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Assessment of oxidative stress in adolescents with acne vulgaris and anxiety disorders.

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Abstract

Objectives: Anxiety disorders (AD) are common comorbid conditions with acne vulgaris (AV). Oxidative mechanisms play roles in the pathogenesis of both AV and AD. We aimed to evaluate the oxidative-antioxidative status in patients diagnosed with AD and AV.

Methods: A total of 126 adolescents (11-17 years old) diagnosed with AV were recruited. Individuals (n=95) who met the inclusion criteria were assessed by the Schedule for Affective Disorders and Schizophrenia for School Age Children (K-SADS) and Global Acne Severity Scale. The subjects were divided into a study group (AV plus AD, n=35) and an acne control group (AV only, n=37), and compared with a healthy control group (n=35). From venous blood, total antioxidant score (TAS), total oxidant score (TOS) and oxidative stress index (OSI) were calculated.

Results: The average age of the subjects (n=95; 53.6% female) was 14.8 ± 1.6 years. Comorbid AD was observed in 36.8% of the subjects. The study and acne control groups were similar in age, gender, acne duration and severity. The TOS and OSI were the highest and the TAS was lowest in the study group, although the differences did not reach statistical significance.

Discussion: We found that AD is common in adolescents with AV, but it seems to have some negligible effects in redox reactions. Further studies are needed to show the relationship between AD and AV in terms of oxidative stress. Nevertheless careful psychiatric assessment and measurement of oxidative-antioxidative levels may be helpful for planning treatment modalities for adolescents with AV and AD.

Keywords: Acne vulgaris, Anxiety disorder, Total antioxidant level, Total oxidant level.

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Introduction

Acne vulgaris (AV) is the most common dermatological problem in adolescents; moderate-to severe forms affect 20% of them [1]. AV is also a distressing condition, leading to many mental health problems. Several studies suggest that AV is commonly comorbid with emotional and behavioural problems. Depression, suicidality, anxiety disorder, social withdrawal, low self-esteem, and body dysmorphic disorder are common problems observed in individuals with AV. Acne and acne-related psychiatric problems have a bidirectional pathway: acne is a stress factor which causes psychiatric problems, and stress factors such as depression and anxiety exacerbate acne lesions [1,2]. Recent studies have focused on the pathophysiological mechanisms underlying mental disorders. One mechanism is the oxidant/antioxidant imbalance in which free radicals and oxidants may lead to psychiatric disorders. Oxidative stress is produced by high levels of oxygen radicals and/or defects in antioxidant defences. Free oxygen radicals may cause lipid peroxidation of neuronal membranes and thereby modulate neurotransmitter functions. The brain is susceptible to this kind of neurotoxic mechanisms [3]. Oxidative stress may play a role in the pathogenesis of a variety of psychiatric disorders such as schizophrenia, depression, bipolar disorder, attention deficit hyperactivity disorder, obsessive compulsive disorder, panic disorders and social phobia [4-10]. Previous studies have shown that anxiety disorders are regulated by GABA and serotonin, both of which are affected by oxidative mechanisms. Increased free radicals may destruct phospholipids and indirectly membranes, and consequently the alterations in membranes may impact on neurotransmitter functions [3,10,11].

The history of oxidative pathways in chronic inflammatory diseases like AV is even older than in psychiatric disorders. Studies have shown that the levels of free oxygen radicals are higher, and the levels of antioxidant enzymes are lower, in the circulation of patients with AV [12-14]. Lipid peroxidation, DNA damage and the secretion of inflammatory cytokines are the main consequences of an imbalance in the levels of oxidants and antioxidants [3,11]. Anxiety disorders are common in individuals with acne [1,2]. Although anxiety can cause oxidative stress, the oxidant/antioxidant imbalance can also affect the level of anxiety and indirectly impact the initiation or progression of acne symptoms. Although several studies have been conducted in adults to investigate the role of oxidative mechanisms in psychiatric disorders, similar studies on comorbid disorders in children and adolescents are lacking. The aim of the present study is to determine the effect of anxiety on AV in terms of oxidative damage. We assessed oxidative stress markers in three groups of subjects: AV patients with anxiety disorders, AV patients without anxiety disorders, and healthy individuals without AV and anxiety disorders. We sought to answer whether anxiety disorders further increase oxidative stress in adolescents with AV.

