Research Article

Study of nonenzymatic antioxidants in schizophrenic patients

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ABSTRACT

Background: Schizophrenia is one of the most debilitating psychiatric disorders. There is now substantial evidence of increased free radical–mediated damage in schizophrenia. These mechanisms are critical role in etiopathogenesis of schizophrenia. The potential toxicity of reactive oxygen species (ROS) is counteracted by a large number of cytoprotective enzymes and nonenzymatic anti-oxidants. Endogenous substances like albumin, bilirubin and uric acid play very important defensive role against reactive oxygen species (ROS) produced in our body. The present study was undertaken to study nonenzymatic antioxidants i.e. serum albumin, bilirubin and uric acid in first episode and chronic schizophrenic patients.

Methods: 50 patients of first episode schizophrenia and 50 patients of chronic schizophrenia were included in the study. 50 numbers of age and sex matched healthy and apparently normal controls were also selected for study. Blood samples were drawn and analysed for albumin, bilirubin and uric acid from all participants.

Results: The study shows significant decrease in serum albumin, bilirubin and uric acid levels in both first episode schizophrenics and chronic schizophrenic patients as compared to controls. When we compared levels of these parameters in first episode schizophrenics and chronic schizophrenics, we did not find significant difference.

Conclusions: Findings in our study is suggesting that decrease in the levels of nonenzymatic antioxidants occurs in attempting neutralization of ROS in schizophrenics. This study supports the defensive role of nonenzymatic antioxidants against ROS in our body.

Keywords: Schizophrenia, Antioxidants, Albumin, Bilirubin, Uric Acid

INTRODUCTION

Schizophrenia is a disturbance that last for six months or longer, including at least one month of delusions, hallucinations, disorganized speech, grossly disorganized or catatonic behavior, or negative symptoms. It is one of the most debilitating psychiatric disorders and has long been the focus of medical, scientific, and societal attention. It has devastating effects on both the patients and their families.1 Epidemiologic surveys identify several risk factors for schizophrenia including genetic susceptibility, early developmental insults, winter birth, and increasing parental age.2 There is now substantial evidence for increased free radical mediated breakdown of phospholipids in schizophrenia, even at the onset of psychosis. Oxidative neuronal injury in the brain may cause abnormal neurodevelopment, neurodegeneration or neuronal membrane impairment. These mechanisms are
critical in the etiopathogenesis of schizophrenia. The potential toxicity of reactive oxygen species (ROS) is counteracted by a large number of cytoprotective enzymes and nonenzymatic anti-oxidants which limit the damage which could be caused by such species. These protective mechanisms function cooperatively in the form of cascade.

Endogenous substances like albumin, bilirubin and uric acid play very important defensive role against reactive oxygen species (ROS) produced in our body. There are very few studies regarding estimation of nonenzymatic endogenous antioxidants like albumin, bilirubin & uric acid in schizophrenics. In the view of above facts, following study was planned to study levels nonenzymatic antioxidants in schizophrenic patients.

METHODS

The present study was carried out in the Department of Biochemistry, Indira Gandhi Government Medical College, Nagpur. The study protocol was approved by the Institutional Ethical Committee. An informed written consent was obtained from all the study subjects who were enrolled in the study.

50 patients of first episode schizophrenia and 50 patients of chronic schizophrenia visiting psychiatry OPD were included in the study. 50 numbers of age and sex matched healthy and apparently normal controls were also selected for study. The patients and controls were in the age group of 20-50 years of both sexes.

Participants were selected on basis of detailed history and clinical examination.

Inclusion criteria

**Criteria for first episode schizophrenic patients**

- Newly diagnosed schizophrenic patients with DSM IV criteria.
- Patients of either sex between 20-50 years of age.
- No history of taking antipsychotic medication at any period of time before study.

**Criteria for chronic schizophrenic patients**

- Chronic schizophrenic patients diagnosed with DSM IV criteria.
- Patients of either sex between 20-50 years of age.
- Patients on atypical antipsychotic medication.

**Criteria for controls**

- Age and sex matched healthy and apparently normal subjects.

