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Original Research Article

OXIDATIVE STRESS AND ANTIOXIDATIVE PARAMETERS IN CHRONIC FATIGUE SYNDROME

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ABSTRACT

Background: The etiology of Chronic Fatigue Syndrome (CFS) is unknown; the recent reports suggest excessive involvement of free radicals generation. Therefore, in this study we assessed the oxidative and antioxidative parameters in CFS patients and also evaluated their correlation with fatigue assessment scale (FAS). **Methods**: Oxidative stress was determined by measuring the levels of Protein carbonyls, Lipid Peroxides (LPO) in plasma and antioxidative parameters like catalase, Glutathione peroxidase (GPx) and Glutathione Reductase (GR) in blood lysate in 25 patients of CFS and 25 healthy patients without CFS. Clinical parameters of CFS were evaluated by FAS**.** **Results**: Activity of enzymes catalase, GR and GPx were significantly reduced in patients with CFS than in controls, and levels of markers of oxidative stress like LPO and protein carbonyls were significantly elevated in CFS patients than in controls. A significant positive correlation was observed between protein carbonyls and FAS among patient group. Additionally, a significant positive correlation was also found between LPO and FAS among CFS group than in control group. **Conclusion:** The result of the present study indicates that patients with CFS have high oxidative stress parameters in their blood and this increased oxidative stress may play a role in the etiopathogenesis of the CFS disease. Furthermore, our results also showed that this increase in oxidative stress parameters is more strongly amalgamated with severity of CFS.

Keywords: Chronic fatigue syndrome, Oxidative stress parameters, Antioxidative parameters.

INTRODUCTION

Chronic fatigue syndrome (CFS) is an unusual overwhelming tiredness that is not comparable to physiologic exhaustion after physical and mental effort and also that cannot be recovered even by restful sleep **(1).** It can show temporary or chronic (>6 months) dimensions **(1).** Etiology behind CFS is not yet fully evaluated but it can be regarded as heterogeneous origin (2,3). CFS could occur within psychiatric or depressive disorders **(4)**, and diseases like fibromyalgia syndrome, cancers, inflammatory bowel disease (IBD), and various other auto-immune disorders **(1,5).** Fatigue is very common in these conditions and can be experienced by up to 90% of patients. Patients with cancers often report the highest prevalence of fatigue during and after the treatment **(1,6).** CFS often presents with typical flu-like symptoms **(3).** Furthermore, this disease-related fatigue is usually more commonly seen in women than in men **(7,8).** CFS is characterized by a cluster of non-specific clinical symptoms such as cognitive dysfunction (often referred as "brain fog"), headache, painful lymph nodes, irritable bowel syndrome, disturbed sleep, sore throat, muscle and joint pain along with morning stiffness, and severe malaise **(3,9),** which serve as diagnostic criteria by Center for Disease Control and Prevention **(10).** Moreover, if fatigue is chronic, then disturbed innervations along with loss of motor neurons could cause direct impaired muscle function that is followed by severe functional limitations in the body **(1,4).** Atrophic muscle may then augment fatigue, resulting in a vicious cycle. Perceived severity in fatigue can then be assessed with the Fatigue Assessment Scale, which is a reliable questionnaire for CFS **(11,12).**

There is evidence that CFS is accompanied by disorders in the oxidative and antioxidative imbalance. An

increased production of oxidative stress parameters and decreased levels of antioxidants are key factors in pathogenesis of CFS **(13-16).** The disease severity can be explained by the increased levels of oxidative stress parameters in underlying diseases **(17).** Increased production of LPO and Protein carbonyls may cause damage to proteins by nitration and nitrosylation, as the reactive oxygen and nitrogen species attack fatty acids, proteins, and mitochondria and mitochondrial DNA (mtDNA) **(18).** CFS has been reported to be accompanied by mitochondrial damage and mitochondrial dysfunctions along with structural changes in the mitochondria **(19,20),** causing lowered activity of the mitochondrial respiratory chain **(18).** Peroxides are one type of ROS that can be found in peripheral blood and they indicate the presence of oxidative stress. Increased IgG autoantibodies serve as a footprint for lipid peroxidation and the consequent immune responses that take place in vivo. There are several inflammatory diseases associated with elevated oxidative stress parameters, but recent studies suggest a very close amalgamation between oxidative stress and pain perception **(21).** Furthermore, oxidative stress is increased in patients with Fibromyalgia syndrome and spinal cord injury as reported recently **(22, 23, 24).** There is little information about oxidative stress in FMS. Several disorders are associated with oxidative stress that is manifested by LPO, protein oxidation and other markers.The primary objective of the present study was to assess the levels of oxidative and antioxidative stress parameters among patients with CFS.

