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High plasma dopamine level as a risk factor for atopic dermatitis

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ABSTRACT

Background: Dopamine is responsible for inflammatory response and plays a role in the skin immune system by modulating T-cells, dendritic cells, and keratinocytes which increases skin inflammatory response in atopic dermatitis (AD). Elevation of dopamine level will affect IL-6, IL-8, IL-23, Th-17, and TNF-α, which promotes keratinocyte proliferation and differentiation, infiltration of inflammatory cells, angiogenesis, vasodilation, and skin barrier disruption on AD.

Objective: This study aimed to establish whether the increase of plasma dopamine level contributes to a risk factor for AD occurrence.

Methods: This is a matched-pair case-control observational analytical study which involves patients with AD and without AD as control. Samples were taken using a consecutive sampling method which fulfilled inclusion and exclusion criteria, matched for gender and age. Plasma dopamine level was measured from venous blood and processed using enzyme-linked immunosorbent assay (ELISA) method. The collected data were then analysed using SPSS version 20.0 with Pearson chi-square test for the odds ratio.

Results: A total of 30 samples with AD (case group) and 30 samples without AD (control group) involved in this study. This study proves that plasma dopamine levels in the case group were significantly higher than the control group ($p<0.05$). Odds ratio for plasma dopamine was 42.2 (95%CI: 9.5-187.2, $p < 0.001$).

Conclusion: This study concludes that high plasma dopamine level is a risk factor for AD.

Keywords: Atopic dermatitis, plasma dopamine, Hanifin and Rajka

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INTRODUCTION

Atopic dermatitis (AD) is a recidive, chronic skin inflammatory disease characterised by pruritus and is associated with skin barrier function, allergen sensitisation and recurrent skin infections, most commonly found in early years of life to childhood but may also be found in adults.[1-3] AD affects 2-5% of the general population and occurs mostly in earlier years of life. Incidence of AD is known to affect as much as 20% of children in childhood and 1-3% of adults across the globe.[1,3-5] It is believed that the cause of AD is multifactorial, such as genetic, environmental, and psychological stress factors.[5]

Psychological stress-induced AD will interfere homeostasis of the neuroendocrinal system which then activates the interaction between central hypothalamic pituitary adrenal (HPA) axis and cutaneous peripheral HPA axis.[4-6] This leads to the release of hormones, neurotransmitters, and cytokines responsible for skin inflammation. Catecholamines such as dopamine, epinephrine, and norepinephrine are essential for the central nervous system.[6] Dopamine regulates the nervous, neuroendocrine, and immune system functions. Dopamine released will attach to dopamine receptors on T-cells and dendritic cells which will take part in AD pathogenesis, resulting in the release of proinflammatory cytokines, skin barrier dysfunction, and increase keratinocyte activities in AD patients. Dopamine receptors found in immune cells such as T-cells and dendritic cells prove that dopamine takes part in regulating the immune system response to stress.[7,8] Dopamine also contributes to inflammatory mediators such as mast cells and Th2 activation which are also a part of the acute phase of AD.[9] Previously conducted studies concerning plasma dopamine levels on AD patients lack sufficient evidence to prove that high plasma dopamine levels are a risk factor for AD. As such, further research is required in this area. This study aimed to prove that high plasma dopamine level is a risk factor for AD.

MATERIALS AND METHODS

This is an observational analytical study with a case-control design. This study was conducted between May to June 2018. This research used Prodia Laboratory as a referral laboratory for plasma

dopamine level measurements with the enzyme-linked immunosorbent assay (ELISA) method. Diagnosis of AD is made by Hanifin and Rajka assessment criteria. DASS (depression, anxiety, and stress scale) questionnaire was used to evaluate stress levels. Research samples were taken from the reachable population using consecutive random sampling method. Cases used were samples of patients diagnosed with AD from Dermatology and Venerology Outpatient Clinic of Sanglah General Hospital Denpasar, which fulfilled both inclusion and exclusion criteria. Each case was paired with one control which fulfilled both inclusion and exclusion criteria, then matched based on sex and age. The inclusion criteria of case group were Indonesian nationals above 18 years old of age, could be both male and female, was in a great general condition, and was willing to participate in the research-proven with signed informed consent. Patients without AD were classified as the control group. Patients with physical trauma, chronic infection and systemic diseases such as Parkinsons, malignancy, along with heart, thyroid, and parathyroid conditions, history of dopamine receptor antagonists (haloperidol, chlorpromazine, domperidone) and agonists (bromocriptine, cabergoline, lisuride, ropinol, rotigotin) were excluded from this study. Data collected were then descriptively and analytically checked, coded, processed, and analysed using SPSS version of 21.

