ORIGINAL ARTICLE

SERUM LEVELS OF IL-2 AND IL-17A ARE RELATED TO CLINICAL TYPE AND SEVERITY OF ALOPECIA AREATA

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ABSTRACT

The aim: To check the link between interleukins serum levels (IL-2, IL-10, IL-17A) and alopecia areata (AA) development, severity, and clinical course.

Materials and methods: Totally 104 patients with AA and 30 matched control individuals were enrolled in the study. The serum levels of IL-2, IL-10, and IL-17A were evaluated in all participants. Severity of Alopecia Tool (SALT) was used to assess the AA severity. The SPSS 22.0 and Python environment were used for statistical analysis.

Results: The comparative analysis has demonstrated that the serum levels of IL-2 and IL-17A in AA patients are higher than in controls ($P = 0.008$ and $P = 0.013$, respectively). The blood level of IL-2 in patients with AA depends on disease severity ($P = 0.006$) and clinical subtype ($P = 0.016$). The serum concentration of IL-17A was also associated with AA severity ($P = 0.010$) and subtype ($P = 0.004$). The positive correlation between SALT score and serum level of IL-17A ($r = 0.33$, $P = 0.001$) and IL-2 ($r = 0.28$, $P = 0.004$) was revealed. The strong positive correlation between IL-17A and IL-2 was also detected ($r = 0.49$, $P < 0.001$). There was no link between AA occurrence, manifestation and IL-10 amount. However, the weak negative correlation between SALT and IL-10 serum level was revealed ($r = -0.20$, $P = 0.042$).

Conclusions: Our findings demonstrated that the serum levels of IL-2 and IL-17A are intercorrelated and associated with AA development, severity, and clinical type. The link between IL-10 serum level and AA was not detected.

KEY WORDS: alopecia areata, interleukin, SALT, serum, Th1, Th17

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INTRODUCTION

Alopecia areata (AA) is a relatively common chronic inflammatory disease characterized by the injury of the hair follicles. AA leads to non-scarring hair loss not only on the scalp, but also on the face and other areas of the skin surface [1]. The nail plate affect is also observed in some AA patients [2].

To date, there are considerable evidences that AA develops due to autoimmune reaction against hair follicles [3]. The numerous studies revealed that the loss of the follicle immune tolerance in AA patients is associated with dysfunction and imbalance of the various T-lymphocytes subsets, including T-helper 1 cells (Th1), T-helper 2 cells (Th2), T-helper 17 cells (Th17), and T-regulatory cells (Treg) [4-7]. It is assumed, that these cells, as well as T-cells secreted cytokines, are the main contributors to AA pathogenesis.

AA is a tissue-specific disease, however the increased blood levels of various cytokines and chemokines are often observed in AA patients. The results have shown that blood IL-2 concentration is significantly higher in patients with AA than in relatively healthy individuals [8-10]. Along with this, Kasumagić-Halilovic et al. [11] revealed no link between serum level of IL-2 and AA clinical type and duration. Also, Tabara et al. [12] did not find relation between IL-2 blood content and AA occurrence in children.

In recent years, much attention to study the role of Th17-derived cytokines, including IL-17A, in AA development has been paid. Various researchers demonstrated that AA patients have elevated blood level of IL-17A compared to AA-free people [10, 12-14]. Morsy et al. [15] also revealed that Narrowband-Ultraviolet B treatment of patients with AA results in decrease of IL-17A serum concentration. However, the significant correlation between serum IL-17A and disease severity was not established.

IL-10 is one of the main Treg-derived cytokines. Gautam et al. [10] found the increased serum content of IL-10 in patients with AA. While the number of other researchers did not find a significant difference in blood concentration of IL-10 between AA patients and matched controls [8, 9]. In addition to the mentioned cytokines, many studies have shown the varying degrees of association between AA occurrence and blood amount of IL-1, IL-6, IL-15, IL-18, IL-12, TNF-α, IFN-γ [16-18]. Also, Katagari et al. [19] found the overproduction of IL-4, IFN-γ and TGF-β1 mRNA in peripheral blood mononuclears of patients with AA. Moreover, the association between gene polymorphisms of some cytokines and their receptors (IL-12, IL-16, IL-17, IL-23, IL-23R) and AA development has been established in various populations [20-23].

To date, many articles devoted to association between the cytokines blood levels and AA occurrence have been published. However, the most results are often contradictory and require further meta-analysis. In addition, there is not enough convincing data on the correlation between

the blood concentration of cytokines in AA patients and clinical course of disease. This would make it possible not only to improve diagnostics, but also to more accurately predict the outcome and treatment effectiveness.

THE AIM

The aim of our study was to check the possible link between interleukins serum levels (IL-2, IL-10, IL-17A) and AA development, severity and clinical course.

