



Evaluation of total oxidative status in adult attention deficit hyperactivity disorder and its diagnostic implications

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ABSTRACT

Adult Attention Deficit Hyperactivity Disorder (A-ADHD) is one of the psychiatric disorders which awareness is growing. The exact causes of A-ADHD are still unknown. In addition to neurochemical and neuroanatomic disorders, genetic and environmental factors are discussed in its etiology. In our study, we aimed to evaluate the oxidative status of A-ADHD patients and investigate whether oxidative metabolites can be used as diagnostic tools or not in A-ADHD. Blood samples were taken from enrolled 50 A-ADHD patients and 31 controls in appropriate way and Total Antioxidative Status (TAS), Total Oxidative Status (TOS), and Oxidative Stress Index (OSI) were studied in Harran University Biochemistry Labs. Results were compared between groups and ROC curve was drawn in order to evaluate diagnostic performances. Patients' TAS, TOS and OSI were significantly higher than controls. There was not a significant difference between comorbid cases and only A-ADHD patients in terms of measured values. A-ADHD can be predicted for TOS over 9.8575 $\mu\text{mol H}_2\text{O}_2$ Eqv./L level with 86% positive predictive value and %100 negative predictive value. In A-ADHD, oxidative balance is impaired. High antioxidant levels may be compensatory against the oxidant increase. Oxidative parameters may be used in A-ADHD diagnosis.

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1. Introduction

35 years ago, preliminary studies of Adult Attention Deficit Hyperactivity Disorder (A-ADHD) were written (Wood et al., 1976). The phenomenon was well described in children but only recent studies have shown its impact across life span (Wilens et al., 2002). Debates whether it exists or not, may be justified because nomenclature of the disorder has several flaws. The diagnostic criteria were made according to the childhood and focusing rather than “attention deficit” is the major problem (Doyle, 2006). However, several improvements have been made for the description of A-ADHD (Gunay et al., 2006; Wender, 1995). It is clear that not all but some of the adults develop adaptive behaviors against symptoms and the course of the disease changes but its effect on functionality still persists (Faraone et al., 2000; Wilens and Dodson, 2004). Why some people recover after childhood and others not is another issue to be studied.

Numerous researches have been conducted regarding neurobiology of pediatric ADHD but A-ADHD studies are relatively few. Several neurochemical and genetic mechanisms are believed to be involved in A-ADHD although the etiology remains unclear (Bulut et al., 2007; Faraone, 2004).

While aerobic life depends on oxygen, sometimes it may be hazardous for living beings which is known as “oxygen paradox” (Davies, 1995). During oxygen involved oxidation–reduction reactions for life energy, several “harmful wastes” called oxidants are produced. Oxidants are removed from the body by antioxidant defense mechanisms. The imbalance of oxidative metabolism is called oxidative stress (Valko et al., 2006). The association between oxidative stress and psychiatric disorders such as schizophrenia, bipolar disorder, depression and anxiety disorders were well studied before (Andreazza et al., 2008; Herken et al., 2007; Selek et al., 2008a,b).

Few studies focused on oxidative stress of either pediatric or adult ADHD (Bulut et al., 2007; Ceylan et al., 2010). We have previously reported that oxidant nitric oxide levels were high and antioxidant superoxide dismutase levels were low in A-ADHD (Selek et al., 2008c). However, a total status of oxidative

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metabolism has not been evaluated, yet. Plasma concentrations of antioxidants can already be measured separately in the laboratory, but these measurements are time-consuming, labor-intensive and costly. The number of different antioxidants in plasma, serum, urine, or other biological samples makes it difficult to measure each antioxidant separately. Since antioxidative effects of antioxidant components of plasma are additive, the measurement of total antioxidative status (TAS) and total oxidative status (TOS) can only reflect the antioxidative status of plasma whose measurement methods were developed by Harran Biochemistry Labs (Erel, 2004, 2005). On the other hand, there may be shifts in TAS and TOS. Thus, Erel also hypothesized that current oxidative status can be stated with oxidative stress index (OSI) which can be figured out by TAS/TOS (Erel, 2005). The general relation between those parameters can be seen in Fig. 1. Therefore, for exploring a specific relationship between oxidative metabolism and suggested diseases, Erel's parameters are useful.

In this study we aim to explore the total oxidative and anti-oxidative status of A-ADHD and investigate whether oxidative metabolites can be used as diagnostic tools or not in A-ADHD.

