by increased levels of MDA and decreased levels of antioxidant enzymes activity was found in adult and elderly schizophrenia patients, which supports the more pronounced oxidative stress in adult and elderly schizophrenia patients when compared to young schizophrenia patients. The statistically more significant increase ($p<0.001$) in the activity of SOD in elderly schizophrenia subjects may be a compensatory regulation in response to increased oxidative stress in elders. The decreased concentrations of the CAT, GSH-Px, G6PD and Cp-ferroxidase support the hypothesis that lipid per oxidation is an important causative factor in the pathogenesis of schizophrenia. These data reveal that antioxidant defense mechanisms might be impaired a lot in normal elderly people and schizophrenia patients with age group above 30 (i.e., adults and elders). As for as gender concerned, we observed a significant raise in the levels MDA, SOD and significant decrease in the levels of selected antioxidant enzymes in schizophrenia male and female subjects when compared with the respective control male and female subjects ($p<0.01$). But we found statistically more significant increase in the levels of MDA and highly significant decrease in the levels of the secondary antioxidant enzymes G6PD and Cp ferroxidase ($p<0.001$) were found in schizophrenia males when compared with schizophrenia females. Supplementation of antioxidants may prevent further oxidative injury in elderly schizophrenia patients.

Key words: Schizophrenia, young and elderly subjects, gender, antioxidant enzymes, malondialdehyde (MDA)

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INTRODUCTION

Schizophrenia is a major mental disorder that has a lifetime risk of 1% and affects at young age (average age at the onset 24 +/-4.6 years) in many cultures around the world. The etiology is unknown, the pathophysiology is complex and most of the patients need treatment and care for the rest of their lives (Mayo, 2006). The signs and symptoms of schizophrenia vary greatly. In general, schizophrenia has symptoms that fall into three categories-negative, positive and cognitive (Frankenburg, 2006). Recently more and more converging evidence indicates that oxidative mechanisms may play a role in schizophrenia (Akyol *et al*., 2004; Lohr and Browning, 1995; Yao *et al*., 2001). Free radicals play a major role in the functioning and development of man. The same is found in many somatic and psychic diseases. Changes in free radical concentration levels may be indirectly caused by activity changes of antioxidant enzymes, which apart from antioxidants are the main defense elements of our organism. Advanced age is associated with an accumulation of free radical damage, which leads to physiological and clinical modifications indicated by the increased lipid per oxidation products in erythrocytes and altered levels of enzymatic antioxidants in schizophrenia patients.

The brain and nervous system possess high potentials for the initiation of free-radical reactions, which, relative to the other tissues, can cause more damage in the brain and nervous system, due to insufficient antioxidant protection and existing intensive aerobic metabolism, accompanied with oxygen free-radical production (Haliwell, 1989). There are several ways by which excess free radicals may be generated in the brain. The metabolism of catecholamine, such as nor epinephrine and dopamine, is probably associated with free-radical formation and conditions associated with increased catecholamine metabolism may increase the free-radical production (Glenberg *et al*., 1991).

Superoxide dismutase (SOD), catalase and glutathione peroxidase (GSH-Px) are the primary enzymes involved in direct elimination of free radicals, whereas glutathione Transferase, glucose-6-phosphate dehydrogenase and copper-binding ceruloplasmin, are secondary antioxidant enzymes, which help in maintaining a steady concentration of glutathione and NADPH necessary for optimal functioning of the primary antioxidant enzymes (Chance, 1954; Gutteridge, 1977; Vendemiale *et al*., 1999).These enzymes block the initiation of free-radical chain reactions (Mahadik and Soheffer, 1996). The hypothesis that reactive oxygen species (ROS) play an important role in schizophrenia as well as neurodegenerative disorders remains speculative and there have been no detailed studies to test this hypothesis. Under normal conditions, a dynamic equilibrium exists between the production of reactive oxygen species (ROS) and the antioxidant capacity of the cell (Granot and Kohen, 2004).

