STUDY OF OXIDATIVE STRESS IN OBSESSIVE COMPULSIVE DISORDER IN RESPONSE TO TREATMENT WITH FLUOXETINE

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ABSTRACT

Oxidative stress has been found to play important role in several neuropsychiatric diseases including Obsessive Compulsive Disorder. A longitudinal case control study was conducted to evaluate the oxidative stress in 30 newly diagnosed obsessive compulsive disorder patients and same number of control patients. Serum thiobarbituric acid reacting substances, plasma ascorbate were assessed to evaluate oxidative stress and Yale Brown obsessive compulsive scale for disease severity before and after treatment with Fluoxetine at the average dosage of 40 mg/day. Improvement in Yale Brown obsessive compulsive scale score by about 43% after 12 weeks treatment was associated with significantly decreased thiobarbituric acid reacting substances and increased plasma ascorbate values ($p < 0.05$). The newly diagnosed obsessive compulsive disorder patients had higher serum thiobarbituric acid reacting substances as well as a lower plasma ascorbate levels than the control population. Thus, the present study suggested a significant role of oxidative stress in obsessive compulsive disorder and showed that a successful treatment with Fluoxetine not only improves the clinical scenario but also reduces the oxidative stress that may further improve the prognosis of the disease.

KEY WORDS

Oxidative stress, Obsessive Compulsive Disorder, Thiobarbituric acid reacting substances, Ascorbate, Fluoxetine.

INTRODUCTION

Obsessive compulsive disorder (OCD) is a common psychiatric disorder marked by obsessions and/or compulsions that are egodystonic and cause significant distress to the patients and their families (1). Its prevalence is around 2 to 3 % in the general population (2, 3). The true etiology of this illness remains unclear till date, but is probably multifactorial, as suggested by several studies. Moreover, according to recent hypothesis, OCD may be the consequence of a developmental pathology affecting serotonergic and/or dopaminergic neuronal system, which have also been suggested as a contributing

factor for the aetiopathogenesis of major depressive illness (4). This hypothesis has been strengthened by the successful use of selective serotonin reuptake inhibitors (SSRI) like Fluoxetine, in the treatment of this disease.

It is reported that a disturbance in the activities of antioxidant enzymes occurs in schizophrenia due to the increased oxidative stress (5). Brain tissues have a high percentage of phospholipids that can easily be peroxidized. Arachidonic acid (AA), docosahexaenoic acid (DHA), diacylglycerol and inositol polyphosphates are generated as second messengers by the neurotransmitters such as dopamine, serotonin, glutamate, acetylcholine, substance P, and γ aminobutyric acid, all of which have been found to be implicated in the aetiopathogenesis of Schizophrenia like disorders (6). Recently, some researchers have also found markers of oxidative stress and free radical induced injury to the brain tissues in OCD patients. The free radicals in the brain are mainly produced by catecholamine metabolism, and its increased metabolism seems to be associated with increased tissue damage (7, 8). It has been reported that basal ganglia

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are particularly vulnerable to damage by free radicals due to the large concentration of catecholamine in this region (9). The comorbidity of OCD and other neurological disorders like Sydenham's chorea and Parkinson's disease raises the chance of basal ganglia involvement in this disorder (10). Today, for the treatment of OCD, Fluoxetine is widely used due to its low side effects, good therapeutic response and good compliance (11). But till date very few studies have been conducted to follow up the association of oxidative stress in response to an effective treatment of OCD. This study was undertaken to find the association of oxidative stress with the antioxidant balance in newly diagnosed OCD patients and in healthy control and the effect of Fluoxetine therapy on it.

MATERIALS AND METHODS

The present study was designed to be a longitudinal case control study. At first, 39 newly diagnosed OCD patients were selected by systematic random cluster sampling from Psychiatry OPD of Burdwan Medical College & Hospital within the period of one year (October 2006 to October 2007). The diagnosis was done using the DSM IV criteria by two psychiatrists. Clinical severity of the disease was assessed by Yale Brown Obsessive Compulsive Scale (YBOCS), which is an established scale for assessing this, along with the therapeutic response to an optimum treatment in OCD (12). Patients with an YBOCS value of 16 or more were included in this study. They all were free from any other chronic, metabolic, psychiatric illnesses, tic disorders, Tourette syndrome or any history of substance abuse at the time of presentation. Similarity in ethnicity, socioeconomic status and dietary habits were also considered as far as practicable during selection of cases. Twenty two of them were females and the rest were males. Average age was 28.1 years with a standard deviation of 4.3. The prognosis and response to the treatment with Fluoxetine was also assessed by using YBOCS. Serum Thiobarbituric Acid Reacting Substances (TBARS) was selected as marker of oxidative stress induced lipid

Table 1: Analysis of mean values of the Y-BOCS, parameters for oxidative stress and antioxidant status between the pretreatment and post treatment OCD group (n = 30)

	Pretreatment value	Post treatment value
YBOCS scale	22.5 ± 2.9*	12.66 ± 1.56*
Serum TBARS in nmol/ml	5.43 ± 0.47*	5.02 ± 0.56*
Plasma ascorbate in mg/dl	0.736 ± 0.09**	0.785 ± 0.09**

Paired sample t test for comparison of means done by SPSS software; *P < 0.001; **P = 0.008.

peroxidation. As ascorbate was found to play the role of chief antioxidant in the brain in several studies (13), plasma ascorbate was selected as the indicator for antioxidant activity. Thirty properly matched healthy persons meeting the inclusion/exclusion criteria were also assessed for serum TBARS and plasma ascorbate.

