Adv Exp Med Biol - Clinical and Experimental Biomedicine (2020) 9: 83–88
https://doi.org/10.1007/5584_2019_470

Published online: 9 January 2020

Depression and Serum Content of Serotonin in Adult Patients with Atopic Dermatitis

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Abstract

Atopic dermatitis (AD) is a chronic skin disease with the etiology not yet conclusively established. Recent reports demonstrate the role of serotonin (5-hydroxytryptamine; 5-HT) in the pathogenesis of AD. The aim of this study was to investigate the relationship between the serum content of serotonin and depression in adult patients suffering from severe AD. There were 31 patients of the median age of 41 years enrolled into the study, who suffered from AD since childhood, and a control group that consisted of 14 healthy subjects. AD was diagnosed on the basis of Hanifin and Rajka criteria. The severity of skin lesions was assessed with the SCORing Atopic Dermatitis (SCORAD) index and that of depression with the Montgomery-Åsberg Depression Rating Scale (MADRS) questionnaire. We found that all of the patients with severe AD characterized by SCORAD >50 had depression. Depression was classified as mild and moderate according to the MADRS score. Serotonin content was significantly lower in the patients with severe AD (MADRS >12), and there was an adverse relation between the serotonin content and the score of depression, the features not noticed in the control group. We conclude that severe AD, as expressed by the intensification of skin lesions, associates with depression and with the lowering of serum serotonin content. The findings point attention to the cognitive and affective problems in AD patients which could worsen the course of the skin disease.

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Keywords
Affective symptoms · Atopic dermatitis · Depression · Serotonin · Skin lesions

1 Introduction

Atopic dermatitis (AD) is a chronic skin disease of yet unknown pathogenesis (Weidinger and Novak 2016; Leung and Guttman-Yassky 2014). From the epidemiological standpoint, there is a global increase in the prevalence of AD which now affects as much as 20% of the population in the developed countries. The prevalence of AD in Poland is estimated at 4% (Sybilski et al. 2015). Pruritus is the most conspicuous symptom that accompanies eczematous lesions, which are usually located in typical body regions, such as the extensor involvement in infants or children and flexural lichenification in adults (Hanifin and Rajka 1980). The disease results from complex genetic, epigenetic, environmental, and immunological interactions with an overlapping epidermal barrier defect (Nowicki et al. 2015).

Recently, a growing body of research has focused on the coexistence of AD and a number of other nonatopic conditions, such as skin infections, cardiovascular diseases, cancer, and, interestingly, mental disorders that involve depression and suicidal attempts (Brunner et al. 2017). The pathogenesis of depression is at present underlain by the monoaminergic hypothesis, in which dysfunction of serotonergic neurotransmission place a key role. The synthesis and release of monoamines is, to a great extent, influenced by inflammatory cytokines (Gałecki and Talarowska 2018). Recent reports have pointed attention to a key role of serotonin (5-hydroxytryptamine; 5-HT) also in the pathogenesis of AD (Rasul et al. 2016; Kawana et al. 2010; Lonne-Rahm et al. 2008). Therefore, the aim of this study was to examine the relationship between the blood level of serotonin and the severity of depression in adult patients suffering from AD.

2 Methods

This study was performed in a group of 31 adult patients (17 women and 14 men) of the median age of 41 years who had developed AD in childhood. The control group consisted of 14 healthy volunteers, gender- and age-matched. Basic characteristics of the groups are presented in Table 1. The diagnosis of AD was confirmed by a dermatologist and an allergist, according to the Hanifin and Rajka (1980) criteria. The severity of skin lesions was determined based on the SCORing Atopic Dermatitis (SCORAD) index, where score over 50 points indicates severe AD (SCORAD 1993). The lowest SCORAD result we found in this study was 50.4 points and the highest was 80.4 points (median of 61.5 points), pointing to the very severe disease. Exclusion criteria were as follows: lack of consent to participate in the study, age below 18 years, inflammatory comorbidities, mild-to-moderate severity of AD lesions, systemic therapy with immunosuppressive, antihistamine or psychotropic drugs, and phototherapy during 6 months preceding the study. The severity of depression was assessed with a validated Polish version of the Montgomery-Åsberg Depression Rating Scale

Table 1 Characteristics of the study groups

		Patients ($n = 31$)	Controls ($n = 14$)
Gender; *n* (%)	Male	13 (41.9)	8 (57.1)
	Female	18 (58.1)	6 (42.9)
Age (years); median (min-max)		41 (24–75)	42 (22–73)
Education; *n* (%)	Secondary	15 (48.4)	2 (14.3)
	Tertiary	16 (51.6)	12 (85.7)
SCORAD (points); median (min-max)		61.5 (50.4–80.4)	0.0

SCORAD SCORing Atopic Dermatitis index

Table 2 Severity of depression according to the Montgomery-Åsberg Depression Rating Scale (MADRS) in adult atopic dermatitis (AD) patients and control subjects

