EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Volume: 3
Issue: 1
25-29
Year: 2016

ROLE OF PSYCHOLOGICAL STRESS ON PLASMA CORTISOL AND INTERLEUKIN-4 IN ATOPIC DERMATITIS

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Article Received on 03/11/2015 **Article Revised on 24/11/2015** **Article Accepted on 15/12/2015**

ABSTRACT
Atopic dermatitis (AD) is a skin inflammatory diseasecharacterized by chronic, itchy skin condition that is very common in children but may occur at any age. The purpose of this study was conducted to determine the relationship of psychological stress, IL-4 and cortisol in atopic dermatitis. Thirty one patients (18 males, 13 females; mean age 24.1 years, range 13–41 years), diagnosis of AD based on the criteria of Hanifin & Rajka , and 28 healthy controls (15 males, 13 females; mean age 25.2 years, range 12–43 years) with no history of atopic diseases, were enrolled in this study.The risk of developing illness due to stress was assessed by providing the questionnaire by Holmes T and RaheR (1967) as social readjustment rating scale to the subjects. Blood sampling was performed for measure IL-4 and cortisol plasma level. Statistical analysis were performed using student-t test to reported mean ± standard deviation and correlation and linear regression anlysis. The psychological stress (stress index) were significantly higherbetween the AD (156.5 + 3,4)and normal control groups (80.3 + 2.9)). The serum IL-4 concentration was higher (5.45 + 1.28 pg/ml) in the AD group than in the normal controls(2.92 + 0.74 pg/ml) and were not significantly different serum concentration of cortisol in AD group between control group. We found a positive correlation between stress index with the severity of diseases (SCORAD index) and plasma concentration of IL-4.

KEY WORDS: Psychological Stress, Plasma Cortisol, L-4, Atopic Dermatitis.

INTRODUCTION
Atopic dermatitis is a chronic inflammatory skin disease, characterized by a complex, heterogeneous pathogenesis, including skin barrier dysfunctions, genetic and immunologic disturbance, with extensive pruritus and symptomatic relaps and remissions.[1,2] The mechanisms of disease exacerbation are still poorlyunderstood, that it is the first disease to present in a series of allergic diseases. Clinical occurrence of atopic dermatitis isoften associated with family dysfunction and psychological stress. In responseto stress, upregulation of stress hormones and neuropeptide mediators in thebrain, endocrine organs, and peripheral nervous systemdirectly affect immune and immunological resident cells in the skin.[3,4] Lesional and non-lesional skin of patients with atopic dermatitis demonstrates increased mast cells and mast cell-nerve fiber contacts. In the setting of stress, sensory nerves release neuromediators that regulate inflammatory and immune responses, as well as barrier function. The pathogenesis of atopic dermatitis is unclear, but it was agreed that the disease is associated with a hypersensitivity to environmental allergens, it is based on the change in the balance of the activity of T helper lymphocyte cells 1 (Th1) and T helper lymphocyte cells 2 (Th2) dominated by role Th2 cells which leads to increased levels of immunoglobulin E (IgE), interleukin-1 (IL-1), interleukin-6 (IL-4) and interferon-γ(INF-γ), to all three is the main mediator in the pathogenesis of atopic dermatitis.[5,6] In response to stress, upregulation of hypothalamus-pituitary- adrenal axis (HPA Axis), activation of HPA axis will release the hormone cortisol, this hormone acts as an anti-inflammatory that can maintain body homeostasis. Likewise, stress activates the simpatico-adrenal medullary system which will stimulate the production of noradrenaline, noradrenalin will activate T cells to produce interleukine-6, as proinflammatory cytokines, IL-4 plays an important role in the pathogenesis of atopic dermatitis.[7] Study by Burke, *et al* (1997) found that in AD occurs weakening HPA response to stress so the

cortisol levels in AD is significantly lower than control group, while increased levels of IL-4. Based on this evidence, the AD happens that low cortisol levels and increased levels of IL-4.[7,8]

The aims of the study to investigate relationship of psychological stress on plasma cortisol level and IL-4 in atopic dermatitis.