Materials and Methods

Subjects

This study was conducted from January 2012 to January 2013 in the child psychiatry and dermatology outpatient units of the state hospital. Patients aged 11-17 years-old and diagnosed with AV by a dermatologist were referred to the child psychiatry unit. Exclusion criteria for the study were: a) comorbid for other inflammatory or autoimmune conditions, b) positive history for psychiatric, neurological or genetic disorders, c) taking psychotropic and/or anti-inflammatory medications or dietary supplements (especially vitamin E), d) positive history for smoking and alcohol/ substance use, e) reluctance to participate in the study.

Procedure

A total of 118 subjects were recruited, but 23 were excluded due to reluctance (n=9), smoking (n=4), taking multivitamins (n=1), positive history for previous psychiatric treatment (n=4) and other chronic neurological/inflammatory diseases (n=5). The remaining 95 subjects were evaluated for acne severity by the dermatologist using the Global Acne Grading Scale. All adolescents and their parents were assessed by an experienced child psychiatrist on the basis of semi-structured DSM-IV criteria applied during a psychiatric interview. The psychiatric assessment indicated that comorbid psychiatric conditions were common. Therefore, we selected the most debilitating disorder defined by the patients as a primary psychiatric disorder.

Among the 95 patients, 35 (36.8%) were diagnosed with anxiety disorder without any comorbid psychiatric disorders. In addition, 23 patients were diagnosed with other psychiatric disorders, including depression (n=12), attention deficit hyperactivity disorder (ADHD) (n=9), nocturnal enuresis (n=1) and chronic tic disorder (n=1). Comorbid anxiety disorders were present in the subjects with depression (n=3), ADHD (n=2) and tic disorder (n=1). The subjects were assigned to two groups: individuals with AV only (acne control group, n=37) and individuals with AV plus anxiety disorder (study group, n=35). A healthy (non-AV) control group (n=35) was also created, consisting of the offspring of the hospital staff. All three groups had similar socio-demographic features, and were further evaluated for oxidative stress.

Measures

Global acne grading system: This system was developed and applied by Doshi et al. [15]. It divides the face, chest and back into 6 sub-areas and evaluates both the severity of the acne and the type of lesions. The total score is classified as mild (1-18), moderate (19-30), severe (31-38) and very severe (>38). Kiddie-SADS (Schedule for Affective Disorders and Schizophrenia for School Aged children): This semi-structured psychiatric interview was developed by Kaufmann et al. for the diagnosis of major psychiatric disorders in children and adolescents aged 6-18 years-old. The system is valid, reliable and widely available in our country [16,17]. The “present and lifetime” version was used.

Blood samples

Blood samples were drawn following a 12-hour fast by a biochemistry expert who was blind to the groups, and stored on ice. The serum was separated by centrifugation at 1200 g for 5 min and stored at -80ºC for further analysis.

Analysis of blood samples

Total antioxidant status (TAS) and total oxidant status (TOS) were measured using the Rel Assay Diagnostics Kit (Rel Assay®, Diagnostics kits, Mega Tıp, Gaziantep, Turkey) and the oxidative stress index (OSI) was calculated as the ratio of TOS to TAS [18-20]. Serum TAS was calculated by the color intensity of all the antioxidant molecules in the sample. Trolox, a water soluble analog of vitamin E, was used as a calibrator, and TAS was expressed in μmol Trolox equivalents per liter [18]. Serum TOS was measured by a calorimetric method in which all the oxidant molecules oxidize ferrous ions. Hydrogen peroxide was used as a calibrator, and TOS was expressed in μmol H_2O_2 equivalents per liter [19].

Ethics

The study was carried out in accordance with the Declaration of Helsinki. Signed informed consent was obtained from the participants and their parents. Permission was obtained from Aydin State Hospital’s Chief Physician Office’s Ethics Unit.

