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Role of Serotonin and Dopamine in Psoriasis: A Case-Control Study

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Abstract

BACKGROUND: Psoriasis is a chronic inflammatory disease mediated by the immune system with increased proliferation of keratinocytes. The exact cause is unknown but as a multifactor, such as infection, trauma and psychological stress have been thought to play a role in its pathophysiology. Dopamine and serotonin are believed to have a strong role in stress conditions and also directly play a role in psoriasis.

AIM: This study aimed to evaluate the role of dopamine, serotonin, and psychological stress in psoriasis.

METHODS: This study used a case-control design involving 30 patients with psoriasis (as a case group) and 30 healthy controls in the Dermatology and Venereology Polyclinic of Sanglah General Hospital Denpasar during the period December 2016 to February 2017. All samples were taken for venous blood examination serum dopamine and serotonin and analysed using the ELISA method. Statistical analysis using an independent t-test, partial correlation, receiver operator characteristic (ROC) curve, and logistic regression model.

RESULT: There were significant differences in serotonin, dopamine, and stress index levels between groups with psoriasis and non-psoriasis (102.68 ± 25.44 Vs. 154.17 ± 20.90; $p < 0.001$), (437.13 ± 164.83 Vs. 138.11 ± 89.51; $p < 0.001$), and (138.5 ± 27.80 Vs. 92.55 ± 42.97; $p < 0.001$). Significant negative correlation was found between serotonin level and stress index ($r = -0.366$; $p = 0.016$) and between serotonin and dopamine ($r = -0.634$; $p < 0.001$) but a positive correlation was found between dopamine and stress index ($r = 0.459$; $p = 0.042$). Serotonin and dopamine showed that it could be used as a biochemical predictive model for psoriasis (AUC > 0.7). Multivariable risk analysis model high serum dopamine was the most important risk factor for the occurrence of psoriasis (adjusted OR: 7.8; 95% CI: 3.45-15.57; $p = 0.024$)

CONCLUSION: Serotonin and dopamine have a significant role in the pathophysiology of the occurrence of psoriasis, and psychological stress can affect psoriasis through its influence on serotonin and dopamine.

Introduction

Psoriasis is an autoimmune chronic-residual skin inflammatory disease, characterised by hyperproliferation of keratinocytes with erythema plaques, hyperkeratosis, and silvery-coated scales — symmetrical distribution of predilection areas of the extensor, scalp, lumbosacral region. The exact cause is unknown but several predisposing factors such as genetics, environmental factors, trauma, infection, drugs and psychological stress [1], [2]. The prevalence of psoriasis is 2% of the world population, but in America and Canada, it is 4.6% and 4.7%. Whereas in Asia around 0.4-0.7% [1], [3]. The number of new cases of psoriasis in our center tends to be rising from years to years.

Currently, several studies prove psychological and neuroendocrine stress that can affect immune responses with clinical manifestations such as atopic dermatitis, alopecia, acne vulgaris, psoriasis, etc. Zangeneh and Fazeli found all stress hormones, catecholamines, corticotrophin releasing hormones (CRH), dopamine significantly increased in psoriasis. Interferon-gamma (IFN-γ) is a proinflammatory cytokine synthesised by T helper 1 cell (Th1), has been known to play a critical role in the pathogenesis of psoriasis. Psychological stressors lead to the dominant role of Th1 cells resulting in excessive IFN-γ synthesis [4], [5].

Dopamine is a neurotransmitter which

together with norepinephrine and epinephrine, is called catecholamine [6], [7]. Catecholamines function to regulate nerve function, neuroendocrine and immune systems. Dopamine can increase the activity of keratinocytes, which play a role in the release of cytokines and chemokines [7], [8]. Some studies show that cells in the immune system can be affected by dopamine. Dopamine agonists stimulate the production of interleukin (IL)-6 and IL-8, where IL-6 and IL-8 play a role in the proliferation and differentiation of epidermal cells, besides IL-8 also stimulates chemotaxis of neutrophils and promotes acute inflammation. In keratinocyte cells of psoriasis patients found a high level of IL-8 expression and high dopamine serum receptors and can result in autoimmunity [8], [9].

Serotonin (5 hydroxytryptamines; 5-HT) is a neurotransmitter whose effect is mediated through different receptor interactions and consists of 14 subtypes [10]. Serotonin is known as a neurotransmitter in the central nervous system and is involved in many processes including cognition and memory. In the other side, serotonin plays an essential role in vasoconstriction, heart rate in the cardiovascular and gastrointestinal systems [11]. Psychological stress can also reduce the synthesis of Serotonin and can affect many immunological processes and cause a decrease in proinflammatory cytokines such as tumour necrosis factor (TNF-α) [12], [13]. TNF-α plays an important role in the pathogenesis of psoriasis, selective activation of serotonin receptors with the 2,5-dimethoxy-4-iodoamphetamine antagonist (DOI) produces a strong blockade of pro-inflammatory cytokines such as the Interleukin-6 cytokine (Il-6) and Interleukin-1b (IL-1b), then DOI antagonist also prevents TNF-α so and increase IL-6 level. If there is a decrease in serotonin, there will be an increase in proinflammatory cytokines that form the basis of the role mechanism of the inflammatory process in psoriasis [11], [12], [13].