MATERIAL AND METHODS

A matched pair case control study was conducted to determine the relationship of psychological stress, IL-4 and plasma cortisol in atopic dermatitis. Thirty one patients (18 males, 13 females; mean age 24.1 years, range 13–41 years), and 28 healthy controls (15 males, 13 females; mean age 25.2 years, range 12–43 years) with no history of atopic diseases, were enrolled in this study.Diagnosis of AD based on the criteria of Hanifin & Rajka,with categories; 1 or more major criteria and at least 3 minor symptoms.[9]

To assess stress index, by using the checklist of Holmes & Rahe (1967), which contains 43 questions about life events. All life events are recorded and summed, when more than 150 indicate the possibility of stress with clinical manifestations.[10]

Blood sampling was performed for measure IL-4 and cortisol plasma level. The clinical data (family history of AD, family or personal history or bronchial asthma or both, onset of cutaneous lesions, and morphology and localization of atopic dermatitis) was recorded. We also assessed clinical skin severity by Scoring of Atopic Dermatitis (SCORAD) index.[11]

The study was approved by the Ethics Committee of the Medical faculty.Statistical analyses were performed by using student-t test to analysed difference mean (mean ± standard deviation) to determine the mean difference between stress index, cortisol and IL-4 level, and linear regression anlysis to calculate thestrength of the relationship between stress index with severity of diseases (SCORAD), plasma level of cortisol and IL-4.

RESULT AND DISCUSSION

During the 6-month study recruited 59 subject consist of cases of AD 31 and 28 healthy person as a control, were investigated in Dermology outpatient clinic Sanglah General Hospital. Atopic dermatitis was diagnosed according to the criteria of Hanifin and Rajka. The clinical data (family history of AD, family or personal history or bronchial asthma or both, onset of cutaneous lesions, and morphology and localization of atopic dermatitis) was recorded. We also assessed clinical skin severity by Scoring of Atopic Dermatitis (SCORAD) index.

In this study calculated the mean difference in plasma cortisol, plasma IL-4, total score of stress level/index between cases and controls. Characteristics and results of laboratory tests of study population can be seen in Table 1 below:

Table1.Characteristics and Laboratory test of the study population

	Cases (Atopic Dermatitis) N=31	**Control N=28**	**p Value**
Gender			
Men (%)	18(30.6)	15 (25.4)	
Women (%)	13 (22.0)	13 (22.0)	p> 0.05
Age (years)			
14- 30 (%)	9 (15.2)	8 (13.6)	
31-40 (%)	15 (25.4)	14 (23.7)	
> 40 (%)	7 (11.9)	6 (10.2)	p > 0.05
Atopic history			
Yes (%)	21 (35.6)	10 (16.9)	
No (%)	10 (16.9)	18 (30.6)	p > 0.05
Onset (years)		--	
< 1 (%)	8 (25.8)	--	
≥ 2- 3 (%)	16 (51.6)	--	
> 3 (%)	7 (22.6)	--	p > 0.05
Severity (SCORAD)		--	
Mild(%)	9 (29.0)	--	
Moderate (%)	15 (48.4)	--	
Severe (%)	7 (22.6)	--	
Average stress levels	160.35 ± 23,56	96.45 ± 19.20	p < 0.05
Stress risk			

Low susceptibility < 100 (%)	12 (20.3)	20 (33.9)	
Susceptibility≥ 100 (%)	19 (32.2)	8 (13.6)	p < 0.05
Cortisol (ug/dl)	5.46 ± 2.16	5.12 ± 2.33	p > 0.05
IL-4 (pg/ml)	5.45 ± 1.28	2.92 ± 0.74	p < 0.05

