JOURNAL OF CLINICAL AND DIAGNOSTIC RESEARCH

How to cite this article:
BIOCHEMICAL DERANGEMENTS IN PATIENTS WITH SCHIZOPHRENIA: A CASECONTROL STUDY. Journal of Clinical and Diagnostic Research [serial online] 2008 August [cited: 2008 August14]; 4: 1001-1008
Available from
http://www.jcdr.net/back_issues.asp?issn=0973-709x&year=2008&month= August &volume=2&issue=4&page=1001-1008&id=260

ORIGINAL ARTICLE

Biochemical Derangements In Patients With Schizophrenia: A Case-Control Study

UMA DEVI P AND MURUGAN. S

ABSTRACT

Aim: The objective of this study was to evaluate and compare the levels of non dietary antioxidants and the status of complete blood count in schizophrenia patients with positive, negative and cognitive symptoms.

Materials and Methods: This was a prospective observational study involving samples of 60 schizophrenia patients who met the established criteria for schizophrenia, and were admitted to the mental health care center, Coimbatore district. Sixty age and sex matched control subjects were also taken. Planned assessments included the levels of uric acid, albumin, bilirubin. Creatinine and complete blood count were performed using standard biochemical methods by applying the Roche/Hitachi Modular D-P automated chemistry analyzer 112.

Results: It is predicted from the results that there was a significant increase in uric acid levels in all the schizophrenics when compared to normal values ($p<0.01$), but a statistically more significant increase in the status of uric acid was found for schizophrenics with cognitive symptoms($p<0.001$). It was observed that there was a significant decrease in serum bilirubin, albumin and creatinine levels in patients with schizophrenia, when compared to controls (0.01). There was no statistically pronounced difference among the levels of albumin, bilirubin and creatinine in schizophrenia patients with positive, negative and cognitive symptoms.

Conclusion: These data reveal that non dietary antioxidant defence mechanisms might be impaired in schizophrenic patients. Understanding these basic pathological processes may yield novel targets for the development of more effective treatments.

Keywords: Schizophrenia, symptoms, haematological status, non dietary antioxidants.

Corresponding Author
Dr. P.Uma Devi
Assistant Professor, Department of Biotechnology,
Karunya University,
Coimbatore. 114, Tamil Nadu. India.
Tel: +91-0422-26144477 , Mobile:+91 9994583372
Fax: 91 0422 2629369 ,
e.mail: umadevipongiya@rediffmail.com

Introduction

Schizophrenia is a disabling group of brain disorders characterized by symptoms such as hallucinations, delusions, disorganized communication, poor planning, reduced motivation, and less sociability.While the incidence of the disorder is relatively low (median value 15.2 per 100,000 persons per year) [1], the condition is one of the major contributors to the global burden of disease [2].

The substantial burden of disease is a reflection of two features of schizophrenia: (a) the disorder usually has its onset in early adulthood, and (b) despite optimal treatment, approximately two-thirds of affected individuals have persisting or fluctuating symptoms [3].The symptoms of schizophrenia

fall into three broad categories: Positive, negative and cognitive symptoms[4].

Radical-induced damage may be important in schizophrenia as there is increasing evidence that oxidative injury contributes to the pathophysiology of schizophrenia [5]. Recently, many reports have shown that schizophrenia is accompanied by an activation of the immune\inflammatory system , including acute phase response as indicated by changes in serum acute phase protein [6],[7],[8],[9] .Some physicians have reported that lower serum albumin (one of the negative acute phase proteins) levels were noted in patients with major depression in Western countries.[10],[11],[12]. However, there were no detailed discussions concerning serum albumin levels and schizophrenia patients with different symptoms. Albumin and bilirubin are metal – binding proteins shown to possess free radical scavenging properties , and may thus be selective antioxidants[11].Therefore the roles of serum albumin and bilirubin in patients with schizophrenia are important, and need to be studied .