MATERIALS AND METHODS

Current case-control and cross-sectional study included 104 patients with AA (58.7 % female and 41.3 % male; average age – 35.7 ± 8.9 years) and 30 matched healthy control individuals (53.3% female and 46.7 % male; average age – 37.4 ± 7.9 years). Patients were treated in the clinical base of the Dermatovenerology department of Sumy State University (medical center «Eledia», Sumy, Ukraine, government license № 597170) and in the Medical clinical center of infectious diseases and dermatology named after Z. Krasovitsky (Sumy, Ukraine). The diagnosis of AA was established on the basis of the clinical and instrumental examination in accordance with the International guidelines for diagnosis and treatment of alopecia areata [24, 25].

Most patients had active stage of AA (86.5%), 13.5% patients had stationary stage (disease duration in all subjects did not exceed 10 months). Family history of AA was detected in 10.8% patients. Severity of Alopecia Tool (SALT) score [25] was used to assess the AA severity. Only patients with S1 (scalp affect area <25 %), S2 (scalp affect area 25%-50%) and S3 (scalp affect area 51%-74%) severity without body involvment and nail lesions were included in the study. The mean SALT score for all AA patients was 25.7 ± 14.2. Also, patients were divided into subgroups according to type of hair loss. Single form (1 patch) was detected in 43.3 % patients, multiple form (< 4 patches) – in 38.5 % patients, and sub-totalis form (> 4 patches) – in 18.3 % patients. The clinical, instrumental and laboratory examination was performed before the start of any treatment.

The principles of Helsinki Declaration and Order of the Ministry of Health of Ukraine № 690 were followed. The study was approved by the Commission on bioethics of Sumy State University. Each participant signed a voluntary written consent before the study.

The detection of IL-2 serum concentration was based on Sandwich-ELISA (Enzyme-linked Immunosorbent Assay) method using Human IL-2 (Interleukin 2) Kit (Elabscience, Wuhan, China) according to manufacturer's instructions. The duplicate evaluation of samples was done. Blood level of IL-10 was measured using IL-10 direct ELISA Kit (Enzyme immunoassay for the quantitative direct determination of IL-10 in human serum and plasma, IBL International GMBH, Hamburg, Germany). The absorbance of each well was measured at 450 nm. The level of IL-17A in blood serum was measured using Human IL-17A ELISA Kit (Enzyme-linked Immunosorbent Assay for quantitative detection of human IL-17A, Invitrogen, Carlsbad, CA, USA) according to manufacturer's protocol. All samples were evaluated in duplicate. Absorbance was measured at 450 nm.

The software program SPSS 22.0 (Chicago, IL, USA) was used for the most statistical analysis. The normality distribution was tested by Shapiro-Wilk method. Continuous data in the manuscript are presented as Mean ± SD. Independent Student's t-test for unpaired samples was used to compare mean values between AA patients and control subjects. The frequencies comparison between two groups was performed by Pearson's chi-squared test. One-way ANOVA with Bonferroni post-hoc test were used to determine the differences of cytokines levels between three subgroups stratified by AA severity and clinical subtype. The correlation analysis was performed by two tailed Pearson's test. The heatmap was created in Python environment (version 3.7) using seaborn package. The P-value of < 0.05 was set as significant threshold for all statistical tests.

RESULTS

The description of the control and AA groups are shown in Table I. Mean age, gender ratio and smokers number did not differ between control and AA patients ($P > 0.05$). At the same time, the serum levels of IL-17A and IL-2 in patients with AA were significantly higher compared to relatively healthy individuals ($P = 0.008$ and $P = 0.013$, respectively). In contrast, the serum concentration of IL-10 in AA patients was lower than in controls, but no statistical difference was found ($P = 0.109$).

The serum level of interleukins in AA patients with different disease severity are presented in Table II. Analysis using ANOVA showed that the blood amount of IL-17A depends on the AA severity ($P = 0.010$). According to post-hoc test the serum IL-17A level in patients with S1 severity was significantly lower than in S3 patients ($P = 0.012$). At the same time, there was no difference between S1 and S2 ($P = 0.290$), and between S2 and S3 ($P = 0.217$). It was found that the blood concentration of IL-2 in patients with AA also depends on the disease severity ($P = 0.006$). The results of the post-hoc analysis were the similar. Thus, in patients with S1 severity, the serum level of IL-2 was significantly lower compared to patients with S3 severity ($P = 0.007$). There were no differences between S1 and S2 ($P = 0.255$), and between S2 and S3 ($P = 0.166$). The significant effect of the alopecia severity on the blood content of IL-10 was not established, either using ANOVA or after the pairwise comparison ($P > 0.05$).