There is accumulating evidence of altered antioxidant capacity in schizophrenia, studies of antioxidant systems in schizophrenia has produced the usual medley of conflicting results. Though many authors demonstrate the antioxidant activity disturbances in schizophrenia, the contribution of age and gender in the pathophysiology of schizophrenia has been documented by only a few and their results are shifting and unpredictable.

So in this study, we investigated the effect of age and gender in the antioxidant activities of erythrocyte Superoxide dismutase (SOD), catalase, glutathione peroxidase (GSH-Px), glutathione Transferase (GST), glucose-6-phosphate dehydrogenase and copper-binding ceruloplasmin (secondary antioxidant enzymes) and malondialdehydes as a sign of lipid per oxidation levels in schizophrenia patients with different age groups.

MATERIALS AND METHODS

Patients

The present study was carried out in the Postgraduate and Research department of biochemistry, Dr. N.G.P Arts and Science College, with the collaboration of Kovai Medical Center and Hospital

(KMCH), a 1000 bedded multispeciality hospital with a separate division for Psychiatry during the month of September 2004 to June 2007. A total of 60 schizophrenic patients of age group 18-65 years of both sexes from good socio-economic background were selected from Udhayam Mananala kaapagam, a mental Health care center, Coimbatore, Tamilnadu, India. They all met DSM-IV (Diagnostic and Statistical Manual of Mental Disorders-IV) criteria (American Psychiatric Association, 2000) for schizophrenia. Schizophrenic subjects were divided into three groups: (1) Schizophrenics with age range between 15-30 years, (2) schizophrenic patients with age range between 31-45 years, (2) schizophrenic patients with age range 46-65 years. Positive and negative symptoms score (PANSS) was performed among schizophrenia patients by trained psychiatrist.

Control

Sixty age and sex-matched healthy normal control subjects with no individual and familial history of mental illness were recruited to participate in this study. They included 30 males and 30 females. Their ages ranged from 15 to 65 years with mean age (28.9±14.1) years. Both patients and controls were recruited during the same period from Coimbatore district. Matching between the patients and controls was done according to sex and age. Study subjects were currently within normal ranges in their routine blood, urine and feces tests, electrocardiograph and radiographs; disorders associated with heart, brain, lung, liver, kidney and other pivotal organs were excluded.

The design and the layout of this project was carried out with the approval the Chairman, Kovai Medical Center and Hospitals and due permission was obtained from the board of institutional review Committee of the Kongu mananala Arakkattalai, before the start of the work. Informed and written consent was obtained from all subjects prior to examination.

Blood Sampling

Blood from forearm vein was collected into 5 mL Vacutainer tubes containing potassium EDTA. Fasting blood samples obtained by venupuncture from patients and controls were drawn into heparinised tubes, which were then centrifuged at 2000 g for 15 min, plasma was carefully removed and the erythrocyte pellet was washed twice with equal volumes of saline and centrifuged at 2000 g for 15 min. Washed pellet was stored at -20°C until analyses were carried out. These packed cells were used for the analysis of antioxidants and TBARS levels.

Determination of Antioxidants and Tbars Levels

Super oxide dismutase (EC 1.15.1.1) and catalase (EC 1.11.1.6) activities were determined by the methods of Das *et al*. (2000) and Aebi (1974). GSH-Px activity: GSH-Px (EC 1.6.4.2) activity was measured by the method of Takahashi (2000). G6PD activity: (EC 1.1.1.49) G-6PD activity was assayed according to the procedure described by Beutler (1984). GST activity (EC 2.5.1.18) toward CDNB was determined according to the method of Habig *et al*. (1974). Cp Ferroxidase activity (EC 1.16.3.1) was determined by the method of Gutteridge and Quinlan (2000). TBARS was estimated according to the method of Ohkawa *et al*. (1979) with minor changes adopted by Devasaghayam *et al*. (2003).