Exclusion criteria for patients and controls

- Acute infectious and inflammatory diseases
- Liver diseases
- Pulmonary diseases
- Renal diseases
- Ischemic heart disease
- Neoplastic diseases
- Diabetes
- Smoking
- Hypertension
- Alcoholic
- Subjects on vitamins and antioxidant supplementation.

Biochemical investigations

After written informed consent, blood samples were drawn from antecubital vein and collected in plain bulbs. Samples were centrifuged for 15 min at 4500 rpm. Serum was analysed for levels of albumin, bilirubin and uric acid.

Estimations were done by using instrument and kits provided by single vendor Transasia Erba diagnostic Ltd. and according to manufacturer procedures i.e. albumin by BCG method, bilirubin by Diazo method and uric acid by Uricase method.

The data collected was expressed as mean and standard deviation (S.D.) and statistically evaluated by Student’s unpaired ‘t’ test. P-value<0.05 was taken as significant, whereas P-value<0.01 was taken as highly significant. P-value >0.05 was considered statistically non-significant (NS).

RESULTS

All the cases (First episode and chronic schizophrenics) and controls in the study were divided into 3 groups.

Group A: It consists of 50 first episode schizophrenic patients.
Group B: It consists of 50 chronic schizophrenic patients.
Group C: It consists of 50 age & sex matched apparently healthy normal subjects.

**Table 1: Age and sex distribution of cases and controls.**

<table>
<thead>
<tr>
<th></th>
<th>Group-A (n=50)</th>
<th>Group-B (n=50)</th>
<th>Group-C (n=50)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>31</td>
<td>30</td>
<td>28</td>
</tr>
<tr>
<td>Female</td>
<td>19</td>
<td>20</td>
<td>22</td>
</tr>
<tr>
<td>M:F</td>
<td>1.63:1</td>
<td>1.5:1</td>
<td>1.27:1</td>
</tr>
<tr>
<td>Age in years</td>
<td>30.88±6.50</td>
<td>32.98±4.36</td>
<td>33.74±9.14</td>
</tr>
<tr>
<td>(Mean±SD)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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Table 2: Levels of serum albumin, bilirubin and uric acid in first episode schizophrenic patients (group-A) and controls (group-C).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group-A (n=50) (mean ± SD)</th>
<th>Group-C (n=50) (mean ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albumin (gm/dl)</td>
<td>3.84±0.25**</td>
<td>4.34±0.31</td>
</tr>
<tr>
<td>Bilirubin (mg/dl)</td>
<td>0.52±0.17**</td>
<td>0.69±0.19</td>
</tr>
<tr>
<td>Uric acid (mg/dl)</td>
<td>4.16±0.73**</td>
<td>5.29±1.03</td>
</tr>
</tbody>
</table>

**P-value < 0.01 was taken as highly significant.

Table 3: Levels of serum albumin, bilirubin and uric acid in chronic schizophrenic patients (group-B) and controls (group-C).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group-B (n=50) (mean ± SD)</th>
<th>Group-C (n=50) (mean ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albumin (gm/dl)</td>
<td>3.90 ± 0.24**</td>
<td>4.34 ± 0.31</td>
</tr>
<tr>
<td>Bilirubin (mg/dl)</td>
<td>0.56 ± 0.17**</td>
<td>0.69 ± 0.19</td>
</tr>
<tr>
<td>Uric acid (mg/dl)</td>
<td>4.20 ± 0.67**</td>
<td>5.29 ± 1.03</td>
</tr>
</tbody>
</table>

**P-value < 0.01 was taken as highly significant.

Table 4: Levels of serum albumin, bilirubin and uric acid in first episode schizophrenic patients (group A) and chronic schizophrenic patients (group B).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group-A (n=50) (mean ± SD)</th>
<th>Group-B (n=50) (mean ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albumin (gm/dl)</td>
<td>3.84 ± 0.25</td>
<td>3.90 ± 0.24*</td>
</tr>
<tr>
<td>Bilirubin (mg/dl)</td>
<td>0.52 ± 0.17</td>
<td>0.56 ± 0.17*</td>
</tr>
<tr>
<td>Uric acid (mg/dl)</td>
<td>4.16 ± 0.73</td>
<td>4.20 ± 0.67*</td>
</tr>
</tbody>
</table>

*P-value > 0.05 was taken as statistically nonsignificant.