2. Methods

2.1. Patients and controls

54 A-ADHD patients between 18 and 45 years of age, diagnosed according to Turgay's Turkish version of Adult ADD/ADHD DSM IV – Based Diagnostic Screening and Rating Scale by two psychiatrists (H.A.S. and S.S.) in the Psychiatry Department of Gaziantep University Hospital were involved. Since the patients were initially diagnosed as A-ADHD, they were free from stimulant and A-ADHD medication. The scale is DSM IV based and it was developed by Turgay for diagnosis and severity evaluation (Gunay et al., 2006). Exclusion criteria were as follows: tardive dyskinesia related to neuroleptics, presence of severe organic condition, use of any antioxidant agent (i.e. vitamins E and C), presence of epilepsy and severe neurologic disorder which were previously found to be associated with oxidative status, presence of infectious disease, excessive obesity and insufficient sampling. Those patients with psychiatric comorbidity were applied Clinical Global Impression–Severity Scale and participants with below score of 2 (“borderline mentally ill”) were accepted for the study (Guy, 1976). 4 patients were excluded due to insufficient sampling.

The control group is formed of 37 healthy subjects who were chosen among the doctors and hospital staff. These were free of any medication for at least 6 weeks prior to blood sampling. None of the control subjects were alcohol drinker, heavy smoker, or had ever taken psychotropic drugs. They had no history or family history of psychiatric disorder.

In order to match sex and age, 6 of the female controls were removed randomly by a random number generator. All subjects gave their written informed consent which had been approved by the local ethics committee in accordance with the Declaration of Helsinki.

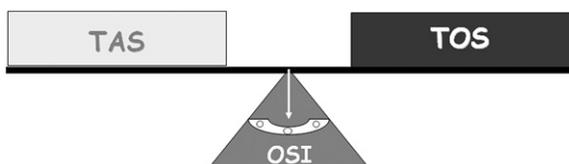


Fig. 1. The relation between oxidative stress markers; total oxidative status (TOS), total antioxidative status (TAS) and oxidative stress index (OSI).

2.2. Sampling

Venous blood samples from left forearm vein were collected into 5 ml vacutainer tubes at 7–8 a.m. after overnight fasting once. The blood samples were centrifuged at 2000 rpm for 10 min to obtain sera. Samples were stored frozen at -40°C before analysis. The biochemical analyses were made after all the blood samples were collected.

2.3. Measurement of the total oxidative status of plasma (TOS)

The total oxidative status of the plasma was measured using a novel automated colorimetric measurement method for TOS (Erel, 2005). In this method Oxidants present in the sample oxidize the ferrous ion–o-dianisidine complex to ferric ion. The oxidation reaction is enhanced by glycerol molecules, which are abundantly present in the reaction medium. The ferric ion makes a colored complex with xylene orange in an acidic medium. The color intensity, which can be measured spectrophotometrically, is related to the total amount of oxidant molecules present in the sample. The assay is calibrated with hydrogen peroxide and the results are expressed in terms of micromolar hydrogen peroxide equivalent per liter ($\mu\text{mol H}_2\text{O}_2 \text{ Eqv./L}$).

2.4. Measurement of the total antioxidative status of plasma (TAS)

The total antioxidative status of the plasma was measured using a novel automated colorimetric measurement method for TAS (Erel, 2005). In this method the hydroxyl radical, the most potent biological radical, is produced by the Fenton reaction, and reacts with the colorless substrate o-dianisidine to produce the dianisyl radical, which is bright yellowish-brown in color. Upon the addition of a plasma sample, the oxidative reactions initiated by the hydroxyl radicals present in the reaction mix are suppressed by the antioxidant components of the plasma, preventing the color change and thereby providing an effective measure of the total antioxidative status of the plasma. The assay results are expressed as mmol Trolox Eqv./L, and the precision of this assay is excellent (Cao and Prior, 1998).

2.5. Determination of oxidative stress index (OSI)

The ratio of TOS to TAS was accepted as the oxidative stress index (OSI). For calculation, the resulting unit of TAS was changed to mmol/L, and the OSI value was calculated according to the following formula: $\text{OSI (arbitrary unit)} = \text{TOS} (\mu\text{mol H}_2\text{O}_2 \text{ Eqv./L}) / \text{TAS} (\text{mmol Trolox Eqv./L})$ (Harma et al., 2006).

For a detailed understanding of measurements, readers should go over Erel's articles (Erel, 2004, 2005).

2.6. Apparatus

A Cecil 3000 spectrophotometer with a temperature controlled cuvette holder (Cecil) and an Aeroset automated analyzer (Abbott) were used (Erel, 2004). The relationship between parameters is shown in Fig. 1.

2.7. Statistical analysis

SPSS[®] for Windows 13.0 statistical program was used for statistics. Graphs were drawn by Statistica 7.0. Parametric statistical analysis was used if the conditions were satisfied. The significance of differences between groups was estimated by *T* test. Chi-square test was used when comparing proportions. Multiple comparisons were made by ANOVA. Differences were accepted as significant when $p < 0.05$. Bivariate comparisons were examined via Pearson

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