Uric acid, a by product of purine metabolism, is one of the major radical-trapping antioxidants in plasma. Uric acid can act as an antioxidant, both by binding iron and copper ions in forms that do not accelerate free radical reactions, and by directly scavenging oxidized species such as singlet O2, HOCI and peroxy radicals. Because of its high concentration, urate might be important as a hydroxyl radical scavenger in vivo.
One role of urate is to help suppress lipid peroxidation in erythrocytes. Uric acid has a protective effect against oxo-heme oxidants which cause membrane peroxidation. Haemoglobin and peroxide are both necessary for lipid peroxidation, while urate and ascorbate protect against this peroxidation [13]. Urate not only protects erythrocytes, but also the DNA-containing longer lived T and B lymphocytes and macrophages.

Creatinine (from greek kreas, flesh) metabolism in general, has attracted considerably less attention. In recent years, however, a series of fascinating new discoveries have been made about the role of creatinine. Circumstantial evidence suggests a link between disturbances in Creatinine (Cr) metabolism and muscle diseases as well as neurological disorders, and beneficial effects of oral Cr supplementation in such diseases have in fact been reported. Total Creatinine Kinase (CK) activity and Creatinine content are lower in the brain than in the skeletal muscle or heart. Even though it might be concluded that the CK system plays a less prominent role in brain physiology, there is ample evidence to establish close correlations between Cr metabolism and CK function on one hand, and proper brain function on the other hand [14].

With its hallucinations, delusions, thought disorder, and cognitive deficits, schizophrenia affects the most basic human processes of perception, emotion, and judgment. Evidence increasingly suggests that schizophrenia is a subtle disorder of brain development, plasticity and oxidative injury indicated by altered levels of non dietary antioxidants in schizophrenic patients. Though there is an accumulating evidence of altered antioxidant capacity in schizophrenia, to the best of our knowledge, there are no reports in literature stating the role of uric acid, albumin, bilirubin and creatinine in patients with different schizophrenia symptoms such as positive, negative and cognitive symptoms. Therefore, in this study, the levels of serum uric acid, albumin, bilirubin and creatinine were investigated in schizophrenia patients with positive, negative and cognitive symptoms. In addition, anthropometric and haematological measurements were also made in the selected schizophrenia patients.

Materials and Methods

Study Population and Data Collection

Patient Groups

A total of 60 schizophrenic patients of the age group 18-65 years, of both sexes, from good socio-economic backgrounds, were selected from Udhayam Mananala Kaapagam, a mental Health care center, Coimbatore, Tamilnadu, India. The patients were divided into three groups with 20 patients in each groups (1) schizophrenics with positive symptoms, (2) schizophrenics with negative symptoms and (3) schizophrenics with cognitive symptoms. They all met DSM-IV (Diagnostic and Statistical Manual of Mental Disorders-IV) criteria (American Psychiatric Association, 2000)[15] for schizophrenia.

Informed and written consent was obtained from all subjects prior to examination. Patients with a history of drug abuse or dependence, serious medical conditions, and severe head injury or seizure disorders were excluded from the study. With the help of a team of psychologists, the participants were interviewed at the time of collection of biological samples, and information regarding their age, family background, family medical history and economic status were collected. Information regarding chronic illness, smoking, alcohol consumption and drug intake was obtained by questionnaires.

Reference groups

Sixty age and sex-matched healthy normal control subjects with no individual and familial history of mental illness or antipsychotic treatment were recruited to participate in this study. They included 30 males and 30 females, their ages ranging from 15 to 65 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.

Eligibility

Inclusion Criteria

1. Age 18-65 years, Both male or female
2. DSM-IV criteria for schizophrenia,
3. Ability and willingness to sign informed consent for participation in the study
4. Study subjects were currently within normal ranges in their routine blood, urine and feaces tests

Exclusion Criteria

1. Evidence of organic brain damage, mental retardation, alcohol or drug abuse
2. Impairment of renal function
3. Hepatic dysfunction
4. A history of pancreatitis
5. Suicide attempt in past year.
6. Cataracts.
7. Pregnant women or a woman who intends to become pregnant.