Note: Mild: SCORAD <20, moderate: ≥20 – 40, Severe:>40

From Table 1 it appears that stress plays a role in the incidence of AD, 19 cases (32.2%) experienced stress risk premises stress index >150. These results are supported by other studies; Monica et al (2013) find that level of anxiety in AD more higher than healthy controls. (monica). Likewise, research by Ho OH S *et al* (2010) of AD patients experience depression anxiety in 30-40% of cases.[12] The plasma cortisol level in AD patients (5.46 ± 2.16 ug/dl), which was not significantly higher compared to the healthy controls (5.12 ± 2.33 ug/dl). In this study the mean levels of IL-4in subjects with atopic dermatitis (5.45 ± 1.28 pg/ml) was significantly higher than control(non-atopic diseases) (2.92 ± 0.74 pg/ml).

This stress assessment was prepared by Holmes and Rahe check list (1967), this is used as an indicator of the stress caused by traumatic life events. The stress induced by these events not only seriously affect the person's health, it can also be cumulative. There are about 43 questions about events of the life of each rated Stress Index is a cumulative total, to estimate the total level of stress experienced. If the total below 100, indicating low susceptibility to stress, do not manifest clinically and more than 100 indicate suspected stress with clinical manifestations.

The stress level in AD patients (160.35 ± 23,56), which was significantly higher compared to the healthy controls (96.45 ± 19.20).[12] By using regression analysis found a positive relationship between stress index with SCORAD (coeficien regression = 0.378) was statistically significant,as shown in the figure 1 below.

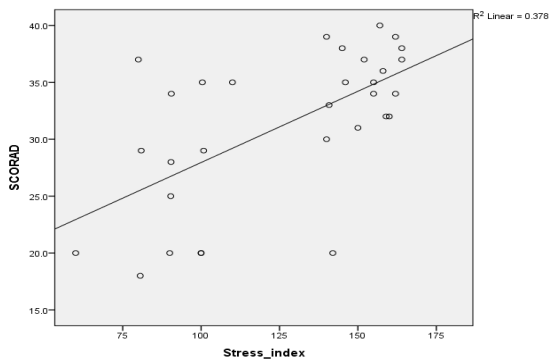

Figure 1: Scatter plot of correlation between the stress index and SCORAD

This study proved that plasma cortisol concentration in atopic dermatitis is slight higher compare to control, but statistically not signifikan. Plasma cortisol level in AD (5,46 ± 2,16 pg/dl), whereas in healthy control (5.12 ± 2.33 pg/dl), there was no significant difference. The same result was found by Buske-Kirschbaum et al (2003), patients suffering from atopic dermatitis were compared subject without atopic dermatitis, statistically no significant difference. All groups of subjects were underwent stress with The Trier Social Stress Test in children (TSST-C) is a laboratory procedure used to reliably induce stress then evaluate saliva cortisol level. The investigators concluded that there was an hyphoreactivity of hypothalamus-pituitary-adrenal (HPA) axis responses in atopic and asthma patients.[8]

Other studies by Mizawa et al (2013) bymeasurement of cortisol-plasma concentration was carried out, the results obtained that, cortisol-plasma concentration for patients with asthma and atopic diseases are significantly lower compare to control group, their study indicated that cortisolsaliva and plasma for patients with atopic diseases are significantly lower compare to control without atopic.[13] Buske (2003) and Elencov (2004) obtaining result of cortisolis a stress hormone that acts as an inhibitor of pro-inflammatory cytokines, but the person with atopic disorder there are breakdown of the HPA axis to response of psychological stress cause of lower cortisol production.[8,14] Similarly, the study of Stenius (2011) measure cortisol in saliva in children with allergic diseases such as atopic dermatitis and ashtma, with result saliva cortisol levels lower than control healthy children.[15] These findings suggest that a blunted adrenocortical response to psychological stress may represent a common feature of chronic allergic inflammatory processes that may be relevant in different forms of chronic manifestation of atopy.[8,14] In this study, the scatter plot analysis, showed correlations increase in cortisol with stress but not significant, as shown in the figure 2 below.