DISCUSSION

Schizophrenia is a heterogeneous syndrome characterized by perturbations of language, perception, thinking, social activity, affect and volition. There are some recent studies focused on roles of free radicals in the pathogenesis of neuropsychiatric disorders and numerous studies indicating that free radical-mediated neuronal dysfunction have roles in the pathophysiology of schizophrenia. Alteration in the oxidant-antioxidant profile is known to occur in schizophrenia. A major contribution to the total antioxidant capacity comes from antioxidant molecules in plasma, such as albumin, bilirubin and uric acid. Thus plasma is an important vehicle that serves as a protective factor against oxidative damage to different blood components and also distributes dietary antioxidants to the rest of the body.

Several studies have shown the antioxidant properties of albumin. Serum albumin is able to scavenge hydroxyl radicals through the reduced Cys34. Albumin not only can inhibit lipid peroxidation by binding copper ions, but also serves as scavenger of both oxygen and carbon-centered free radicals.

Our results (Table 2 & Table 3) show a highly significant decrease in serum albumin levels of first episode schizophrenic patients as well as in chronic schizophrenic patients as compared to controls (p<0.01). We found no significant difference (Table 4) in the levels of serum albumin between first episode and chronic schizophrenic patients.

Our findings correlate with the findings of Chi-Un Pae et al, who observed significantly decrease in levels of plasma albumin in first episode schizophrenic patients and in the risperidone-treated chronic schizophrenia patients as compared to controls. They also observed no significant difference in the levels of albumin between first episode and chronic schizophrenic patients. Our results are in accordance with Reddy R et al, who found significantly decreased levels of plasma albumin in first episode schizophrenics.

Yao JK et al also demonstrated significantly lower plasma albumin in chronic schizophrenic patients. It was observed that male patients with schizophrenia either during haloperidol treatment or in a drug-free condition had significantly lower levels of plasma albumin compared with age- and sex-matched healthy volunteers. Umadevi P and Murugan S reported significantly lower serum albumin levels in schizophrenics.

Our findings have fair correlation with findings of Huang Tao-lai, who studied 106 patients with schizophrenia with help of review of medical charts over a 1-year period. The statistical results showed significantly lower serum albumin levels in patients with schizophrenia than in the control group.

Decrease in serum albumin level in first episode schizophrenics may be indicative of immunological or acute phase protein response or oxidative stress. Decrease in plasma albumin level may indicate oxidative stress in chronic schizophrenia. Decreased level of serum albumin due to oxidative stress can be explained by the fact that oxidized human serum albumin (oxy-HSA) has significantly greater liver and spleen uptake clearance than normal human serum albumin (HSA) and oxy-HSA leaves the circulation rapidly.

There is ample evidence suggesting that bilirubin possesses antioxidant property. Both conjugated and unconjugated bilirubin protects serum lipids against damage inflicted by in situ generated peroxyl radicals. A mechanism is proposed that bilirubin can scavenge the chain-carrying peroxyl radical by donating a hydrogen atom attached to the C-10 bridge of the tetrapyrrole molecule to form a carbon-centered radical Bil. In plasma, ascorbate and bilirubin, the latter in a site-specific manner, appear to be much more effective in...
protecting lipids from peroxidative damage by aqueous oxidants than all the other endogenous antioxidants.\textsuperscript{19,20}

Our study shows highly significant decrease in serum bilirubin levels in first episode schizophrenic patients as well as in chronic schizophrenics as compared to controls (Table 2 & Table 3) (p<0.01). We found no significant difference in the levels of serum bilirubin between first episode and chronic schizophrenic patients (Table 4). Our findings are supported by earlier workers, namely Reddy R et al and Chi-Un Pae et al.\textsuperscript{9,12}