The participants were asked to fast overnight before coming for clinical examination, where their weight, height, waist circumference and blood pressure were measured. Body Mass Index (BMI) was calculated and blood samples were taken. Fasting plasma, glucose, cholesterol and triglyceride levels were estimated. BMI was also measured for the selected groups. Waist circumference was measured at the level midway between the lowest rib margin and the iliac crest. In men, a waist circumference of 100 cm and under was defined as normal, of over 100 cm as obese, and in women, 90 cm was defined as the cut-off point.

Clinical charts were prepared for patients and control subjects to know whether they were overweight or obese or not. Thus, it was known from the clinical charts that none of the subjects in the reference group was overweight or obese.

Ethical considerations

The design and the layout of this project was carried out with the approval of 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 and Determination of plasma constituents

Assessments for the present analyses included fasting blood samples for glucose, cholesterol and triglycerides. The metabolic fasting sample was drawn between 8 and 10 a.m., after at least 8 hour's fasting, before medication administration.

Haemoglobin concentration was determined using cyanmeth reagent, and other haematological parameters were measured. Uric acid was estimated as described by Kageyama et al.,[16]. Bilirubin levels of serum were measured by the method of Ehrlich (1883)[17]. Serum albumin protein levels were measured by using bromocresol green, as described by Doumas et al [18] respectively. Creatinine levels were estimated by the rate of change in absorbance using alkaline picrate, as described by Bowers, 1980 [19].

All the operations were in accordance with the guidelines of the apparatus; and samples were done in triplets. Statistical analysis between control and patient groups were performed by Student's't' test. The results were expressed as a difference between the two values. All the values were presented as a mean value ± SD.

Results

a (statistical significance compared to control group)

b (statistical difference between positive and negative group)

c (statistical difference between positive and cognitive group)

d (statistical difference between negative and cognitive group

Demographic and clinical characteristics of selected schizophrenia patients and control subjects are presented in [Table/Fig1].There were no significant effects of gender or age at onset of schizophrenia, duration of illness, and height on the schizophrenia patients with different symptoms. Women and men did not differ with respect to duration of illness. The groups did not differ in the proportions of medication intake, or in terms of physical co morbidity, including diabetes mellitus (data not shown). There was a significant main effect on weight between control and patient groups. Genetic predisposition was more in schizophrenia patients with positive symptoms as compared to patients with other symptoms. Almost all the patients had sleep disturbances.

[Table/Fig 1] Demographic profile: Age, Height, Weight and Body Mass Index of Normal Healthy persons and Schizophrenia Patients

Demographic Characteristics of Cases and Controls

Parameter	Schizophrenia Patients with			Control
	Positive Symptoms	Negative Symptoms	Cognitive Symptoms	
Age (Years)	19 to 58 (29.8 ± 11.5) years	20 to 59 (32.7 ± 12.3) years	22 to 51 (36.9 ± 8.9) years.	15 to 65with mean age (28.9±14.1) years
Mean age of onset of schizophrenia (Years)	23 ± 5.0	27± 6.0	25± 6.0	NA
Mean duration of schizophrenia(years)	9.0 ± 6.0	7.0 ± 6.0	9.0 ± 6.0	NA
Gender : Male Female	10 10	10 10	10 10	30 30
Blood Pressure Systolic (mmHg) Diastolic (mmHg)	112 ± 13.2 74 ± 9.6	112± 13.2 74 ± 9.6	112± 13.2 74 ± 9.6	112± 13.2 72± 13.2
Height (cm)	161.31± 1.21	162.27± 1.19	163.24± 1.19	163.25± 1.02
Weight (Kg)	66.74 ± .37	67.44 ± .65	67.39 ± .58	62.64 ± .53
Sleep disturbance	17	12	14	Nil
BMI Normal (< 25) Overweight (≥ 25 <30 Obese(≥ 30)	12 6 2	11 6 3	16 3 1	20 Nil Nil
Family History Positive\Negative	3\20	1\20	2/20	NA

The mean levels of haematological parameters in schizophrenia patients and their controls are presented in [Table/Fig 2]. Results showed that there was no significant change in the levels of Hb and total RBC count among controls and schizophrenics. There was a significant decrease in MCT value in all types of schizophrenia patient groups as compared to the control group. WBC and platelet counts were found to be significantly elevated in schizophrenia patients with positive, negative and cognitive symptoms when compared to the control group (p 0.01, p 0.01, and p 0.001 respectively).

