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DNA damage and antioxidants in treatment naïve children with obsessive–compulsive disorder

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ABSTRACT

The current study aimed to investigate whether serum antioxidant levels and DNA damage differ between the children and adolescents with Obsessive Compulsive Disorder (OCD) and healthy controls. The study included 31 children (Male/Female, 22/9; age range 7–17 years), with treatment naïve OCD diagnosed according to Diagnostic and Statistical Manual of Mental Disorders-V (DSM-V) and 28 age- and gender-matched healthy control subjects. Children's Yale Brown Obsession Compulsion Scale (CY-BOC) was applied to the children. Glutathione peroxidase (GPx), superoxide dismutase (SOD), coenzyme Q (CoQ), and 8-Hydroxy-2-Deoxyguanosine (8-OHdG) were all measured by the enzyme-linked immunosorbent assay method. GPx, CoQ and 8-OHdG levels were found to be significantly higher in the OCD group, compared to the control group ($p=0.010$, $p=0.034$, $p=0.010$, respectively); however, no significant difference was found in the SOD levels between two groups ($p=0.10$). There were no correlations between the CY-BOC scores, depression scores, duration of the disease and biochemical parameters ($p > 0.05$, for all). Children with OCD were found to have higher antioxidant levels and oxidative DNA damage. The findings of this study support the role of oxidative stress in the pathogenesis of OCD. In this regard, any possible effect of adding antioxidants to conventional treatment can be investigated.

1. Introduction

Obsessive–Compulsive Disorder (OCD) is a neuropsychiatric disease characterized by repeating and undesirable urges and images, as well as the ritualistic behaviors performed to avoid them (American Psychiatric Association, 2000). In approximately 80% of the cases, symptoms of OCD start in childhood and adolescence (Pauls et al., 1995). The prevalence of OCD has been reported as 1–3% in children (Heyman et al., 2001). OCD has etiologies that are largely multi-factorial, involving complex interactions between genetic and environmental factors (Pauls, 2010). Environmental factors such as stress and traumatic life events occur in 50% of the cases with OCD (Gothelf et al., 2004; Samuels, 2009).

Free radicals are necessary for the maintenance of physiological conditions, although the excessive production of free radicals can be harmful to body (Krolow et al., 2014). Oxidative stress implies an imbalance between reactive oxygen species (ROS) and antioxidant defense mechanisms. Brain tissue is vulnerable to oxidative stress due to its higher demand for oxygen (Bouayed et al., 2009; Halliwell, 2006; Ng et al., 2008). Oxidative stress also impairs normal brain functions through the inhibition of neurogenesis, altering neuronal transmission, and inducing mitochondrial dysfunction (Hovatta et al., 2010).

The antioxidant defense system involves enzymatic and non-enzymatic components. Superoxide dismutase (SOD) and glutathione peroxidase (GPx) are anti-oxidant enzymes (Valko et al., 2007). Coenzyme Q (CoQ) is a non-enzymatic antioxidant (Massaad and Klann, 2011). CoQ is a lipid-soluble vitamin-like substance and is an important cofactor in mitochondrial electron transport from complex I to complex III (Ernster and Dallner, 1995). It is found in high concentrations in the brain and heart (Beal, 2002). 8-Hydroxy-2-Deoxyguanosine (8-OHdG) is a biochemical marker of ROS-mediated DNA damage (Berk, 2009).

In studies conducted on adults with OCD over the past decade, it has been reported that oxidative stress may play a role in the pathogenesis of the disease (Ersan et al., 2006; Kuloglu et al., 2002; Selek et al., 2008). Basal ganglia, which contain high levels of catecholamine, are assumed to play a role in the etiopathology of OCD. In addition, it has been shown that basal ganglia were more sensitive to oxidative damage (Ersan et al., 2006). The catecholamine metabolism is the major source of free radicals in the brain, and increased catecholamines are associated with increase

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in free radical-related damage (Chakraborty et al., 2009). A previous study on 28 untreated children with OCD revealed high total oxidant status (TOS) and low total antioxidant status (TAS) in them (Kandemir et al., 2013).

Most of the oxidative stress analyses have been performed on adult with OCD. To the best of our knowledge, oxidative DNA damage has not been evaluated in child and adolescent treatment naïve OCD patients. In this study, we hypothesized that increased oxidative stress can occur in OCD and disease severity may be correlated with parameters of oxidative stress in children and adolescents with OCD. Therefore, the current study aimed to investigate whether serum SOD, GPx, CoQ and 8-OHdG levels differ between the children and adolescents with OCD and healthy controls. The current study also aimed to investigate whether there is an association between SOD, GPx, CoQ and 8-OHdG levels and severity of OCD.