Chi-Un Pae et al observed significantly lower bilirubin levels in first episode schizophrenics as well as in risperidone-treated chronic schizophrenics as compared to controls.\textsuperscript{12} They also observed no significant difference in the levels of bilirubin between first episode and chronic schizophrenic patients. Reddy R et al reported significant decrease in bilirubin levels in first episode schizophrenics.\textsuperscript{9}

Our findings have fair correlation with the findings of Yao JK et al, Umadevi P and Murugan S, Teresa M et al.\textsuperscript{14,15,21}

Yao JK et al also demonstrated significantly lower plasma bilirubin levels in chronic schizophrenic patients either during haloperidol treatment or in a drug-free condition compared with age- and sex-matched healthy volunteers.\textsuperscript{14} Teresa M et al found lower bilirubin levels in schizophrenic patients than control.\textsuperscript{21}

Decrease in bilirubin in schizophrenia may be indicative of oxidative stress.\textsuperscript{9,14} Yasukawa R et al observed increased urinary excretion of biopyrins during the psychotic state in patients with schizophrenia.\textsuperscript{22} Biopyrrins are bilirubin oxidative metabolites which are generated from bilirubin as a result of this scavenging action against free radicals. The decreased levels of sr. bilirubin in schizophrenics can be explained by the fact that bilirubin on oxidative degradation forms products like biopyrrins which are readily excreted in urine.\textsuperscript{22}

Various studies have demonstrated antioxidant property of uric acid.\textsuperscript{23-25} At physiological concentrations, urate reduces the o xo-heme oxidant formed by peroxide reaction with hemoglobin, protects erythrocyte ghosts against lipid peroxidation, and protects erythrocytes from peroxidative damage leading to lysis. It was found that urate is much more easily oxidized than deoxynucleosides by singlet oxygen and is destroyed by hydroxyl radicals at a comparable rate.\textsuperscript{23} Uric acid can be oxidized following nonenzymatic degradation and has been proven to be a selective antioxidant, capable of reacting with hydroxyl radicals and hypochlorous acid.\textsuperscript{24} Uric acid also has the ability to bind iron and inhibit iron-dependent ascorbate oxidation, preventing an increased production of free radicals that can further contribute to oxidative damage.\textsuperscript{25}

Our results (Table 2 & 3) show highly significant decrease (p<0.01) in serum uric acid levels in first episode schizophrenic patients as well as in chronic schizophrenic patients as compared to controls. We found no significant difference in the levels of serum uric acid between first episode and chronic schizophrenic patients (Table 4).

Our findings are in accordance with Reddy R et al, who found significantly decreased levels of plasma uric acid in first episode schizophrenics. Chi-Un Pae et al reported that average uric acid level was lower in first episode schizophrenic patients as well as chronic schizophrenic patients as compared to controls whereas, no significant difference was observed in the levels of uric acid between first episode and chronic schizophrenic patients.\textsuperscript{9,12} Our findings correlate with findings of Yao JK et al who estimated plasma uric acid levels in male (chronic) schizophrenic patients and observed that these patients with either a haloperidol treatment or a drug free condition had significantly lower levels of plasma uric acid than age and sex matched normal control subjects.\textsuperscript{26} Decrease in levels of uric acid may be suggestive of oxidative stress in schizophrenia.\textsuperscript{9,26} Decreased level of serum uric acid due to oxidative stress can be explained by the fact that uric acid is oxidized by singlet oxygen and is destroyed by hydroxyl radicals during its antioxidant action.\textsuperscript{23}

In conclusion, we observed significant decrease in serum levels of albumin, bilirubin and uric acid in both first episode schizophrenics and chronic schizophrenic patients as compared to controls. When we compared levels of these parameters in first episode schizophrenic and chronic schizophrenics, we did not find a significant difference. Findings in our study suggest that decrease in the levels of nonenzymatic antioxidants occurs in attempting neutralization of ROS in schizophrenics. This study supports the defensive role of nonenzymatic antioxidants against ROS in our body.

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REFERENCES