MADRS score	Depression	AD patients ($n = 31$)	Controls ($n = 14$)
0–11	None; *n* (%)	0	14 (100%)
12–19	Mild; *n* (%)	5 (16.1%)	0
20–29	Moderate; *n* (%)	26 (83.9%)	0

Table 3 Severity of depression according to the Montgomery-Åsberg Depression Rating Scale (MADRS) and severity of skin lesions according to SCORing Atopic Dermatitis (SCORAD) index in adult atopic dermatitis (AD) patients

		SCORAD	
Depression	Patients ($n = 31$)	Median (min-max)	*p*
Mild	5	52.2 (50.4–60.5)	0.002
Moderate	26	63.2 (52.4–80.4)	

Table 4 Severity of depression according to the Montgomery-Åsberg Depression Rating Scale (MADRS) vs. serum serotonin content in adult atopic dermatitis (AD) patients and in controls

	AD patients	Controls	
	Median (min-max)	Median (min-max)	*p*
MADRS (score)	24 (18–28)	4 (1–7)	<0.001
Serotonin level (ng/mL)	85.7 (45.0–110.3)	294.9 (220.4–394.5)	<0.001

(MADRS) (Montgomery and Asberg 1979). Blood for the 5-HT assessment was drawn from the elbow vein in both patients and control subjects between 7.00 and 9.00 a.m. The samples were left for clot for 2 h at room temperature and then were centrifuged at 3500 RPM for 10 min, frozen, and stored at −80 °C until use. The serum content of 5-HT was assayed using a commercial ELISA kit (R&D System, Minneapolis, MN).

Data were presented as medians and minimum-maximum values. The Kruskal-Wallis and Mann-Whitney U tests were used to compare differences between the serum 5-HT content and AD severity in the groups with mild and moderate depression. Relationships among these indicators were evaluated with Spearman's rank correlation coefficient. A p-value of <0.05 defined statistically significant differences. The evaluation was performed using a commercial StatSoft Statistica v13.1 package (Dell Software; Round Rock, TX).

3 Results

All of the AD patients had depression according to the MADRS scale as opposed to none of the controls (Table 2). A positive significant correlation was found between the severity of skin lesions and the severity of depression ($r = 0.64$, $p < 0.001$). Patients with moderate depression had a significantly higher SCORAD score compared to patients with mild depression ($p = 0.002$) as presented in Table 3.

The median blood serum content of 5-HT was 85.7 ng/mL (min-max: 45.0–110.3 ng/mL, $p < 0.001$) in the AD patients who had mild-to-moderate depression, whereas it was outstandingly higher in the control subjects with no depression (median: 294.9 ng/mL; min-max: 220.4–394.5 ng/mL) (Table 4). In this study we noticed no AD patients who would not have a degree of depression according to the MADRS scale (Table 2). There was no appreciable difference in the content of 5-HT depending on the severity of depression ($p = 0.54$) (Fig. 1).

4 Discussion

Contrary to a popular belief that atopic dermatitis is a childhood disease, the incidence of AD among adults is on the rise. In a recently

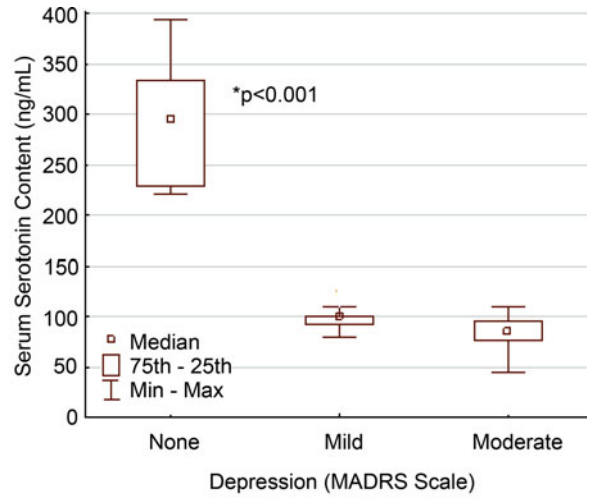

Fig. 1 Serum 5-HT level in atopic dermatitis patients with mild-to-moderate depression, according to the Montgomery-Åsberg Depression Rating Scale (MADRS), and in healthy control subjects without depression symptoms. The asterisk denotes a significantly higher 5-HT content in the control subjects when compared to AD patients with mild and moderate depression