[Table/Fig 2]Hematological Profile of Normal Healthy persons and Schizophrenia Patients

Parameter	Control	Schizophrenia Patients with		
		Positive Symptoms	Negative Symptoms	Cognitive Symptoms
Hb g/dl	13.9± 1.5	13.4± 1.7	13.1± 1.4	13.3± 1.2
HCT %	39.8± 5.3	37.5± 5.1*	37.9± 4.7*	37.1± 4.7*
RBCcount(×0^6) cells\ cu m.m	5.11 ± 0.08	5.01 ± 0.04	5.04 ± 0.02	5.03 ± 0.05
WBC (× 10^3)	6.2± 2.3	7.9 ± 2.5**	6.9± 2.3	7.1 ± 2.2*
Plt (× 10^5)	261± 93	278± 79**	270± 92*	272± 870*

. *: p<0.01; **: p<0.001;

[Table/Fig] 3 summarizes all analyzed biochemical parameters. Among them, the average levels of uric acid were significantly high in all schizophrenia patients as compared to healthy control subjects. Elevation of uric acid was statistically more significant in patients with cognitive symptoms when compared with schizophrenia patients with positive and negative symptoms. In contrast, the mean levels of albumin and bilirubin were lower significantly in schizophrenics when compared with control subjects. When intra group comparison was made, no statistically noticeable difference was found among schizophrenia patients with different symptoms. There was also no significant change in the level of creatinine in controls as well as patients with different symptoms.

[Table/Fig 3] Status of Uric acid, Albumin, Bilirubin and Creatinine in Schizophrenia patients and Normal Healthy persons

Biochemical Constituents	Control	Schizophrenia Patients with		
		Positive Symptoms	Negative Symptoms	Cognitive Symptoms
Uric acid (mg\dl)	5.78±0.73	6.19±0.78a	6.33± 0.81a	7.02±0.97acd
Albumin (mg\ml)	4.48±0.97	3.13±0.74a	3.21±0.84a	3.38±0.92a
Bilirubin (mg\dl)	0.73±0.13	0.59±0.11a	0.54±0.15a	0.53±0.12a
creatinine (mg\dl)	0.89 ±0.02	0.77 ±0.01a	0.79 ±0.03a	0.77 ±0.01a

Discussion

Albumin and bilirubin are metal-binding proteins shown to possess free radical scavenging properties, and may thus be selective antioxidants [20]. In the present study, we evaluated the levels of albumin and bilirubin, which significantly contributes to total antioxidant status (TAS). Results showed that the levels of these antioxidants are reduced significantly in schizophrenia patients as compared to control groups.The antioxidant property of bilirubin, the end product of heme catabolism in mammals, was first demonstrated by Stocker et al [21]. In vitro studies have demonstrated that bilirubin exerts an antioxidant effect [22] in either free or albumin-bound form [23].

Several authors have suggested that psychological stress induces the production of reactive oxygen species (ROS). Several studies have supported the idea that bilirubin exerts antioxidative effects in vivo, and it was reported that psychological stress provokes bilirubin oxidation in vivo [24].We investigated whether the concentration of bilirubin is changed in serum from schizophrenia patients with different symptoms. The concentration of bilirubin in schizophrenia patients with different symptoms was significantly lower than that of healthy volunteers. These finding supports the findings of Tsuyoshi et al [25], and suggest that schizophrenia patients are associated with a decrease in the levels of bilirubin in human serum.