Table 1 Subject characteristics data on case and control groups

Variables	Groups		p-value
	Case	Control	
	n = 30 (%)	n = 30 (%)	
Age			
18-35	20 (66.6)	18 (60)	
36-55	4 (13.3)	5 (16.6)	
>55	6 (20)	7 (23.3)	
Mean ± SD	35.7 ± 13.3	39.4 ± 16.6	0.356
Sex			
Male	9 (30.0)	13 (43.3)	
Female	21 (70.0)	17 (56.6)	
Stress scale			
Normal	4 (13.3)	17 (56.6)	
Low	8 (26.6)	10 (33.3)	
Moderate	12 (40)	3 (10)	
High	6 (20)	0 (0)	
Plasma dopamine (pg/ml)			
Mean ± SD	32.1 ± 11.0	14.7 ± 8.7	< 0.001*

*Significant p-value if p<0.05

Table 2 Comparison between case and control groups plasma dopamine values

Variable	Groups		p-value
	Case	Control	
Dopamine (pg/ml) Median [IQR]	32.3 [11.0]	12.3 [8.7]	<0.001*

*Significant p-value if p<0.05; IQR= Interquartile Range

RESULTS

This study involved 60 research subjects categorised into 30 cases with AD and 30 cases without AD. The subject characteristics data of both case and control groups which consist of age, sex, and stress scale are listed in Table 1.

Shapiro-Wilk normality test showed that data obtained were not normally distributed due to p-value of both case and control group of < 0.05. The comparison between plasma dopamine median value of case and control group can be seen in Table 2.

The values in Table 2 were obtained using a Mann-Whitney test to determine whether there was a significant difference between case and control groups plasma dopamine levels (p < 0.001).

Receiver operating characteristic (ROC) analysis result showed that cut off point of plasma dopamine value was 18.2, with 96.7% sensitivity and 86.7% specificity. Dopamine plasma value was considered high when it is >18,2 pg/ml and considered normal if it was ≦18,2 pg/ml. This data is shown in Figure 1.

Table 3 explains how high plasma dopamine level attributed to AD risk factor as much as 42.2 times (OR = 42.2; 95%CI: 9.5-187.2; p < 0.001) compared with normal plasma dopamine values.

Multivariant logistic regression test results in this research, as shown in Table 4 showed that high plasma dopamine values increased the risk of AD for 44.7 times following adjusted odds ratio calculation.

DISCUSSION

Based on the analysis, high dopamine level increase the risk of getting dermatitis atopic 42 times compared to the non-high dopamine level (OR: 42). Mean age of subjects with AD found in this study was 35.7±13.3. A study in China showed similar results where subjects with AD found in adults had a mean age of 41.8±14.3.[10] This study also showed that AD was more prevalent in females at 21 subjects (70%) compared to males at nine subjects (30%). There was no notable difference in the prevalence of AD between males and females. The study conducted by Wang states that AD in adults, particularly between 18-28 years old had a higher