2. Methods

2.1. Study sample

The study was conducted in the Department of Child Psychiatry at Dicle University Training and Research Hospital. The study data were collected between January 2014 and January 2015. A total of 47 OCD cases admitted and 42 cases agreed to participate in the study. Because, 11 cases were excluded based on the exclusion criteria (see below), finally 31 children (aged between 7 and 17 years; M/F: 22/9), with treatment naïve OCD were included. The diagnosis of OCD was done according to Diagnostic and Statistical Manual of Mental Disorders-V (DSM-V). Children who had mental retardation, history of head trauma, receiving oral contraceptives, psychotropic drugs, previous or current glucocorticoid therapy and vitamins; and those with body mass index ≥ 30, chronic systemic disorders, and clinically active infection were excluded in order to prevent interference with biochemical parameters. Simple tic disorder patients were included. Simple motor tic disorder was present in 16.1% ($n=5$) of the patients with OCD. Other psychiatric disorders were excluded from the study. The control group consisted of age- and gender-matched healthy children, who applied to hospital for routine check-up. Control subjects were residing at similar places with the patient group and did not have a disease or history of medical problems which potentially influential on oxidant–antioxidant status. Two experienced child psychiatrist evaluated the patients. Inter-rater agreement was 0.80. The study was reviewed and approved by the Non-Interventional Clinical Research Ethics Committee at Dicle University, issue date 13.02.2012, number 396. The parents of the participants provided written volunteer informed consent.

2.2. Study procedures

Psychiatrists recorded sociodemographic features and clinical data of the participants. This was followed by a structured psychiatric interviews (K-SADS-PL and Y-BOCS), administration of the self-reported Children's Depression Inventory (CDI). Height and weight were measured. Body mass index was calculated. Finally, a 2 ml of venous blood sample was obtained for biochemical tests.

2.3. Forms and scales

2.3.1. Sociodemographic data and clinical data form

This form included questions about age, gender, height, weight, educational status, parental educational status and occupations, parental consanguinity, number of siblings, history of psychiatric disorders, and tic disorder symptoms.

2.3.2. Kiddie schedule for affective disorders and schizophrenia, present and lifetime version (K-SADS-PL)

The schedule was originally developed by Kaufman et al. (1997) (K-SADS-PL)and was adapted to Turkish by Gökler et al. (2004). K-SADS-PL is administered during an interview with the parents and children, and the final evaluation is performed using input from all data sources. This scale evaluates the presence of common psychopathologies, including OCD, in children and adolescents.

2.3.3. Children's yale brown obsession compulsion scale (CY-BOC)

CY-BOC is a semi-structured tool to measure the severity of OCD signs within the past week (CY-BOC; Scahill et al., 1997). There are five major sections: instructions, obsession screening list, items to determine the severity of obsessions; compulsion screening list, and items to determine the severity of compulsions. Information is gathered from the child and his/her parents. The validity and reliability of the Turkish version of this scale was carried out by Yucelen et al. (2006).

2.3.4. The children's depression inventory (CDI)

The Children's Depression Inventory developed by Kovasc based on the Beck Depression scale was used in this study (CDI; Kovacs, 1985). However, questions specific to the childhood period such as school success and relationship with friends were added. The scale contains 27 items and was adapted to Turkish language by Oy (1991): Each item is scored as “0”, “1”, or “2” points depending on the severity of the symptom. The highest score is 54 points. High scores indicate the level or severity of depression. The cutoff point for the scale is 19 points.

2.4. Biochemical analysis

Blood samples were obtained in the morning between 10.00 h and 12.00 h. The samples were collected in gel tubes with EDTA. Blood samples were stored at $+4$ °C until centrifugation. Then, blood samples were centrifuged at 5000 rpm for six minutes. The sera were transferred to 1.5 ml polypropylene tubes and stored at $-80°$ centigrade until analysis. Different kits were used for measurement of SOD, GPx, CoQ and 8-OHdG. The measurements were performed in the same day. Serum levels of SOD, GPx, CoQ and 8-OHdG were determined with an enzyme linked immunosorbent assay (ELISA) method (Hangzhou Eastbiopharm CO. LTD China), according to the manufacturer's instructions. Briefly, samples were added to monoclonal antibody Enzyme well, which is pre-coated with SOD monoclonal antibody, incubated; then, SOD antibodies labeled with biotin were added, and combined with Streptavidin-HRP to form immune complex; after that incubation and washing were carried out again to remove the uncombined enzyme. Then Chromogen Solution A, B were added, so the color of the liquid changed into the blue, and at the effect of acid, the color was finally become yellow. The absorbance was measured at 450 nm

2.5. Statistical analysis

The statistical analysis was performed using SPSS 18.0 software package. The Chi-square test was used to evaluate the presence of a difference between the groups in terms of gender, parental consanguinity and history of psychiatric disorders. The student's *t*-test was used to compare normally distributed numerical variables between independent groups, and the Mann–Whitney *U* test was used to compare not-normally distributed variables. The effect of age was adjusted using a two-way ANOVA and ANCOVA tests. The Pearson's correlation analysis was used to evaluate correlation coefficients and statistically significance for normally distributed variables, and the Spearman's correlation analysis was used to evaluate not normally distributed variables. A p value below 0.05