Albumin, the most abundant plasma protein, is an important extracellular antioxidant regulating glutathione levels in lung epithelial cells [26],[27]. Bilirubin protects albumin from oxidative damage and acts in concert with vitamin E to inhibit the oxidation of low density lipoproteins [28]. The potential importance of these nondietary antioxidants is emphasised by the current observations that plasma albumin correlated positively with dopamine function.

In the present study, we also observed that serum uric acid levels were elevated than that of the control groups ($p<0.01$). Further, it is evident from our results that the levels of uric acid increased more significantly in patients with cognitive symptoms. There was no detectable change in the levels of uric acid between positive and negative symptomatic people, even though they differed significantly in their

uric acid values when compared with control groups. Previous reports indicated that levels of plasma proteins including albumin, uric acid and bilirubin in blood, are reported to be lower in haloperidol-managed [29] and first episode schizophrenic patients [30].

Serum uric acid (UA) like other antioxidants such as albumin, bilirubin, or vitamins A, C and E, is a powerful free-radical scavenger and increases in response to oxidative stress [31] [32]. Uric acid formation may even provide a significant antioxidant defense mechanism against nitration by peroxynitrite in rat heart during hypoxia [33)]. It is therefore postulated that serum uric acid level is an important marker in oxidative stress.

High levels of serum uric acid (UA) in the elderly may cause cerebral strokes that lead to cognitive dysfunction. This finding suggests that reducing serum UA might decrease the occurrence of cognitive dysfunction.
"Even minimal elevations in serum UA are associated with structural and functional brain changes, specifically involving the development of ischaemic injury," noted lead author Tracy D. Vannorsdall, PhD, Department of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine, Baltimore, Maryland, United States.

In this cross-sectional, observational study, 180 adults were enrolled from the Johns Hopkins Aging, Brain Imaging, and Cognition Study. Participant ages ranged from 20 to 96. All completed neuropsychological testing to assess cognitive abilities and clinical tests including non-fasting blood samples for serumUA.

In normal, healthy adults, cerebral ischaemia is often indicated by hyper intensities in the cerebral white matter, which is detected by magnetic resonance imaging (MRI). These white matter hyper intensities (WMH) are increasingly common in "advancing age, cerebral atrophy, cerebrovascular risk factors such as hypertension and stroke, dementia, schizophrenia and cognitive dysfunction in the non-demented," the authors noted. In this study, images from brain MRI were used to calculate the "WMH burden" -- the ratio between the WMH volume and total brain volume.

Data analysis established that higher serum UA levels were associated with greater WMH burden (r =.232; P =.002); they were also associated with lower scores in 4 of the 8 areas of cognitive functioning. Greater WMH burden was associated with lower performance in 7 of the 8 areas of cognitive functioning (P values <.05). These results indicate an association between higher serum UA levels and lower cognitive performance.

The researchers add, however, that "once a term for WMH volume was added to the regression models, the UA-cognition associations were attenuated." In this latter analysis, the levels of UA were no longer predictive of cognitive dysfunction. Further analysis also determined that the previously detected association between verbal learning/memory and WMH burden no longer existed, once serum UA levels were included in the model.

The inhibitory interaction of UA with nitric oxide (which mediates vascular tone) and the decreased capacity for vasodilatation in the cortex of patients with WMH, both support impaired vascular tone as a possible mechanism for UA influence on cortical function. Both increased production and decreased excretion of UA may result in elevated serum levels. Future clinical trials could determine whether medications that reduce production of serum UA, even within normal levels, would also decrease the occurrence of cerebral ischaemia and related cognitive dysfunction [34]

Conclusion

As per the previous results, the levels of the blood antioxidants albumin, uric acid and bilirubin were reduced [35],[36], and total antioxidant capacity was low [37]. In this study, we analyzed the various disturbances of the non-dietary antioxidant systems in schizophrenics with various symptoms. . These results demonstrate altered membrane dynamics and non-dietary antioxidants in schizophrenia.. These results may suggest that the cause of these disturbances are basic biochemical anomalies of the central nervous system, observed in schizophrenia, and evoke the potential role of antioxidants in the therapeutic strategy and their implication in preventive and early intervention approaches in populations at risk for schizophrenia.