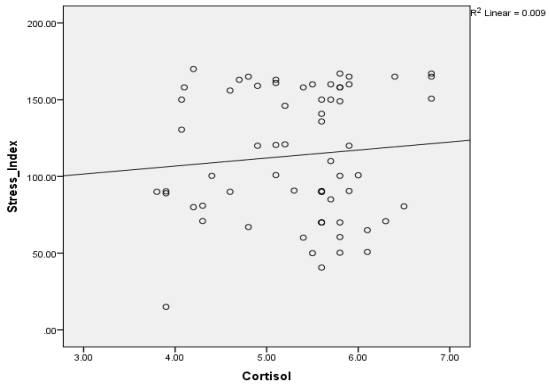

Figure 2: Scatter plot of correlation between the stress index and plasma cortisol levels

IL-4 is a inflammatory cytokine which works synergistically with TNF-α and IL-1 to cause inflammation, a common feature of chronically stressed individuals. It has been used as a biomarker of chronic stress in many mechanistic and epidemiological studies because it can be easily measured from blood and it can capture pathophysiology of the immune system which is an important stress response system.[6,7]

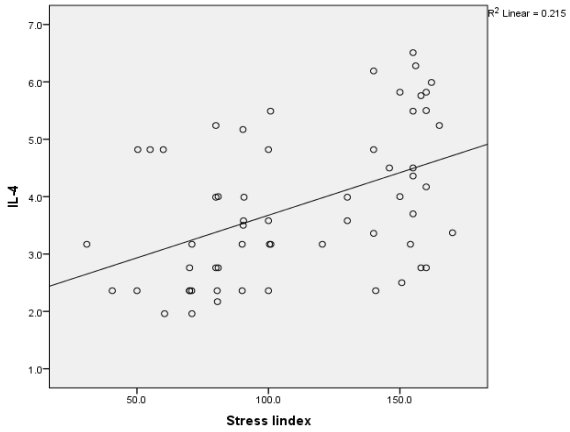

Figure 3: Scatter plot of correlation between the Stress index and plasma IL-4

It is widely recognized or establish theory IL-4 plays an important role in the pathogenesis of AD, IL-4 is a proinflammatory cytokine. Increased IL-4 in the plasma as a result of the immune response antigen-antybody reaction. There is some evidence that, in humans and experimental animals, psychological stress may suppress or enhance immune functions, depending on the nature of the stressor and the immune variables under consideration. The possibility that psychological stress may affect the production of pro-inflammatory and immunoregulatory. IL-1, IL-4 and IFN-γ, take part in the homeostatic responses to psychological stress and that stress-induced anxiety is related to a T-helper-1-like response.Likewise, with the regression analysis, apparent the positive correlation between the stress index and the plasma levels of IL-4.[16]

This suggests that stress with stress hormones affect the balance of T cells producing pro-inflammatory and anti-inflammatory, namely Th1-Th2 cytokines, in atopic dermatitis (AD) increased IL-4 production. New evidence suggests that IL-4 may be a crucial factor controlling mast cells as well as IgE production in allergic disease. The significance of the FCεRII/CD23 in regulating IgE synthesis and its role in Langerhans' cell/antigen interactions in atopic dermatitis represents an intriguing area in need of further study.[6,16]

Therefore, these results suggest that the plasma cortisol level is a useful biomarker to evaluate the stress in AD patients and to help physicians in order to plan more effective treatment strategies for these patients.[15]

CONCLUSION

Our study suggests that AD patients might be under psychological stress, and the severity of AD war correlated with the intensity of the stress (stress index). Plasma IL-4 as pro-inflammatory marker was higher in AD than non-atopic healthy control, but cortisol as anti-inflammatory was slightly increased butstatisticaly not significant.

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