Statistical analysis

Statistical analysis was performed with the Statistical Package for Social Sciences (SPSS) for Windows 17.0. Descriptive statistics (mean, standard deviation, frequency and ratio), group statistics and distributions of the groups were analyzed

by the one-sample Kolmogrov-Smirnov test. The chi-square test was used for categorical variables. For numerical variables, the two acne groups were compared using t-test and the Mann Whitney U test. For comparisons between the three groups, ANOVA and Tukey's post hoc test was used. P values less than 0.05 were accepted as statistically significant.

Results

The average age of the subjects with AV (n=95; 53.6% female, 46.4% male) was 14.8 ± 1.6 years. There were no differences in ages and gender between AV and healthy control groups. Subjects with AV with anxiety disorders (n=35) and without any psychiatric disorders (n=37) were enrolled further investigation. The anxiety disorders in the study group (n=35) included social anxiety disorder (n=20), specific phobia (n=3), obsessive compulsive disorder (n=4), panic disorder (n=1), separation anxiety disorder (n=1), generalized anxiety disorder (n=3), anxiety disorder-nonspecified (n=3). The most common anxiety disorder in the study group, social anxiety disorder (57%), involved social phobia, performance, and test anxiety. Individuals in the study group did not vary from those in the acne control group in sociodemographics or clinical features of acne (Table 1). Anxiety did not show an additive effect on the severity of acne.

Table 1. *Comparison of clinical features between the study group and acne control group.*

Features		Study group (n=35)	Acne control group (n=37)	P
Female/Male		20/15	19/18	0.62*
Age (years)		14.7 ± 1.9	15.1 ± 1.4	0.35**
Age of acne onset (years)		12.7 ± 1.6	13.1 ± 1.4	0.22**
Acne duration (months)		18.7 ± 9.3	18.5 ± 10.0	0.93**
Acne severity class (n)	Moderate	14	14	0.83***
	Severe	10	14	
	Very severe	11	9	

*Chi-square test, ** t-test, ***Mann Whitney U test. Values are shown as mean ± standard deviation.

The oxidant/antioxidant status of the two acne groups and a healthy control group was compared (Table 2). The TOS in the study (AD with AV), acne control and healthy control groups was 3.85 ± 2.1, 3.22 ± 1.8 and 3.05 ± 1.8 μmol H_2O_2 Eq/L, respectively. A post hoc analysis indicated that the differences in the oxidative stress parameters (TAS, TOS, OSI) between the groups were not significant, although the OSI and levels of oxidant molecules were highest in the study group.

Table 2. *Oxidant /antioxidant status of the groups.*

Parameters	Study Group (n=35)	Acne control group (n=37)	Healthy control group (n=35)	P*
TAS (μmol Trolox Eq/L)	1.51 ± 0.2	1.55 ± 0.2	1.58 ± 0.2	0.281
TOS (μmol H_2O_2 Eq/L)	3.85 ± 2.1	3.22 ± 1.8	3.05 ± 1.8	0.162
OSI (arbitrary units)	2.52 ± 1.3	2.10 ± 1.2	1.97 ± 1.2	0.168

*one way ANOVA

TAS: Total Antioxidant Capacity; TOS: Total Oxidant Capacity; OSI: Oxidative Stress Index. Values are shown as mean ± standard deviation.

