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The role of psychological stress in atopic dermatitis through an increase of IL-31



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ABSTRACT

Introduction: Atopic dermatitis occurs due to multifactorial interactions such as genetic, environmental, impaired skin barrier function, immunological factors, infection and post-psychological stress. Th1 cells and some proinflammatory cytokines such as IL-6, IL-10 and others play a role in the pathogenesis of atopic dermatitis, also IL-31. IL-31, including cytokines of the IL-6 family expressed mainly on CD4 T cells. Many researchers also associate stress with the occurrence of atopic dermatitis, stress will trigger the release of these cytokines from immune cells (e.g. IL-6, TNF α). The aim of the study is determine correlation between stress and increase in IL-31 level in person with atopic dermatitis

Method: We designed a case-control study including 58 patient, range from 14-65 years old. Diagnosis of atopic dermatitis is established based on Hanifin and Rajka criteria, and the severity based on SCORAD.

Venous blood was collected for IL-31 examination, stress index was measured by interview according to the Holmes-Rahe stress scale test method.

Result: In this study, the stress index in atopic dermatitis was 102.26 + 11.71, and in control 61.35 + 19.87 there was a significant difference with $p < 0.005$. IL-31 levels in atopic dermatitis were 274.44 + 95.35, higher than controls 129.44 + 85.45, significantly with $p < 0.005$. The results of linear regression between stress index and severity of dermatitis (SCORAD), appeared to have a moderate positive correlation with $r = 0.04$. OR 4.56 (95% CI 2.78-11.56).

Conclusions: From this study it can be concluded that stress increases IL-31 levels and positively correlates with the severity of atopic dermatitis.

Keywords: Stress, IL-31, atopic dermatitis, SCORAD, cytokines

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INTRODUCTION

Atopic dermatitis is not yet fully understood, but several factors, such as genetics, immune response, skin barrier, focal infection and psychological stress.^{1,2} Interaction of these factors causes a displacement in the T cell response, the Th2 response which then switches on (Th1), which causes the release of proinflammatory cytokines (e.g. Interleukin (IL) -4, IL-5, IL-6, Tumor necrosis factor (TNF), and IL-31.^{1,2} IL-31 also spoke by discussing problems with the barrier function of the skin through basal cell proliferation epidermis.^{3,4}

Psychological stress (stress) also plays a role in the recurrence of atopic dermatitis, studies that have introduced several biochemical markers as stressors, for example; resistance exposed insulin, C-reactive protein, and several proinflammatory cytokines. IL-31 as a cytokine proinflammation belongs to the IL-6 cytokine family expressed mainly by activation of T cells CD4 + and signaling through its receptor consisting of alpha-31 receptor (IL-31RA), which is present in immune cells that play a role in atopic pathogenesis dermatitis.^{5,6} To find out the stress index/scale, interviews were conducted using the Holmes-Rahe method stress scale test. Assessing stress with Life Events Scales, in 1967, Thomas Holmes and Richard Rahe

developed the Social Suitability Assessment scale (SRRS). Then Holmes and Rahe developed their scale by considering that stress was accepted from the events of one's experience and changing one's life.^{7,8} Based on these backgrounds, the role of stress in atopic dermatitis is very important so researchers are interested in knowing whether stress is related to atopic dermatitis, how stress relates to IL-31 and whether IL-31 is related to atopic dermatitis.

METHODS

Study design

This study uses a case-control design. Case was atopic dermatitis patient who went to the Outpatient Dermato-Venereology Clinic at Sanglah Hospital, Denpasar, have not received any treatment, aged 14 - 65 years. Control is healthy subjects did not suffer from atopic dermatitis or other allergic diseases. Between cases and controls were matched, based on sex and age with a range of 5 years.

Procedures

The diagnosis of atopic dermatitis is established based on typical clinical features according to Hanifin & Rajka's criteria. After two groups received sufficient information and were willing to sign an informed letter consent. Then a deep

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history is taken to get the stress index/scale by the Holmes & Rahe method. The stress index (scale) is determined by summing the value of the question to 43 questions about life events (life events) for the past 3 months. When the total score is > 100 hence it is susceptible to stress. Venous blood 2 ml was collected for IL-31 examination. Statistical analysis was performed with SPSS version 20. Performed analysis of data normality, comparative analysis, correlation/regression analysis and analysis analysed, with p values <0.05 were considered significant, comparative analysis, Chi-square, determinant coefficients and analysis univariate/multivariate.

RESULTS

General characteristic of research subject consists of gender, aged, onset of atopic dermatitis, family

history, atopic history, SCORAD SCORE, level of IL-31 serum, and index stress. The result of the study shown in [table 1](#).

In this study, IL-31 serum levels in atopic dermatitis were 274.44 + 95.35, significantly higher than controls 129.44 + 85.45 (p<0.005). The stress index in atopic dermatitis was 102.26 + 11.71, and in control 61.35 + 19.87 there was a significant difference with p<0.005. The results of linear regression between stress index and severity of dermatitis (SCORAD), appeared to have a moderate positive correlation with r = 0.04 as shown in [Figure 1](#). High IL-31 is a risk factor for atopic dermatitis with OR 4.56 (95% CI 2.78-11.56).