The severity of the disease, oxidative stress and antioxidant activity were assessed before starting the treatment. The treatment was done with Fluoxetine for 12 weeks. The average daily dosage was 20 mg/day at morning initially that was increased to 40 mg/day given as a single morning dose within a week. The patients were asked not to take any other type of medication during this period. After completion of the treatment schedule, five patients did not turn up and four patients did not comply with the treatment either due to side effect of the drug or due to irregular dosage intake. Thus, 30 patients, who turned up after full compliance with the treatment regimen, were assessed for the same parameters for the disease severity, oxidative stress, and antioxidant activity after 12 weeks of therapy. Results were analyzed for differences in means by paired sample t test using SPSS software. The overall study was carried out in accordance with the Helsinki declaration made in 1975 and was approved by institutional ethical committee.

Serum TBARS was measured by its reaction with thiobarbituric acid (TBA)(14). Estimation of plasma ascorbic acid : Plasma ascorbate was oxidized by Cu^{2+} to form dehydroascorbic acid, which reacted with 2, 4 dinitrophenylhydrazine to form a red bis-hydrazone, which was measured at 520nm (15).

RESULTS

Analysis of mean values of the Y-BOCS, parameters for oxidative stress and antioxidant status between the pretreatment and post treatment OCD group are shown in the Table. Significant clinical improvement in YBOCS is seen after 12 weeks treatment with Fluoxetine. Oxidative stress indicator serum TBARS, and the plasma ascorbate were also found to be significantly decreased and increased respectively, after treatment ($p < 0.05$). The mean serum TBARS and plasma ascorbate in control group was 4.1 ± 0.51 nmol/ml and 0.95 ± 0.15 mg/dl respectively. The mean serum TBARS was higher and plasma ascorbate lower in newly diagnosed OCD patients than the control population.

DISCUSSION

The present study was undertaken to analyze the association

of oxidative stress in OCD and changes in it after an effective treatment of the disease. The patients showed significant improvement after a 12 week therapy with Fluoxetine. A decrease in the mean value of YBOCS below 13 among the post treatment patients, i.e. a decrease of about 43 %, suggested a significant improvement in the disease after treatment (16). At the same time, the oxidative stress indicator i.e. serum TBARS and the antioxidant parameter i.e. plasma ascorbate, were found to be significantly decreased and increased respectively ($p < 0.05$). Our findings thus indicated that an increased lipid peroxidation was associated with an impaired antioxidant balance in the untreated OCD patients.

As the selected cases did not have any past or present history of any chronic metabolic or oxidative stress related disease other than the OCD itself, the major source of increased lipid peroxidation in them before treatment could be suggested in their brain tissues themselves. This is supported by another study in which an increase in the lipid peroxidation product TBARS was found in several neurological disorders including OCD (9). Similarly, a significant decrease in plasma ascorbate in the pretreatment group signified a compromised ascorbate in the brain tissues. Ascorbate has been found to play the role of chief antioxidant in the brain in several earlier studies (11) and its compromised level has been found to be associated with several neurological and psychiatric diseases (17,18,19). In our present study the reduced plasma ascorbate in the pretreatment group, thus, could be suggested due to an increased lipid peroxidation in brain tissues of OCD patients. These findings were strengthened by the fact that the level of plasma ascorbate became significantly improved along with a significant reduction in the level of the lipid peroxidation product (TBARS) ($p < 0.05$) in the patients after significant improvement in the disease process as evident from an improvement in the mean YBOCS value. These findings clearly suggested a reduced oxidative stress that could have resulted in the improvement of the redox balance in OCD patients after therapy with Fluoxetine. Hence, it can be proposed from these findings that an improvement in the disease status was associated with a significantly improved overall redox balance in the OCD patients after an effective treatment in the present study population. The improved redox balance might play a definite contributory role in improvement of the overall pathogenesis of the disease process itself.

In conclusion, the present study thus, clearly established a relationship between the redox balance, oxidative stress and antioxidant defense with the disease process in OCD of this population group and so, suggests that an improved

antioxidant defense may have significant role in improvement of the disease along with drug treatment in the OCD. Hence, the compromised antioxidant status in the brain tissues of OCD patients may be improved by increasing the intake of ascorbic acid in proper amount, which is relatively cheap and easily available in various foods and medicated forms. Further studies, are however needed to predict more accurately the dependence of the OCD on oxidative stress and vice versa, comprising of brain tissue material from suitably created animal models. Also, the role of the drug Fluoxetine in improving the redox balance in these patients needs to be evaluated by future studies involving other anti obsessive drugs through multicentric placebo controlled trials.

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