Activities of SOD, CAT, GSH-Px, GST and Cp ferroxidase were expressed as Units per gram hemoglobin. Results of TBARS levels were expressed as nanomoles per gram hemoglobin. All reagents used were of analytical reagent grade, obtained from Sigma Chemicals, St. Louis, MO, U.S.A and were used without further purification. To measure SOD, CAT, GSH-Px activities and TBARS levels, uv-visible spectrophotometer (Systronics 117) was used to examine each parameter under their excited wavelengths, respectively. All the operations accord with the guidelines of the apparatus and samples were done in triplets. Statistical analysis between control and patient groups were performed by students t-test. The results were expressed as a difference between the two values. All the values were presented as a mean value±SD.

RESULTS

Results in Table 1 summarize all analyzed biochemical parameters. Table 1 describes significant decrease in erythrocyte antioxidant enzymes activities and TBARS levels in all the study groups compared to the control group. Within the control groups, people with age group of above 45 were facing more oxidative stress compared with the subjects who were of below 45-age range ($p<0.01$). Among schizophrenia patients, it was found that there was an increased free radical mediated oxidative damage in adult and elderly schizophrenics ($p<0.001$) compared with schizophrenic patients with age group of below 30. The MDA levels are very highly increased ($p<0.001$) in elderly schizophrenic patients when compared to normal young subjects (Table 1). The SOD levels are increased in normal elderly group when compared to normal young subjects ($p<0.01$) where as it is highly increased in adult and elderly schizophrenics patients ($p<0.001$) when compared to the normal young controls (Table 1). There was no significant change in the catalase activity in normal elderly people when compared to normal young subjects. Decrease in catalase activity is also observed in adult and elderly schizophrenic patients ($p<0.001$) when compared to normal young controls. But decrease in catalase activity in elderly schizophrenic patients is significant when compared to normal young schizophrenics (Table 1). There were no significant differences among the age groups of schizophrenic patients in the level of GST. Results showed that there was a significant decrease in the level of G6PD in elderly schizophrenics compared with control.

As far as gender concerned, we found significant difference in the tested parameters of G6PD and Cp ferroxidase between male and female subjects in both schizophrenia and control groups. These two enzymes were highly deficient in males compared with females. However, there were significant differences among the study and control subjects with the same gender in some test parameters (Table 2).

Table 1: The activities of red blood cell antioxidant enzymes and TBARS levels in young, adult and elderly schizophrenia and control subjects (Values are mean±SD)

Parameters	Age range 15-30 years (Young) (n = 23)	Age range 31-45 years (Adult) (n = 19)	Age range 46-65 years (Elderly) (n = 18)
Schizophrenia subjects			
SOD (U g^{-1}) of Hb	417.210±47.20a	379.690±19.90a	342.09±45.71ab
CAT (U g^{-1}) of Hb	9.920±0.61a	8.970±0.53a	7.12±0.25ab
Gpx (U g^{-1}) of Hb	51.970±1.24a	43.810±1.19a	42.81±1.19ab
GST (U g^{-1}) of Hb	1667.000±42.0a	1631.000±29.0ab	1701.00±39.0ab
G6PD (U g^{-1}) of Hb	8.046±3.69a	7.034±3.87ab	7.98±3.77ab
Caeruloplasmin ferroxidase (U g^{-1}) of Hb	62.980±19.8a	65.480±20.92ab	66.91±19.23a
Lipid peroxides nmol (MDA g^{-1}) of Hb	11.930±0.378a	14.910±0.276a	15.38±0.173ab
Parameters	Age range 15-30 years (Young) (n = 17)	Age range 31-45 years (Adult) (n = 24)	Age range 46-65 years (Elderly) (n = 19)
Control subjects			
SOD (U g^{-1}) of Hb	297.84±32.09	299.91±52.74	323.60±42.07a
CAT (U g^{-1}) of Hb	12.98±0.740	12.07±0.810	12.73±0.430
Gpx (U g^{-1}) of Hb	67.32±3.690	70.18±4.020	72.41±3.290a
GST (U g^{-1}) of Hb	1523.00±53.00	1520.00±61.00	1549.00±52.00a
G6PD (U g^{-1}) of Hb	17.98±1.920	17.99±1.860	18.02±1.700a
Caeruloplasmin ferroxidase (U g^{-1}) of Hb	87.42±35.34	84.50±40.23	81.31±42.85a
Lipid peroxides nmol (MDA g^{-1}) of Hb	7.75±0.634	8.59±0.412*	10.98±0.509a

