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A study of oxidative stress biomarkers in obsessive compulsive disorder

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ABSTRACT

Background: Existing literature supports the potential role of oxidative stress in pathogenesis of psychiatric disorders like schizophrenia, depression, anxiety disorders, substance use disorders and neurodevelopmental disorders. Role of oxidative stress has also been implicated in obsessive compulsive disorder (OCD).

Method: Our study was conducted in a tertiary care teaching hospital of North India. This cross-sectional observational study aimed at evaluating the markers of oxidative stress (Superoxide dismutase, Glutathione Peroxidase, Catalase, Malondialdehyde, serum cortisol) in three groups - patients with OCD, their non-affected first degree relatives, and healthy controls. Markers of oxidative stress were estimated in all 30 participants in each group.

Results: Significantly higher levels of malondialdehyde and lower levels of plasma catalase, superoxide dismutase & glutathione peroxidase were found in patients, compared to their first degree relatives and healthy controls. Levels of plasma catalase, superoxide dismutase & glutathione peroxidase in first degree relatives were also significantly lower than healthy controls.

Conclusion: Higher levels of oxidative stress markers are associated with OCD and their first-degree relatives. The correlational nature of the present study, and the lack of a psychiatric control group, however, do not allow for conclusions regarding causation or the findings' specificity to OCD.

1. Introduction

Oxidative stress results from a disequilibrium between pro- and anti-oxidant homeostatic mechanisms. The resultant free radicals and reactive oxygen species, which can be produced both from physiological (ageing) and pathological (stress, psychiatric illnesses, infections, inflammations, pharmacological treatment)processes, are potentially neuro-toxic (Sies, 1991). The nervous system is vulnerable to free-radical-induced damage due to its high oxygen demand (Pellmar, Neel, & Lee, 1989), low catalase activity (Paul, Fulton, & Heppner, 1989), excessive amounts of iron and polyunsaturated fatty acids, and only moderate amounts of superoxide dismutase and glutathione peroxidase (Mariani, Polidori, Cherubini, & Mecocci, 2005). These factors result in the production of large amounts of free radicals that can damage cellular structures.

Oxidative stress in a system is measured as an estimate of the free radicals present. However, because free radicals have a relatively short half-life determination of their levels is cumbersome. Instead, they can be indirectly estimated by measuring levels of antioxidant enzymes such as catalase, superoxide dismutase, glutathione and malondialdehyde, or by levels of transition elements such as copper, zinc, iron (Leff et al., 1994)and vitamins such as vitamin A,C, E (non-enzymatic antioxidant structures) (Ersan, Bakir, Erdal Ersan, & Dogan, 2006). Oxidative stress has been studied as a plausible pathophysiological process in the development of psychiatric disorders such as schizophrenia (Flatow, Buckley, & Miller, 2013),depression (Palta, Samuel, Miller, & Szanton, 2014), bipolar disorder (Brown, Andreazza, & Young), generalised Anxiety Disorder (Bulut et al., 2013) and social anxiety disorder (Krolow, Arcego, Noschang, Weis, & Dalmaz, 2014). The present study explores the role of oxidative stress in obsessive compulsive disorder (OCD).

OCD, with a lifetime prevalence of 0.5–2% (Gururaj et al., 2016), typically onsets in the early 20 s (Organization, 2001), and is among the top ten causes of disability from mental illnesses (Organization, 2001). Some inroads have been made into the etio-pathogenesis of OCD including the role of monoamine neurotransmitters like serotonin and norepinephrine in OCD (Abramowitz, Taylor, and McKay, 2009; Greist, Jefferson, Kobak, Katzelnick, and Serlin, 1995; Greenberg et al., 1998)

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and the role of genetic factors (Pauls, Alsobrook, Goodman, Rasmussen, & Leckman, 1995; van Grootheest, Cath, Beekman, & Boomsma, 2005). Heritability of obsessive compulsive symptoms seemingly differs between childhood-onset (45–65%)and adult-onset (27–47%) cases (van Grootheest et al., 2005); moreover, first degree relatives (FDRs) have a four fold higher risk of developing OCD compared to healthy controls (Pauls, 2008). Role of immune mechanisms has been studied in OCD. Group A $Beta_3$ streptococcal infection has been associated with obsessive-compulsive symptoms (Arnold & Richter, 2001) that are possibly triggered by cross-reactivity between anti-streptococcal antibodies and basal ganglia proteins (Swedo et al., 2010). Recent data also suggest a role of oxidative stress in the etio-pathology of OCD (A. Behl, G. Swami, S.S. Sircar, M.S. Bhatia & B.D. Banerjee, 2010; Kuloglu, Atmaca, Tezcan, Gecici, 2002; Madhura, 2015) in both adults and children (Aebi, Wyss, Scherz, & Skvaril, 1974; Goldberg & Williams, 1998).

The current study aimed to study markers of oxidative stress– superoxide dismutase, glutathione peroxidase, catalase, malondialdehyde, serum cortisol – in drug-naïve patients of OCD, their FDRs and healthy controls (HCs). A secondary aim was to study associations between levels of oxidative stress markers and clinical variables such as symptom severity.