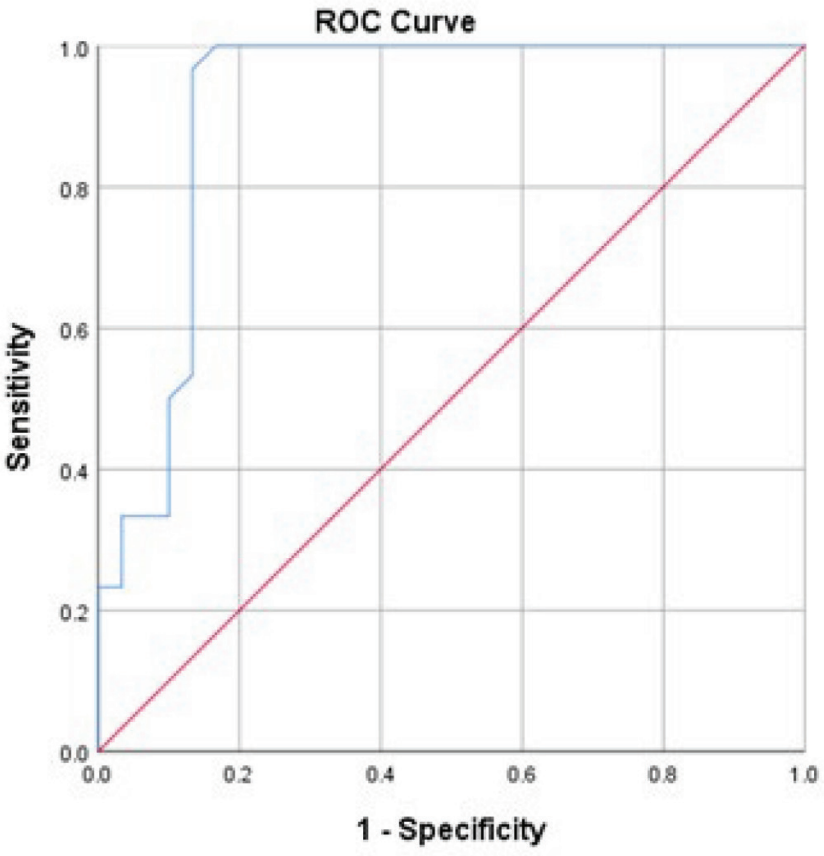

Figure 1 ROC curve of plasma dopamine value

Table 3 **High plasma dopamine values involvement in AD pathogenesis result in analysis**

Variables	Groups		OR	95% CI	p-value
High plasma dopamine	**Case** n=30 (%)	**Control** n=30 (%)			
Yes (>18.2)	29 (96.6%)	0 (0%)	42.2	9.5-187.2	<0.001*
No (≤18.2)	1 (3.3%)	30 (100%)			

*Significant p-value if p<0.05; OR= Odds Ratio; CI= Confidence Interval

Table 4 **Multivariant logistic regression test results**

Variables	Adjusted OR	95% CI	p-value
High dopamine	44.7	7.5-244.6	<0.001*
Stress	5.7	1.0-32.2	0.451
Sex	0.49	0.08-3.06	0.046*

*Significant p-value if p<0.05; OR= Odds Ratio; CI= Confidence Interval

presentation of 59.2%. Still, the presentation of the male was only slightly higher (53.1%) compared to female. Research results of adulthood AD in each country may differ due to response difference of AD treatment and management.[8-10]

This study showed that those with high dopamine values had a significantly higher median of 32.3 [11.0] compared to the control group with a median of 12.3 [8.7] with p-value <0.001. Plasma dopamine level of the case group ranged from the minimum of 18.0 pg/L to 125.9 pg/L maximum, while the plasma dopamine level of the control group ranges from the minimum of 5.5 pg/L to 18.0 pg/L. This shows that there was a significant difference in plasma dopamine median values between case and control groups, where the plasma dopamine level was notably higher compared to the control group. One study conducted by Nicolae *et al*. in Romania on 2013 supports these findings, where they found out that 13 subjects (11%) with AD had the plasma dopamine level > 100 pg/L, while no plasma dopamine level > 100 pg/L was found on a control group of patients without AD.[11] To date, research concerning measurements of plasma dopamine value on AD subjects remain inconclusive.

Pearson chi-square test was used in this study to analyse plasma dopamine values with the results of the odds ratio of 42.2, with a 95% confidence interval of 9.5-187.2. This showed that high plasma dopamine level was a risk factor for AD. Individuals with high plasma dopamine values had 42.2 times increased risk of developing AD compared to individuals with normal plasma dopamine values. Multivariate logistic regression test used in this study shows that the adjusted odds ratio of those with high plasma dopamine level had 44.7 times increased the risk for developing AD. The aforementioned proves dopamine is a risk factor for AD. High dopamine levels, along with genetic, immunologic, and environmental factors are attributable to AD. Therefore, high plasma dopamine values can be used as a marker for AD occurrence.[8,11]

Dopamine stimulation on dopamine receptors of T cells and dendritic cells affects differentiation of T cells CD4+ to Th1, or Th17 cells which will ultimately lead to the release of inflammatory mediators such as IL-10 and TNF-α on AD.[8] Nevertheless, dopamine levels on AD are still not yet fully understood. Still, it is confirmed that there is an increase of Th17 cells presentation on peripheral blood of AD patients which correlates with AD severity.

CONCLUSION

High plasma dopamine level is a risk factor for AD.

CONFLICT OF INTEREST

None.

ETHICAL CLEARANCE

This research approved with the code 736/UN.14.2.2/PD/KEP.2018 by the Research Ethics Commission of Medical Faculty of Universitas Udayana/Sanglah General Hospital.

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AUTHORS CONTRIBUTION

Contribution of all authors stated on the contribution form.

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