Acknowledgements

The corresponding author is grateful to The Chanceller (Dr. Paul Dhinakaran), the Vice-Chanceller (Dr.Paul P. Appasamy and the Registrar (Dr. Anne Mary Fernandez) of Karunya University, Coimbatore, India, for providing encouragement and financial support to carryout this research publication.

References

[1]. McGrath J, Saha S, Welham J, El Saadi O, MacCauley C. A systematic review of the incidence of schizophrenia: The distribution of rates and the influence of sex, urban city, migrant status and methodology. BMC Med 2004 ; 2:13

[2]. Murray CJ, Lopez AD. The global burden of disease: A comprehensive assessment of mortality and disability from diseases, injuries, and risk factors in 1990 and projected to 2020. Boston: Harvard School of Public Health1996; 990.

[3]. Bhugra, D. The global prevalence of schizophrenia. PloS. Medicine 2005; 2 (5), 372–373.

[4]. Frances R Frankenburg, Schizophrenia, emedicine Specialties Medicine 2006; 1-10.

[5]. Akyol, O, Zoroğlu, SS, Armutcu,F, Sahin,S, Gurel, A. Nitric oxide as a physiopathological factor in neuropsychiatric disorders. In Vivo 2004; 18 (3):377-90.

[6]. Swartz CM. Albumin decrement in depression and cholesterol decrement in mania .J Affect Disord 1990;19;173-6

[7]. Maes M,Wauters A, Neels H, Scharp'e S,Van Gastel A , D'Hondt P,Peeters D, Cosyns P, Desnyder R .Total serum protein and serum protein fractions in depression ;relationships to depressive symptoms and glucocorticoid activity.J Affect Disord 1995;34;64-9.

[8]. Song C, Dinan T, Leonard BE. Changes in immunoglobulins, complement and acute phase protein levels in the depressed patients and normal controls. J Affect Disord 1994; 30; 283-8.

[9]. Maes M, Delange J ,Ranjan, R,Meltzer HY, Destnyder R,Cooremans W, Scharp'e S .Acute phase proteins in schizophrenia ,mania and major depression; modulation by psychiatric drugs. Psychiatry Res 1997; 66; 1-11.

[10]. Maes M, De Vos N, Demedts P, Annick Wauters, Neels H.Lower serum zinc in major depression in relation to changes in serum acute phase proteins. J Affect Disord 1999; 56; 189-94.

[11]. Yao JK, Reddy R, Van Kammen DP. Abnormal age-related changes of plasma antioxidant proteins in schizophrenia. Psychiatry Res 2000; 97:137-51.

[12]. Gabay C, Kushner I. Acute-phase proteins and other systemic response to inflammation. N Engl J Med 1999; 340; 448-54.

[13]. Jacquelyn Beals, 2007 High Levels of Uric Acid May Cause Cerebral Strokes, Affecting Cognitive Function: Presented at ANA, Doctors Guide. Presentation title : Cerebral Ischemia Mediates the serum Uric acid &cognitionAssociation, Abstract, 25:1-2.

[14]. Markus Wyss and Rima Kaddurah-Daouk, Creatine and Creatinine Metabolism, Physiological Reviews 2000; 80 (3): 1107-1213.

[15]. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders (DSM-IV- Association; 2000)

[16]. Kageyama NA. Direct colorimetric determination of uric acid in serum and urine with uricase-catalase system. Clin Chim Acta. 1971; 31:421-26.

[17]. Doumas B T, Watson W A, Biggs H G. Albumin standards and the measurement of serum albumin with bromcresol green. Clin Chim Acta.1971; 31:87-96.

[18]. Bowers ,L.R.Kinetic serum creatinine assays I. The role of various factors in determining specificity. Clin Chem,1980; 26:551-554.

[19]. Jeffrey K Yao, Ravinder Reddy and Daniel P. Van Kammen. Abnormal age-related changes of plasma antioxidant proteins in schizophrenia.Psychiatry Research 2000; 97 (2-3); 137-51.