Statistical comparison was done between: age-matched Controls and Schizophrenics.*: MDA was estimated as TBARS. *: $p<0.01$, a*: $p<0.001$, a (statistical comparison between age group < 30 and > 30 of control vs schizophrenics). b (statistical comparison between age group < 30 and > 30 of schizophrenics)

Table 2: Enzymic antioxidant and MDA status of control and schizophrenia male and female subjects (Values are mean±SD)

Parameters	Total (n = 60)	Male (n = 28)	Female (n = 32)
Schizophrenia subjects			
SOD (U g^{-1}) of Hb	345.130±32.43	359.67±20.27c	347.21± 47.20d
CAT (U g^{-1}) of Hb	9.920±0.61	08.07±0.53c*	9.89±0.43d
GSH-Px (U g^{-1}) of Hb	51.970±1.24	49.67±1.98c	48.09±1.75d
GST (U g^{-1}) of Hb	1632.000±21.00	1798.00±37.00c	1646.00±39.00
G6P (U g^{-1}) of Hb	8.094±3.47	7.28±334ac*	8.46±3.10d
Caeruloplasmin ferroxidase (U g^{-1}) of Hb	67.600±39.7	60.92±37.9c *	68.12±54.7d
Lipid peroxides nmol (MDA g^{-1}) of Hb	10.610±0.289	10.98±0.234c	11.38±0.173d
Parameters	Total (n = 60)	Male (n = 30)	Female (n = 30)
Control subjects			
SOD (U g^{-1}) of Hb	288.87±12.98	286.39±82.56	291.470±61.32
CAT (U g^{-1}) of Hb	13.42±0.74	13.92±0.32	12.980±0.51
GSH-Px (U g^{-1}) of Hb	69.66±2.54	70.18±4.02	72.410±3.29
GST (U g^{-1}) of Hb	1562.00±38.00	1554.00±47.00	1576.000±52.00
G6P (U g^{-1}) of Hb	17.26±1.76	16.99±1.79	17.210±1.54
Caeruloplasmin ferroxidase (U g^{-1}) of Hb	86.32±43.1	84.87±65.7b	86.650±44.8
Lipid peroxides nmol (MDA g^{-1}) of Hb	7.21±0.428	7.32±0.401	7.078±0.751

a: Statistical significance between male and female of schizophrenic subjects, b: Statistical significance between male and female of control groups, c: Statistical significance between control and schizophrenia males, d: Statistical significance between control and schizophrenia females. Statistical comparison was done between gender matched: Controls and Schizophrenics, Controls and Schizophrenics (male) and Controls and Schizophrenics (female). a, b, c, d: $p<0.01$ *: $p<0.001$

DISCUSSION

The free radicals play an important role in the genesis of structural and functional changes of neuronal membrane; free radicals adversely modify biologically active molecules and whole cells and are implicated in a variety of degenerative diseases and ageing (Głód *et al*., 2000; Tabner *et al*., 2002).

The brain contains both enzymatic and non-enzymatic antioxidants against free radical damage. As the intensity of lipid per oxidation and antioxidative defense in erythrocytes to a certain extent reflects the state of the cell membranes of different tissues, including brain tissue (Vilkov *et al*., 1991). We investigated antioxidant status and MDA levels in erythrocytes of schizophrenic patients and control subjects of different age groups.