MATERIALS AND METHODS:

This study comprised of 2 groups, study group which had 25 patients with CFS (Mean age 37.14±9.72; 6 males and 19 females) and control group consisting of 25 age matched healthy subjects without CFS (Mean age 34.5±10.0), who were non-alcoholic, non-smokers, non-diabetic without any kind of cardiac, respiratory and endocrinal disease. Subjects were excluded if they met criteria for Fibromyalgia syndrome, rheumatoid arthritis and psychiatric disorders. Patients of CFS were recruited from the Department of Medicine, at the HIMS Sitapur, Uttar Pradesh. Diagnosis of CFS was made using criteria from NICE Guidelines. Healthy relatives of the patients and hospital staff served as controls.

Before enrolling in the study, written informed consent was obtained from both the groups of subjects using documents that got approved by the Institutional Ethics Committee of (HIMS Sitapur). All data were coded to remove any identifiable information. Four ml of venous blood was collected from patients of both the groups. Both the groups completed a structured questionnaire, which assessed the biographical information, medical, personal and family history. Quality of life was assessed using fatigue assessment scale (FAS). (The FAS is a 10-item scale evaluating symptoms of chronic fatigue patients its a self-reported instrument that assesses the impact of fatigue and functional impairment) **(25).**

Oxidative parameters were assessed by measuring Lipid Peroxides (LPO) levels (Ohkawa et al 1979) and Protein carbonyls group (Levine and Williams, 1994) in plasma whereas antioxidative parameters were assessed by measuring the levels of Catalase (Aebi 1974), GPx (Pagila and Valentine; 1967) and GR (Hazelton and Lang; 1995) in the RBC lysate in 25 patients and in equal number of healthy controls.

Statistical analysis: Statistical analysis was performed by using SPSS statistical software (16.0 versions). Quantitative variables were presented as the mean ± standard deviation, and compared by independent t-test. Pearson correlation was done to find the pattern of associations in the two groups. A value of $p<0.05$ was considered statistically significant and $p<0.01$ is considered highly significant.

RESULTS:

Baseline characteristics for CFS patients and control group are depicted in Table 1. Symptoms of muscle twitching, lack of energy, morning tiredness, night time tiredness, disturbed sleep, morning stiffness, morning fatigue, headache, disequilibrium in climbing stair and anxiety were more commonly seen in patient group than in the control group. No significant difference was found in weight loss, jaw pain, abdomen pain and fever (data not shown).

The fatigue assessment scale score (FAS) was significantly greater in CFS cases tan controls (48.5±4.8 Vs 14.3±4.2; $p<0.05$). All the patients had normal laboratory tests for erythrocyte sedimentation rate (ESR), and Alanine Aminotransferase (ALT) (Table 1).

Oxidative and antioxidative parameters: A signify-cantly increased level of LPO ($p<0.05$), and protein carbonyls ($p<0.05$), (Table 2) whereas a significantly decreased levels of catalase ($p<0.05$), GR ($p<0.05$) and GPx ($p<0.05$) (Table 3) were found among patients' group than in control group. A positive correlation was found between LPO and clinical symptoms of FAS among patients' group ($p<0.05$). Furthermore, a significant

positive correlation was also found between Protein carbonyls group and clinical symptoms of FAS among patients' group than in control group.

DISCUSSION:

The important finding of this study is that patients with CFS have significantly elevated levels of oxidative stress markers compared to control group. This directly indicates elevated levels of ROS and oxidative stress in patients with CFS. The results corroborate earlier findings that CFS is generally accompanied by induction of O&NS pathways.

The data in this study also extend to previous studies that show that CFS is accompanied by a reduced activity of antioxidants. Decreased antioxidant capacity may impair the defenses against ROS and RNS and O&NS **(26).** Recently, it has been reported that CFS is often accompanied by reduced levels of catalase, coenzyme-Q10, and glutathione peroxidase, all of which are strong antioxidants **(27-29).** This reduced antioxidant activity leads to increased oxidative damage to lipids, proteins and DNA. Additionally, there is a lowered anti-inflammatory and increased proinflammatory activity in the body, due to reduced production of NFκB, COX-2 and proinflammatory cytokines **(27-29).**

The results of this present study are also in agreement with decreased antioxidants and increased oxidative stress parameters. Our findings are also in concurrence with report of Maes et al.2012 **(30)** who reported significantly increased protein carbonyls and decreased plasma glutathione in CFS patients when compared with controls. Furthermore, study reported by Maes et al, 2011 **(31)** showed that oxidative stress levels were higher and superoxide dismutase levels were lower in with CFS, and an imbalance existed in oxidant and antioxidant levels in CFS patients.