Based on this perspective, we would like to evaluate the role psychological stress causes a rise in dopamine and a decrease in serotonin reduction as a risk factor for psoriasis.

Material and Method

Study design and subject

The study used a case-control design that took place in the Dermatology and Venereology Polyclinics in Sanglah General Hospital Denpasar, Bali-Indonesia during the period December 2016 to February 2017. The case group consisted of new or old case psoriasis who had not received any systemic treatment or two weeks had stopped treatment. Control is a healthy person or does not suffer from other allergic skin diseases. The two groups after being informed were asked to sign the informed consent sheet. Socio-demographic characteristics such as age, gender, body mass index were recorded and also the clinical type of psoriasis, clinical form of psoriasis and severity were calculated by the Psoriasis Area Severity Index (PASI) [14]. Stress index was evaluated using questions from the Social Readjustment Rating Scale by assessing a live event from an index of 10 – 200 [15]. Both groups performed venous blood collection to examine serum dopamine and serotonin using the method ELISA.

Statistical analysis

Statistical analysis was performed using SPSS version 25.0 for windows. Partial correlation was used to find a correlation between stress index, dopamine level and serotonin level by controlling age, gender, and body mass index. Independent sample t-test or Mann Whitney U test was used to compare numerical variables such as serotonin serum, serum dopamine, and stress index in patients with psoriasis and non-psoriasis group. Receiver operator curve (ROC) analysis and risk analysis model using logistic regression were performed to determine the role of serotonin and dopamine in psoriasis. All tests were considered significant if the value of $p < 0.05$.

Result

Subject characteristics

There were no significant differences in sex, age, body mass index between patients with psoriasis and non-psoriasis group ($p > 0.05$). However, the group of people with psoriasis tends to have a family history of psoriasis (59%). In the case group (psoriasis person) there were more people with a moderate psoriasis category (44%) based on the PASI category, with clinical types of maculopapular (64%), and type I psoriasis (70%) (Table 1).

Table 1: Subject characteristics

Characteristics	Case (n = 60) Psoriasis	Control (n = 60) Non-Psoriasis	p-value
Gender (n, %)			
Male	48 (49%)	50 (51%)	0.058
Female	12 (54%)	10 (46%)	
Age (years) (Mean ± SD)	45.54 ± 11.2	46.21 ± 0.68	0.562
Family history of psoriasis			
Yes	20 (72%)	4 (28%)	0.003*
No	40 (44%)	26 (56%)	
BMI (n, %)			
High (> 25 kg/m^2)	32 (59%)	22 (41%)	0.063
Normal (≤ 25 kg/m^2)	28 (43%)	38 (57%)	
Type of Psoriasis (n, %)			
Type I	42 (70%)	-	
Type II	18 (30%)	-	
Psoriasis area severity index category (PASI) (n, %)			
Mild	20 (34%)	-	
Moderate	26 (44%)	-	
Severe	14 (22%)	-	
Clinical type of psoriasis (n, %)			
Maculo-papular	38 (64%)	-	
Gutate	16 (27%)	-	
Erythrodermic psoriasis	6 (9%)	-	

*Significant ($p < 0.05$).

Differences of stress index, serotonin level, and dopamine level between psoriasis and non-psoriasis group

There were significant differences in serotonin levels between groups with psoriasis (102.68 ± 25.44) and non-psoriasis (154.17 ± 20.90) ($p < 0.001$), a person with psoriasis had lower serum serotonin levels compared to a non-psoriasis person. There were significant differences in dopamine levels between groups with psoriasis (437.13 ± 164.83) and non-psoriasis (138.11 ± 89.51) ($p < 0.001$), a person with psoriasis had higher serum dopamine levels compared to non-psoriasis. There were significant differences in stress index between groups with psoriasis (138.5 ± 27.80) and non-psoriasis (92.55 ± 42.97) ($p < 0.001$), a person with psoriasis had a higher stress index compared to non-psoriasis (Table 2).