Present results indicate that there is increase in free radical generation and decrease in antioxidant defense mechanism in normal elderly subjects when compared to normal young subjects (Table 1). Highly significant increase in MDA and decrease in antioxidants were observed in adult and elderly people complicated with schizophrenia. Lipid per oxidation is an autocatalytic process, which ultimately results in cell death (D'Souza and D'Souza, 2002). Because of continuous generation of free radicals by the oxidation of hemoglobin, erythrocytes are exposed to continuous oxidative stress, which ends in insufficient neutralization of free radicals causes oxidation of cellular lipids (Afanas'ev, 2005). Therefore it is claimed that the long term complications of schizophrenia patients are related to the accumulation of increased free radicals and lipid per oxidation.

In this study we have also found that erythrocyte catalase activity is highly decreased in normal elderly subjects when compared to normal young subjects; whereas it is slightly reduced in other groups. Decreased activity of catalase with ageing might be due to its inactivation by increased oxidative stress (Akila *et al*., 2007). These findings show that antioxidant activities are affected with ageing and there was age related lipid per oxidation and per oxidative damage increases with aging process. This free radical mediated per oxidative injury has a role in pathophysiological changes of ageing. In conclusion, the antioxidant defense mechanisms are not sufficient to prevent age related increase in oxidative damage in schizophrenia and dietary intake of a variety of antioxidants might be beneficial for preserving the normal function in elderly people and schizophrenics with the age of above 45 years.

Present study also shows that there is a significant difference in the test parameters between male and female subjects in both schizophrenia and control groups. As for as the levels of these enzymes in males and females of schizophrenics concerned, there is no significant deviation in values except G6PD, catalase and Cp ferroxidase, whose deficiencies were more pronounced in males than that of females suffered with schizophrenia. However, there were significant differences among the study and control subjects with the same gender in some test parameters was observed (Table 2).

G6PD activity was found to be highly decreased in schizophrenics with negative symptoms. The role of G6PD deficiency in psychiatric disorders has not been definitely established, studies varying from reports of acute psychotic cases to surveys of enzyme activity in hospitalized populations (Dern *et al*., 1963; Fieve *et al*., 1965; Bowman *et al*., 1965; Nasr *et al*., 1982). The first study dates back to 1962, when Dern *et al*. (1963) reported a temporary psychosis during primaquine administration in two G6PD-deficient subjects several weeks after the subsidence of acute hemolytic anemia. Interestingly, the activity of the hexose monophosphate shunt, whose first step is catalyzed by G6PD, can be stimulated in the brain by monoamine transmitters, perhaps in relation with the detoxication of monoamine-oxidase-dependent metabolites (Hothersall *et al*., 1982; Maker *et al*., 1981).

Several research groups have reported the role of G6PD in schizophrenia patients. They could not confirm or deny the results of Dern *et al*. (1963) and Bocchetta (2003). A survey conducted in hospitals of Newyark stated that G6PD-deficiency rates were in excess in males from four hospitals, but the results were in the opposite direction at the fifth hospital of Newark. Nonsignificant excess in the catatonic subtype was also reported in females when the lowest 10% G6PD enzyme activity was analyzed. In another study, no catatonic/paranoid differences were found in 783 Afro-American men hospitalized for schizophrenia in Alabama (Bowman *et al*., 1965). In view of such controversial results, the hypothesis of a role of G6PD deficiency in schizophrenia is still a matter of debate. It was concluded that the discrepancies were probably due to unreliability of subcategories of schizophrenia as well as to the choice of samples of chronic patients as opposed to the acute hemolysis-related psychosis (Dern *et al*., 1963).

Human Caeruloplasmin (Cp) is officially known as ferroxidase or iron (II): oxygen oxidoreductase. Our results showed the decreased ferroxidase in all schizophrenics. Erythrocytes have been extensively studied as a susceptible target for oxidative damage, since they are long-lived cells and very rich in Fe^{2+}-containing molecules, primarily Hb, that generates oxygen radicals (Fung and Zhang, 1990; Glen *et al*., 1994) Recently, Kim *et al*. (1998) observed that Cp can catalytically remove hydrogen peroxide in the presence of thiols.