The probable cause of the imbalance between oxidant and antioxidant levels in CFS is still unknown. Furthermore, large numbers of studies have reported increased levels of oxidative stress markers, such as LPO levels and many others in CFS patients, suggesting that this disturbed level of oxidative and antioxidative imbalance may have a role in the pathophysiology of the disease **(29,30,31).**

Additionally, in this study we have also tried to show the relationship in between oxidative stress and CFS. However, efforts to explain the pathogenesis of CFS and other chronic fatigue conditions by oxidative stress mechanisms are not new. Kennedy et al reported increased oxidative stress markers that are also found associated with clinical symptoms in CFS, this study was in concordance with our study report **(32).** Logan et al reported the role of oxidative stress markers in CFS, that may be important for future research, as it clearly suggests the use of antioxidants in the management of CFS. Specifically, the dietary supplements glutathione, N-acetylcysteine, alpha-lipoic acid, oligomeric proanthocyanidins, Ginkgo biloba, and Vaccinium myrtillus (bilberry) and zinch along with CoQ10 may be beneficial **(33).** Free radicals and other types of damaging reactive oxygen species (ROS) are produced in oxidative metabolic and physiological processes; their activity is also thought to increase in patients with CFS. Although the etiology of CFS is unknown, symptoms (especially fatigue and all-day tiredness) may be associated with an imbalance between oxidative and antioxidant status.

As it is clearly known that increased LPO results in oxidative stress, which indirectly reflects intracellular ROS generation. ROS have been implicated in many symptoms in CFS including fatigue, one of the most prominent symptoms in CFS, by inducing peripheral and central hyperalgesia **(34).** Therefore, for this reason we thought that oxidative stress might affect the disease symptoms. In the present study we have found a significant positive correlation between LPO and clinical symptoms of CFS among patients' group.

Furthermore, in the present study, a significant positive correlation was also found between protein carbonyls group and symptoms of CFS among patients' group than in control group. These correlations match with the study findings of Kennedy et al, **(32)** who have also reported significant correlation between oxidative stress and symptoms of CFS patients.

CONCLUSION:

In conclusion, this study reports an oxidant and antioxidant imbalance in CFS. The elevated oxidant levels and reduced antioxidant levels showed that CFS may be related to free radical-mediated disorders. This elevated oxidative stress may have a role in the etiopathogenesis of CFS.

Conflicts of Interest: None declared

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Table 1: Clinical and biochemical characteristic among patient and control group:

Variables	*Patients n=25*	*Control n=25*	*p-value*
	Mean ±SD	*Mean ±SD*	
Age (years)	36.14±9.72	34.5±6.30	N.S
FAS	44.5±5.8	17.3±4.2	<0.05
ESR	27.2±9.7	24.9±8.2	N.S
ALT	39.8±14.1	37.6±14.4	N.S

Study Group = CFS patients, Control Group = Healthy subjects, p<0.05 is considered significant and N.S is considered not significant.

Table 2: Oxidative parameters among patient and control group

Oxidative stress parameters	*patients n=25 Mean ±SD*	*Control n=25 Mean ±SD*	*p-value*
Lipid Peroxides (LPO)	323.3±99.5	101.2±78.3	<0.05
Protein carbonyl	171.9±65.4	91.3±30.2	<0.05

Table 3: Antioxidative parameters among study and control group

Antioxidative parameters	*patients n=25 Mean ±SD*	*Control n=25 Mean ±SD*	*p-value*
Catalase	33.0±11.1	67.3±19.6	<0.05
Glutathione peroxidase (GPx)	38.9±10.7	76.9±15.1	<0.05
Glutathione Reductase (GR)	23.9±14.2	58.1±9.2	<0.05

Table 4: Pearson correlation analysis in between Oxidative parameters, Antioxidative parameters and FAS

Parameters	Groups	FAS
		r
Lipid Peroxides (LPO)	CFS patients	-.319*
	Controls	-.051
Protein Carbonyl	CFS patients	-.190*
	Controls	.161
Catalase	CFS patients	-0.081
	Controls	.104
Glutathione peroxidase (GPx)	CFS patients	-0.118
	Controls	-.123
Glutathione Reductase (GR)	CFS patients	0.048
	Controls	-.112

r=Simple regression, *p<0.05 (significant)

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