published study of Barbarot et al. (2018) involving adult populations in the USA, Canada, Japan, and Europe, the disease was observed in 4.9% of adults. The literature abounds with research on the coexistence of AD and depression. A study by Cheng et al. (2015) conducted in a group of 8208 Taiwanese adolescents and adults revealed that AD is a risk factor for developing depressive disorders. Similar conclusions were reached by Wei et al. (2016), who have examined patients suffering from atopic diseases. The Northern Finland Birth Cohort study consisted of the observation of 12,058 children born in 1966 and followed up to the age of 31, with focus on the possible development of atopy. The study has revealed a threefold increase in the incidence of depression (hospitalized) in both men and women suffering from atopic diseases, with AD being diagnosed in 691 individuals (Timonen et al. 2001). In a Polish study of Chrostowska-Plak (2013) entailing 89 patients, significant relationships have been noticed between patient-reported pruritus, severity of depression (evaluated by the Beck questionnaire), and the impairment of quality of life (assessed by the Dermatology Life Quality Index). A study of Vinnik et al. (2017), which included 56 AD patients, has found a significant seasonal variation in the rate of depressive symptoms evaluated by the Hamilton Depression Scale. The results of the present study corroborated the previous observations in that the adult patients with AD are significantly more prone to depression. It is worth noting that severe AD and depressive symptoms were found in all of the patients investigated. Thus, the severity of AD dermatitis predisposes to the development of depression, which is consistent with the observations of other authors (Kim 2012). The risk of developing affective disorders by patients with AD apparently remains underrated, and the notion of "psychodermatological care", postulated in the recently published European guidelines for AD treatment, is marginalized (Wollenberg et al. 2018).

Serotonin (5-HT) is a highly hydrophilic biogenic amine derived from the exogenous amino acid tryptophan due to the action of decarboxylases. The main source of 5-HT are gastrointestinal cells, platelets, immune cells (lymphocytes, monocytes and macrophages), mast cells, and central nervous system neurons particularly the dorsal raphe nucleus (Herr et al. 2017; Kim 2012). After release, 5-HT is subjected to a reuptake mechanism underlain chiefly the serotonin reuptake transporter (SERT). High SERT expression is shown by enterocytes, platelets, and neurons of the central

and peripheral neural systems. Twenty-one subtypes of serotonin receptors (presynaptic and postsynaptic) are identified. They are structurally stratified into seven classes: 5-HT_1 (subtypes: 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1D}, 5-HT_{1E}, 5-HT_{1F}), 5-HT_2, 5-HT_3, 5-HT_4, 5-HT_5, 5-HT_6, and 5-HT_7. The main function of serotonin is neurotransmission (Kritas et al. 2014). The so-called serotonin concept of depression pathogenesis assumes a dampening of serotonin neurotransmission resulting from dysfunction of its receptors, particularly 5-HT_{1A} and 5-HT_{2A} (Carhart-Harris and Nutt 2017; Rasul et al. 2016).

The role of 5-HT in the pathogenesis of AD has been confirmed by Hosogi et al. (2006) and Rasul et al. (2013) who show this monoamine is responsible for histamine-independent pruritus occurring in AD lesions. In a study of Rasul et al. (2016) consisting of 28 patients (18 women and 10 men), expression of 5-HT, 5-HT_{1A}, and 5-HT_{2A} receptors, along with SERT, has been examined immunohistochemically in both lesional and non-lesional skin. The expression of 5-HT_{1A} and that of SERT were higher in lesional skin, whereas that of 5-HT_{2A} was higher in non-lesional skin. Furthermore, the severity of depression, assessed by MADRS, correlated positively with 5-HT_{1A} expression and adversely with 5-HT_{2A} expression. In non-lesional skin, expression of 5-HT_{2A} correlated positively also with disease severity, assessed by SCORAD.

5-HT plays a key role in communication between the immune and nervous systems due to its pleiotropic effect on various immune cells (Herr et al. 2017; Kim 2012), including modulation of T lymphocytes which largely contribute to the development of AD. Katoh et al. (2006) have shown that platelet-derived 5-HT, along with 5-HTR1 and 5-HTR7 receptors, induces the conversion of monocytes into dendritic cells which also play a role in the AD pathogenesis. Soga et al. (2007) have confirmed that 5-HT plays an essential part in activating monocytes and preventing their apoptosis. That study has also revealed a significantly higher serum 5-HT content in 11 patient suffering from AD (SCORAD = 37 points) when compared to the control subjects. A role of 5-HT in the pathogenesis of AD is also confirmed by reports on the efficacy of serotonin reuptake inhibitors in treatment of this disease (Eskeland et al. 2017; Ständer et al. 2009). However, it is difficult to relate those findings to the present observations due usually to a limited number of patients in the previous studies, lower severity of skin lesions, and a lack of the assessment of depression.

In conclusion, this study demonstrates that the severity of skin lesions and pruritus in adult atopic dermatitis correlated with the intensity of depressive symptoms. Moreover, a significant decrease in 5-HT serum content was noticed in AD patients when compared to healthy control subjects. We conclude that it is advisable to monitor the affective and cognitive brain function in patients suffering from AD. Depression if unnoticed could lead to otherwise treatable exacerbation of the skin condition.

Conflicts of Interest The authors declare no conflicts of interest in relation to this article.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study was approved by the Bioethics Committee of the Medical College of the Jagiellonian University in Cracow, Poland.

Informed Consent Informed consent was obtained from all individual participants included in the study.

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