[20]. Stocker R, Yamamoto Y, McDonagh AF, Glazer AN, Ames BN. Bilirubin is an

antioxidant of possible physiological importance. Science 1987; 235:1043–46.
[21]. Wu TW, Fung KP, Wu J, Yang CC, Weisel RD. Antioxidation of human low density lipoprotein by unconjugated and conjugated bilirubins. Biochem Pharmacol 1996; 51:859–62.
[22]. Neuzil J, Stocker R. Free and albumin-bound bilirubin are efficient co-antioxidants for alpha-tocopherol, inhibiting plasma and low density lipoprotein lipid per oxidation. J Biol Chem 1994; 269:16712–719.
[23]. Yamaguchi T, Shioji I, Sugimoto A, Yamaoka M. Psychological stress increases bilirubin metabolites in human urine. Biochem. Biophys. Res. Commun 2002; 293, 517–520.
[24]. Tsuyoshi Miyaoka, Rei Yasukawa, Hideaki Yasuda, Maiko Shimizu, Soichi Mizuno, Tsuruhei Sukegawa, Takuji Inagaki and Jun Horiguchi. Urinary excretion of biopyrrins, oxidative metabolites of bilirubin, increases in patients with psychiatric disorders. doi:10.1016/j.euroneuro.2004.11.002.
[25]. Halliwell B. Albumin – an important extracellular antioxidant? Biochem Pharmacol 1988; 37:569–571.
[26]. Cantin A M, Paquette B, Richter M, Larivee P. Albumin-mediated regulation of cellular glutathione and nuclear factor kappa B activation. Am J Respir Crit Care Med 2000; 162:1539 - 46.
[27]. Neuzil J, Stocker R. Free and albumin-bound bilirubin are efficient co-antioxidants for alpha-tocopherol, inhibiting plasma and low density lipoprotein lipid peroxidation. J Biol Chem 1994; 269:16712–719.
[28]. Yao JK, Reddy R, van Kammen DP. Abnormal age-related changes of plasma antioxidant proteins in schizophrenia. Psychiatry Res 2000; 97(2-3):137–151. doi: 10.1016/S0165-1781(00)00230-4.
[29]. Reddy R, Keshavan M, Yao JK. Reduced plasma antioxidants in first-episode patients with schizophrenia. Schizophr Res 2003; 62(3):205–12.
[30]. Pascual C, Karzai W, Meier-Hellmann A, Oberhoffer M, Horn A, Bredle D, Reinhart K: Total plasma antioxidant capacity is not always decreased in sepsis. Crit Care Med 1998; 26:705-9.
[31]. MacKinnon KL, Molnar Z, Lowe D, Watson ID, Shearer E. Measures of total free radical activity in critically ill patients. Clin Biochem 1999; 32:263-68.
[32]. Teng RJ, Ye YZ, Parks DA, Beckman JS, Urate produced during hypoxia protects heart proteins from peroxynitrite-mediated protein nitration.
Free Rad Biol Med 2002; 33:1243-49.
[33]. Jacquelyn Beals. High Levels of Uric Acid May Cause Cerebral Strokes, Affecting Cognitive Function: Presented at ANA. Doctors Guide. Presentation title: Cerebral Ischemia Mediates the Serum Uric Acid and Cognition Association. Abstract 2007; 25; 1-2.
[34]. Yao JK, Reddy RD, van Kammen DP, McElhinny LG, Korbanic CW. Reduced level of the antioxidant proteins in schizophrenia. Biol.Psychiat 1998a; 43:123S.
[35]. Yao JK, Reddy R, van Kammen DP. Reduced level of plasma antioxidant uric acid in schizophrenia. Psychiatr. Res 1998b; 80: 29-39.
[36]. Yao JK, Reddy R, McElhiney LG, van Kammen DP. Reduced status of plasma total antioxidant capacity in schizophrenia. Schiz.Res 1998c; 32: 1-8.