Discussion

AV is common in adolescence. Although AV is not a life-threatening disorder, it can cause serious mental health problems [2]. In fact, anxiety disorders are considered to be common in individuals with AV. In our study, 36.8% of the subjects with acne had an anxiety disorder, which is consistent with prior studies [2,21,22]. On the other hand, psychiatric problems exacerbate acne lesions [2,22]. So, we tested the impact of anxiety disorders on acne in terms of oxidative stress. We found that the TOS was highest in the study group (acne plus anxiety), intermediate in the acne control group (acne only), and lowest in the healthy control group. This result is consistent with previous findings that the TOS is higher in patients with anxiety disorder and with AV than in healthy controls [10,14,23]. Atmaca et al. showed that oxidant substrates decrease after psychopharmacological treatment of anxiety disorders [11]. Anxiety may increase vulnerability to oxidative stress in acne patients. At the same time, anxiety increases stress. Neuroendocrine mediators triggered by stress not only lead to proliferation and differentiation of sebaceous cells, but also indirectly affect lipogenesis [24]. Furthermore, stress stimulates the adrenal glands and causes aggravation of acne [22,24]. There is a vicious cycle between stress, acne and anxiety: anxiety increases inflammation and acne, and at the same time acne and stress increase anxiety levels [25]. In this view, selective serotonin reuptake inhibitors have been studied as a treatment modality for acne [26]. A recent study by Ceylan et al. showed that lipid hydrogen peroxide levels are significantly higher in children with anxiety disorders. The authors also found no differences in paraoxonase or arylesterase antioxidant activity between the anxiety and healthy control groups [27].

The impact of anxiety on acne was observed biochemically in our study, but a clinical effect of anxiety on acne severity was not observed. The acne grading scores of the two acne groups were similar. A possible reason for this similarity is that minor increases in oxidative stress may not lead to major inflammatory changes observable as dermatologic lesions. Severe acne in adolescence results in a poor body image and has more psychological consequences [2]. In the light of our data, we can infer that internal stress (biological pathways, neuroendocrine factors and neurotransmitters, anxiety itself) rather than external stress (severity of acne) may be sensitive to

anxiety and a higher TOS. Future research is needed on this topic. We found that TAS was lowest in the study group, but the differences among the three groups were statistically negligible. Heterogeneity in the anxiety disorders may have contributed to this result. Previous results on TAS in psychiatric disorders are inconsistent [3]. Some studies showed no difference in anxiety disorders, whereas other studies found a lower TAS in, for example, obsessive compulsive disorder [8,23]. Normal or lower antioxidant status may play a role in the imbalance in oxidative processes.

It has been reported that oxidative stress may also cause emotional stress and thereby inversely affect itself. Anxiety influences the immune system and leads to an impairment in lymphocytes [25]. This effect may be another reason for the comorbidity of anxiety and acne. However we found no difference in acne severity between the study group and the acne control group, which is consisted with the findings of Aktan et al. [27]. In fact, severity of acne was rated according to clinical presentation of lesions rather than histopathologic appearance. Possible factors on clinical presentations of acne such as severity and onset of anxiety were not evaluated. Although TAS and TOS oppose each other, a negative correlation between these two parameters is not a rule. A balance between oxidative and antioxidative mechanisms is reflected by the OSI, which is a good indicator for redox state [18-20]. We observed a higher but negligible OSI in the study group, suggesting a slight imbalance in the redox state.

Our study has some limitations. Our sample size was small. Confounding factors such as food, environment, previous medications, liver function and body mass index were not controlled. We used the TAS/TOS parameters to measure redox state, although a wide range of biomarkers can be used for this assessment. Finally, we cannot generalize the results. However, the diagnostic evaluation is based on a semi-structured clinical interview, which is a strong part of our study. Experimental studies showed that oxidative stress pathways operate differently depending on the severity of anxiety [25]. Further clinical studies will enlighten the relationship between anxiety levels and oxidant-antioxidant status. In conclusion, our study showed that anxiety disorders generally did not affect in oxidative-antioxidative mechanisms in patients with acne. Mechanisms by which redox reactions affect anxiety and acne should be clarified in future studies. In addition, noninvasive and disease-specific oxidative stress measures and methods need to be developed, so clinicians can use these tests routinely. In the light of new studies on oxidative stress, novel treatment and preventive modalities will likely be developed. Although antioxidants are novel drugs in chronic diseases, clinicians must keep in mind the dose dependent toxicity and pro-oxidant roles of such drugs [25]. Future studies should focus on the use of antioxidant drugs and/or diets for anxiety disorders and acne, as well as anti-anxiety drugs for acne and other conditions with an imbalanced redox state.

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