Table 2: Comparison of stress index, serotonin level, and dopamine level, between psoriasis and non-psoriasis group

Variable	Mean ± SD (Psoriasis)	Mean ± SD (Non-Psoriasis)	Mean differences	95% CI	p
Dopamine serum (ng/ml)	437.13 ± 164.83	138.11 ± 89.51	299.06	230.50-367.04	< 0.001
Serotonin serum (ng/ml)	102.68 ± 25.44	154.17 ± 20.90	51.49	39.14-63.82	< 0.001
Stress index	138.5 ± 27.80	92.55 ± 42.97	45.95	27.24-64.65	< 0.001

Correlation between stress, serotonin, and dopamine

A correlation test was carried out using partial correlation test by controlling the variables of age, sex, body mass index to determine the correlation between stress index, dopamine level, and serotonin level. There was a significant negative correlation between serotonin level and stress index ($r = -0.366$; $p = 0.016$), a significant negative correlation between serotonin and dopamine ($r = -0.634$; $p < 0.001$). This shows an inverse correlation between serotonin and dopamine and also between serotonin and stress index. However, there is a moderate positive correlation between dopamine and stress index ($r = 0.459$; $p = 0.042$), this indicates that the higher stress index will be followed by an increase in serum dopamine (Table 3).

Table 3: Correlation between stress index, dopamine level, and serotonin level after controlling for age, gender and body mass index

Variable	Stress Index		
	n	r (coefficient correlation)	p
Serotonin level	120	-0.366	0.016
Dopamine level		0.458	0.042
	Dopamine Level		
	n	r (coefficient correlation)	p
Serotonin level	120	-0.634	< 0.001

A predictive model of serotonin and dopamine as a biochemical marker in psoriasis

Predictive models were carried out using analysis of receiver operator characteristics curve (ROC) on serotonin and dopamine parameters in psoriasis and non-psoriasis groups as the dependent variable in this study. Serotonin and dopamine showed that it could be used as a biochemical predictive model for psoriasis (AUC > 0.7) (Figure 1).

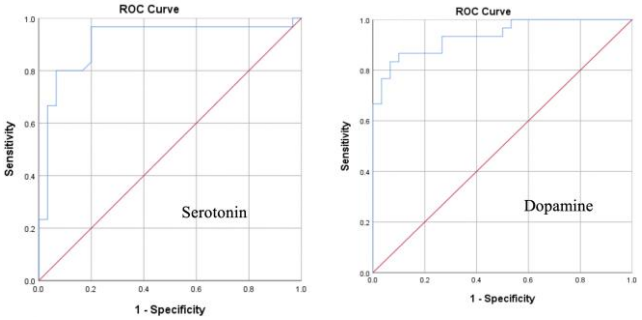

Figure 1: ROC analysis of serotonin (left) and dopamine (right) as a biochemical marker in psoriasis

Dopamine has sensitivity, specificity, and cut-off values of 87%, 90%, and 320 ng/ml respectively and serotonin has a sensitivity value of 94%, specificity of 64%, and a cut-off value of 141 ng/ml (Table 4).

Table 4: Area under the curve (AUC), cut-off value, sensitivity, and specificity of serotonin and dopamine in psoriasis

Parameter	AUC	95% CI	Cutt-off value	Sensitivity	Specificity	p
Serotonin	0.912	0.82-0.94	141 ng/ml	94%	64%	< 0.001
Dopamine	0.937	0.87-0.98	320 ng/ml	87%	90%	< 0.001

Risk analysis model for serotonin and dopamine in psoriasis

Risk analysis is based on the cut-off values of ROC of serum dopamine and serotonin, for serum dopamine values higher than 320 ng/ml classified as high dopamine serum levels, and lower ones are referred to as normal values. Then for serum serotonin, a value lower than cut off value is calcified as a low serum level, and a higher value is classified as normal.

Table 5: Risk analysis model of serotonin and dopamine level in psoriasis

Parameter		Univariable Model					Multivariable Model		
		Psoriasis	Non-Psoriasis	OR	95% CI	p	Adjusted OR	95% CI	P
		n (%)	n (%)						
Serotonin	Low	42 (70%)	14 (24%)	7.7	2.4-24.4	0.023*	5.4	2.23- 8.56	0.016*
	Normal	18 (30%)	46 (76%)						
Dopamine	High	50 (83%)	16 (27%)	15.6	4.7-30.8	0.019*	7.8	3.45- 15.57	0.024*
	Normal	10 (17%)	44 (73%)						

*Significant ($p < 0.05$).

In univariable risk analysis mode low serotonin level (OR: 7.7; 95% CI: 2.4-24.4; $p = 0.023$) and high dopamine levels (OR: 15.6; 95% CI: 4.7-30.8; $p = 0.019$) proved to be a risk factor of psoriasis. In a multivariable risk analysis model, high serum dopamine was the most important risk factor for the occurrence of psoriasis (adjusted OR: 7.8; 95% CI: 3.45-15.57; $p = 0.024$). People with high-level serum

dopamine have a risk of 7.8 times higher to develop psoriasis compared to a person who has low serum dopamine level (Table 5).