2. Method

2.1. Study design

This was an observational, analytical study conducted over a period of one year (July 2015 to July 2016), in the Psychiatry department of King George's Medical University, U.P., a tertiary care teaching hospital in North India.

2.2. Study sample

Participant recruitment was by purposive sampling. On specified days of the week, first two newly registered patients with OCD, in the adult psychiatry outpatient services were screened. Those fulfilling the following inclusion criteria were invited to participate in the study – a) *International Classification of mental and behavioural Disorders 10th edition (ICD-10 DCR)* criteria for OCD; b)Drug-naïve or drug-free for at least 3 months; c) Aged between 18 and 45 years; and d) First-degree relative (FDR)available for participation in the study. Comorbid psychiatric illnesses (except tobacco use disorders) were exclusion criteria. For each patient recruited into the study, a healthy FDR, and an HC (from among non-blood relatives of other patients attending adult outpatient psychiatry services) were also recruited. Inclusion criteria for FDRs and HCs were – a) Age between 18 and 45 years; b) Score < 3 on the General health questionnaire (GHQ); and c) No past or current psychiatric/chronic medical illness (except tobacco use disorder). Exclusion criteria for all three groups were – a) If they were taking any prescription anti-oxidants; b) Recent history of febrile illness; and c) Women who were currently pregnant or lactating. Written informed consent was obtained from all the participants.

2.3. Tools

Data was collected for socio-demographic information and clinical details – duration of illness, age at onset, family history – on a structured format. *Mini International Neuropsychiatry Interview version 6.0.0 (MINI) (*Sheehan et al., 1998*)* was used to screen for psychiatric illnesses in the patients (comorbidities) and FDRs and HCs. An ICD-10 DCR diagnosis of OCD was confirmed in the patients. The *Yale Brown Obsessive Compulsive Scale(Y-BOCS)* (Goodman et al., 1989) was used to assess the symptom severity of OCD. Y-BOCS is a clinician-rated, 10-item scale (five items for obsessions and five for compulsions), each item rated from 0 (no symptoms) to 4 (extreme symptoms),with a total score ranging 0–40. This scale has been widely used and has well-replicated thresholds for remission, relapse, and recovery (Farris, McLean, Van Meter, Simpson, & Foa, 2013). The 12-item *General Health Questionnaire (GHQ-12)* was used to screen for general (non-psychotic) psychiatric morbidity in the FDRs and HCs (Goldberg & Williams, 1998).

3. Procedure

Assessments on all participants were carried out at a mutually convenient time. For assessment of oxidative stress markers, the following protocol was followed: after overnight fasting, blood samples were drawn for estimation of liver function, fasting blood sugar and blood cholesterol levels. Those patients with high cholesterol or deranged liver function/blood sugar were dropped from the study. If the above parameters were within normal limit, levels of superoxide dismutase, glutathione peroxidase, catalase, malondialdehyde, and serum cortisol were estimated. Assessment of fasting blood sugar and liver function test were done in the biochemical laboratory of the department of Psychiatry, King George's Medical University. Assessment of blood cholesterol, serum cortisol, superoxide dismutase, glutathione peroxidase, catalase, malondialdehyde were done in the department of Biochemistry, King George's Medical University.

3.1. Oxidative stress markers estimation: Lysate prepared from the plasma acted as the enzyme source

3.1.1. Catalase estimation

2.0 ml of phosphate buffer and 1 ml. of diluted (0.2 M) hydrogen peroxide were taken in a cuvette; to this 0.02 ml lysate was added and mixed thoroughly. The decrease in absorbance at 240 nm was recorded on a spectrophotometer after every 30 s for 3 min against a blank reagent. The results were expressed as unit/mg protein (AEBI et al., 1974).

3.1.2. Superoxide dismutase estimation

Nicotinamide adenine dinucleotide in the presence of phenazine metho-sulfate generates the superoxide radical. This free radical reduces nitro-blue-tetrazolium to a formazan with a dark blue color. When the lysate (superoxide dismutase source) is added to the above reaction mixture, it precipitates another reaction to neutralize the free radical. The reduction of NBT is thus slowed down and this gives a measure of superoxide dismutase activity in the lysate. The results are expressed as U/mg protein (McCord & Fridovich, 1969).

3.1.3. Glutathione peroxidase estimation

During conversion of hydroperoxide radical into non-reactive hydroperoxides, glutathione peroxidase utilizes reduced glutathione as a cofactor. The amount of glutathione utilized, i.e. converted to oxidized glutathione, is a measure of the enzyme activity. The results are expressed as unit/min/mg protein (Paglia & Valentine, 1967).

3.1.4. Malondialdehyde estimation

Lipid peroxide content in the plasma was measured as thiobarbituric acid reactive substance. Acetic acid detaches lipids and proteins from tissues. Protein in the reaction mixture is dissolved by the addition of sodium dodecyl sulfate. Thiobarbituric acid reacts with lipid peroxides, lipid hydroperoxides and unsaturated fatty acids, generating a color adduct with an absorption maxima at 532 nm. The results are expressed as unit/mg protein (Ohkawa, Ohishi, & Yagi, 1979).

3.1.5. Cortisol estimation

Cortisol level in the serum was estimated by COBAS® Elecsys 2010 cortisol assay kit as per the manufacturer's protocol. The results are expressed as nmol/L.