DISCUSSION

Many studies have stated that psychological stress is a trigger of atopic dermatitis.⁵ This study shows

Table 1 Subject Characteristics, Stress, and IL-31 level

Characteristic	Atopic Dermatitis n = 30	Control n = 28	p / OR (CI 95%)
Gender			
Male	16 (27.5%)	16 (27.5%)	
Female	14 (24%)	12 (21%)	p>0.005
Aged			
ears old	12 (22%)	11 (17%)	
26-45 years old	10 (17%)	9 (15%)	
45 years old	8 (14%)	8 (14%)	p>0.005
Onset of atopic dermatitis			
< 1 years	3 (10%)	-	
1-5 years	5 (16%)	-	-
10 years	20 (76%)	-	
Family history			
Yes	19 (33%)	4 (2%)	p<0.005
No	11 (17%)	28 (48%)	
Atopic history			
Yes	10 (17%)	3 (1.5%)	
No	20 (35%)	25 (46.5%)	p<0.005
SCORAD score			
Mild	13 (43.3%)	-	-
Moderate	11 (36.7%)	-	
Severe	6 (20%)	-	
Serum IL-31 (pg/mL)	274.44 ±11.71	129.44 ±85.45	p<0.05
High	16 (27.5%)	6 (10%)	OR : 4.13 (CI 95% : 1.32-13,27)
Normal	14 (24%)	22 (38.5%)	
Index stress	102.26 ± 11.71	61.35 ±19.87	p<0.05
Stress	17 (29.3%)	15 (25.8%)	OR: 3.57 (CI 95%: 1.08 – 11.79)
Non-stress	8 (15%)	18 (29.9%)	

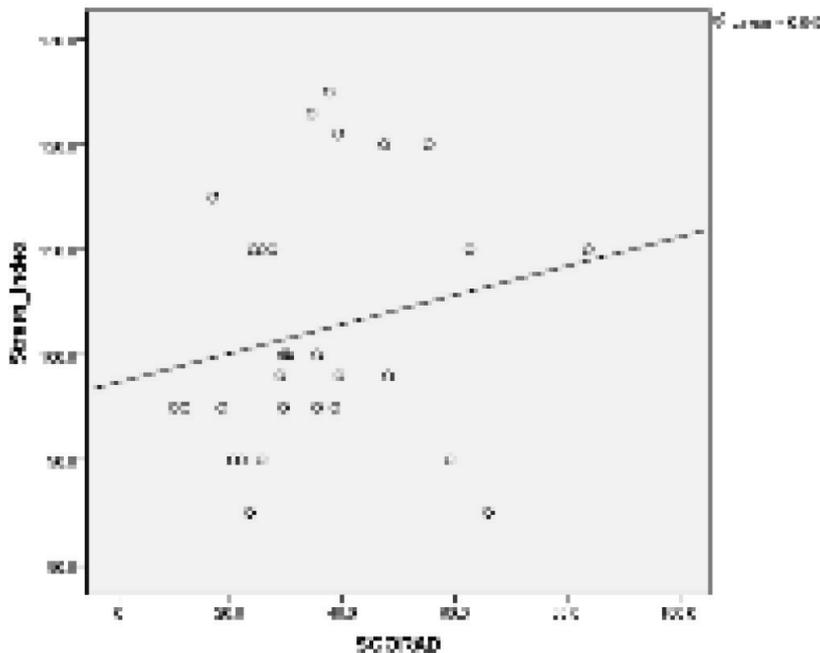


Figure 1 Scatter plot correlation between stress index with severity (SCORAD) correlation coefficient (r) = 0.04

the magnitude of stress factors being a trigger of atopic dermatitis. Based on research conducted at Surakarta 8 Junior High School in December 2014, it can be concluded that there is a relationship between stress levels and an increased risk of atopic dermatitis in adolescents at Junior High School 8 Surakarta.⁹ Study about role of stress at atopic dermatitis by Wardhana et al. shown the result that psychological stress (stress index) was significantly higher in AD (156.5 ± 3.4) compared to normal control group (80.3 ± 2.9).¹⁰ Another study by Wardhana et al. concluded that stress is a risk factor for DA with an odds ratio of 5.3, and the stress index is positively correlated with the severity of DA.⁶ According to Kondoru et al. IL-6 is an immunological biomarker of psychological stress, IL-31 is a family of IL-6, with stress analysis can also increase IL-31.¹¹

IL-31 is associated with the IL-6 cytokine family expressed mainly by activation of CD4 + T cells and signalling through heterodimeric receptors consisting of IL-31 alpha receptor (IL-31RA) and oncostatin M receptor beta (OSMR). These receptors are expressed on the surface of keratinocytes, monocytes and dorsal radical ganglions that cause pruritus. In studies with mouse models, excessive IL-31 expression induces severe pruritus in atopic dermatitis.¹² IL-31 is also associated with

a disruption in the function of the skin barrier through the proliferation of basal epidermal cells.¹³

CONCLUSION

In this study There was a significant difference between stress index in atopic dermatitis was 102.26 ± 11.71 , and at control 61.35 ± 19.87 ($p < 0.005$). Higher IL-31 levels were found in person with AD compared to normal control, and high level of IL-31 was associated with increased risk of AD. There was a positive correlation between stress index and severity of AD.

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ETHICAL CONSIDERATION

Current study has been approved by the Committee of Ethics Faculty of Medicine, Universitas Udayana/ Sanglah General Hospital, Bali, Indonesia. All study according to declaration of Helsinki based on human right and all sample has received inform consent and signed an agreement document before any data collection.

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