The nervous system-including the brain and peripheral nerves-is rich in both unsaturated fatty acids and iron. The high lipid content of nervous tissue, coupled with its high aerobic metabolic activity, makes it particularly susceptible to oxidative damage. The high level of iron may be essential, particularly during brain development, but its presence also means that injury to brain cells may release iron ions, which lead to oxidative stress via the iron-catalyzed formation of ROS (Bauer and Bauer, 1999; Andorn *et al*., 1999).

The glutathione peroxidase-like activity of Cp together with its ferroxidase activity would completely remove the primary reactants required for both Fenton chemistry and lipid per oxidation in brain. In addition, those brain regions that are rich in catecholamines are exceptionally vulnerable to free radical generation. The catecholamine adrenaline, noradrenaline and dopamine can spontaneously break down (auto-oxidise) to free radicals, or can be metabolized to radicals by the endogenous enzymes such as MAO (monoamine oxidases). One such region of the brain is the substantia nigra (SN), where a connection has been established between antioxidant depletion (including GSH) and tissue degeneration (Perry *et al*., 2002). A number of *in vitro* studies have shown that antioxidants-both endogenous and dietary-can protect nervous tissue from damage by oxidative stress. Significant

decrease in Cp ferroxidase in males is due to the fact that there is a correlation between level of Cp with age and sex. There is low concentration of Cp at birth, gradually increases to adult levels and slowly continues with age and the decreases. At the end adult females have higher concentration of Cp than males (Chatterjea and Shinde, 2006).

Examination of oxidative stress and antioxidant status revealed that the MDA level, an indicator of oxidative stress was found to be significantly raised in schizophrenics compared to control subjects ranging in age from 15 to 65 years. Increased TBARS levels in erythrocyte from our schizophrenia patients are consistent with the previous results (Herken *et al*., 2001; Hui-Chun *et al*., 2006; Keshavan *et al*., 1993; Horrobin *et al*., 1991). Further, the elderly subjects in the age of >45 years had a greater degree of oxidative stress as compared to those below 45 years of age and the effect was evident both in controls and schizophrenics. Present results indicated that elderly and adult schizophrenics had greater degree of oxidative stress as compared to control (Table 2). This shows that age seems to affect the level of oxidative stress however there was no effect of gender on MDA level in controls as well as schizophrenics (Table 1, 2). The raised MDA level in adult and elderly schizophrenics reflects the oxidative injury due to aging as well as disease severity, which is attributed to free radical formation that abstracts hydrogen atoms from lipoproteins causing lipid per oxidation, of which MDA is the main product (Halliwell, 1994; Frei, 1994) and their delayed neutralization in the presence of low antioxidant concentration and condition is further aggravated by antipsychotic agents (Benedicta and Vivian, 2003; Ansari, 1996).

CONCLUSION

Based on our results, we may conclude that there is increase in free radical generation and decrease in antioxidant defense mechanism in elderly people and elderly patients when compared to normal young subjects. Decreased antioxidant status may lead to insufficient neutralization of free radicals, which causes the oxidation of cellular lipids, proteins, nucleic acids, glycolipids and glycoprotiens (Afanas'ev, 2005). This oxidative effect also causes damage to the vascular endothelial cells, as evident from increased MDA levels observed in our study in elderly schizophrenia patients. The increased levels of lipid peroxides can cause oxidative injury to blood cells, cross linking of membrane lipids and proteins, imbalance of prostacyclin, prostaglandin and vasoconstriction (Akila *et al*., 2007).

This free radical mediated per oxidative injury has a role in pathophysiological changes of ageing. The above data reveal that antioxidant defense mechanisms might be impaired significantly in adult and elderly schizophrenic patients. These findings also provide a theoretical basis for the development of novel therapeutic strategies, such as antioxidant supplementation and may suggest the hope for use of antioxidants in clinical trials to prevent and treat elderly schizophrenic patients.

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