Discussion

It has been widely known that stress has a close relationship with immunity in the human body [16]. In general, chronic stress can dampen the adaptive immune system and also innate immunity (natural killer cell activity), increasing the proinflammatory cytokine cascade. This occurs through activation of the hypothalamus-pituitary-adrenal axis of the autonomic nervous system [12], [17]. It should be noted that the chronic increase in proinflammatory cytokines can act as a mechanism of feedback to the central nervous system (CNS) and have significant consequences on an individual's psychological well-being. In people with psoriasis, it is very common for a decrease in quality of life, depressed mood disorders, a tendency for a higher stress, social stigma, and problems in work caused by psoriasis itself. This condition makes psoriasis not something that is caused by immunology, but it is also characterised by an issue of mental disorders such as stress and depression [12], [16], [17].

Many studies have provided an increase in proinflammatory mediators in chronic stress disorders; these include increases in IL-1, IL-6, and TNF-α in the blood and cerebrospinal fluid [18], [19]. The proinflammatory cytokines in the central nervous system can affect the metabolism of monoamine neurotransmitters (dopamine, serotonin, and norepinephrine) which causes a decrease in availability, synthesis, and increased uptake of neurotransmitters that have a potential effect on inflammation and development of chronic stress into mood disorders [19]. Apart from that, proinflammatory cytokines such as TNF-α, IL-1, and IL-6 which are released by macrophages due to chronic inflammation and pro-inflammatory mediators produced by keratinocytes on the skin that experience psoriasis can reach the brain by penetrating the blood-brain barrier [12], [18]. Proinflammatory cytokines that have arrived in the brain will trigger a sickness behaviour (fatigue, fever, somnolence) which will then mediate the onset of depression and ongoing stress [10], [12]. Through this mechanism, it can be seen that stress affects inflammation and can trigger psoriasis as well as vice versa so that this will become a chain of never-ending circling pathophysiology [12], [20], [21]. It was also found in our study that stress correlated with dopamine levels which had a significant role in the occurrence of psoriasis.

Serotonin (5-HT) is a neurotransmitter involved in many regulatory processes in the body and biological functions, psychological processes in the CNS, and also the role of peripheral tissue [21], [22]. In vivo studies, serotonin plays a role in cell signalling, and modulation of the peripheral immune system includes T cells, mast cell macrophages, dendritic cells, and platelets [23]. Specifically, the receptors of serotonin are expressed in T cells, where the result of sensitisation is the release of proinflammatory cytokines because of the response of serotonin secreted by mast cells which binds to the 5HT-2 receptor [24]. The response also affects the maturation and proliferation of T cells. The ratio of Th1: Th2 is also affected by serotonin, a change in ratio <1 is associated with a higher risk of autoimmune disease. Serotonin receptors are also expressed in CD8 cells, monocytes, dendritic cells, mast cells [18], [25]. A decrease in serotonin will cause an increase in production of inflammatory mediators such as TNF-α, IFN-γ, IL-1β, IL-6, IL-8 which will carry out activation on nuclear factor-KB and induce activation of keratinocytes and trigger deterioration of keratinocytes and worsening of psoriasis symptom [13], [26], [27]. This is consistent with the findings of this study that low serotonin is a risk factor for psoriasis.

It is well known that skin diseases such as psoriasis and atopic dermatitis are strongly influenced by the incidence of stress and dopamine has a very close relationship in the configuration of stress. Dopamine is an important neurotransmitter in the central nervous system and locomotive control, cognition, emotion, immunology, and neuroendocrine secretion [21]. Study by Mori et al. in the mouse animal model (in-vitro) shows that the intervention of dopamine 1 (D1) receptor antagonist (SCH 23390) decreases the expression of IL-4, IFN-γ observed in 3-hour conditions (rapid phase immunological reactions) and 24 hours (slow phase immune reaction) on rat skin [28]. It can be seen that D1 like receptors are selectively expressed in Th2 cells, which suggests that dopamine can trigger the differentiation of Th2 cells. This indicates that D1-like dopamine receptor can induce degranulation of mast cells and trigger the release of proinflammatory cytokines. The role of dopamine in controlling Th2 cells in modulating the immune system is very important in psoriasis [5], [28]. In this study found a significant association between high dopamine levels as a risk factor for psoriasis.

The limitation in this study is that apart from psychological stress parameters, this study did not examine depression scale experienced in the study group, then the limited number of samples became a lack of generalisation to the population of the results of this study.

In conclusion, serotonin and dopamine have a significant role in psoriasis, and psychological stress can affect serotonin and dopamine levels which have an indirect effect on psoriasis. More detailed research on the biomolecular mechanism of the role of serotonin and dopamine using a larger number of samples is needed.

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