The overall pattern of assessing the link between AA clinical subtype and serum cytokine levels was similar to the results of the previous analysis (Table III). It was found that the IL-17A amount depends on the AA subtype ($P = 0.004$). Thus, in patients with single AA, the serum concentration of IL-17A was significantly lower than in patients with subtotalis form ($P = 0.002$). But there was no difference between single and multiple alopecia ($P = 0.437$), and between multiple and subtotalis alopecia ($P = 0.082$). The content of IL-2 in the blood also depended on the number of alopecia patches ($P = 0.016$). The serum level of IL-2 in patients with single AA was lower compared to individuals with AA subtotalis ($P = 0.013$). At the same time, no difference was found between single and multiple forms ($P = 0.479$), and between multiple and subtotalis AA types

Pairs			P-value
SALT	–	IL-17A	0.001
SALT	–	IL-2	0.004
SALT	–	IL-10	0.042
IL-17A	–	IL-2	< 0.001
IL-17A	–	IL-10	0.360
IL-2	–	IL-10	0.117

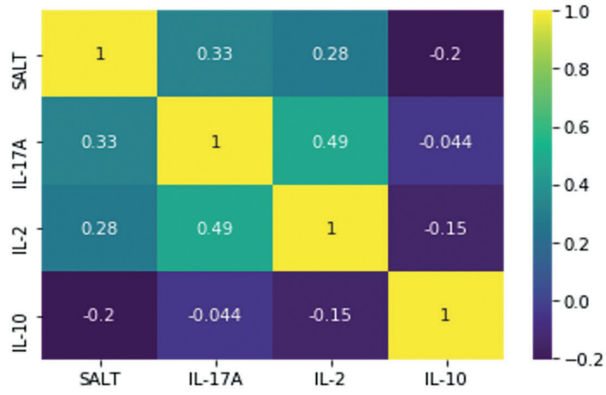

Fig. 1. Correlation analysis between interleukins serum level and SALT score. The P-values and heat map with correlation coefficients are presented.

Table I. Characteristics of controls and alopecia areata patients

Parameter	AA n = 104	Control n = 30	P
Age, years	35.7 ± 8.9	37.4 ± 7.9	0.361
Female, (%)	61 (58.7)	16 (53.3)	0.604
Male, (%)	43 (41.3)	14 (46.7)	
Smokers, (%)	32 (30.8)	7 (23.3)	0.430
IL-17A, pg/ml	9.927 ± 5.063	7.185 ± 4.272	0.008
IL-2, pg/ml	28.528 ± 13.225	21.855 ± 10.995	0.013
IL-10, pg/ml	8.683 ± 3.758	9.986 ± 4.339	0.109

Notes: n – number of individuals; AA – alopecia areata.

Table II. Serum level of interleukins in alopecia areata patients depending on the severity

Cytokines	S1 (n = 58)	S2 (n = 36)	S3 (n = 10)	P
IL-17A, pg/ml	8.853 ± 5.016	10.592 ± 4.984	13.763 ± 3.443	0.010
IL-2, pg/ml	25.609 ± 12.831	30.296 ± 13.073	39.100 ± 10.124	0.006
IL-10, pg/ml	9.285 ± 3.737	8.074 ± 3.630	7.389 ± 4.034	0.165

Notes: n – number of individuals; S – severity of alopecia areata based on SALT score.

Table III. Serum level of interleukins stratified by clinical subtype of alopecia areata

Cytokines	Single (n = 45)	Multiple (n = 40)	Subtotalis (n = 19)	P
IL-17A, pg/ml	8.502 ± 4.593	10.042 ± 5.356	13.059 ± 4.179	0.004
IL-2, pg/ml	25.138 ± 13.344	29.081 ± 12.363	35.397 ± 12.455	0.016
IL-10, pg/ml	9.201 ± 3.797	8.778 ± 3.734	7.257 ± 3.541	0.167

Notes: n – number of individuals.

(P = 0.240). No significant association of AA clinical form with serum IL-10 level was found (P > 0.05).

The correlation between the SALT score and the serum interleukins levels in patients with AA was also analyzed (Figure 1). The significant positive correlation between SALT score and blood concentration of IL-17A (r = 0.33, P = 0.001) and IL-2 (r = 0.28, P = 0.004) was detected. The significant correlation was also found between the SALT score and IL-10 blood amount, wherein the relation was negative (r = -0.20, P = 0.042). Regarding the correlation between the serum levels of various interleukins in AA patients, the strong positive correlation was found between IL-17A and IL-2 (r = 0.49, P < 0.001). Figure 1 presents the heat map displaying the values of all obtained correlation coefficients.

DISCUSSION

IL-2 is glycosylated globular protein mainly secreted by activated Th1 cells. This lymphokine acts on T, B, NK cells and monocytes, stimulating their growth, development and subsequent differentiation [26]. In addition, IL-2 plays an important role in the control of Treg cells [27]. The over-pro-

duction of IL-2 mRNA was detected in affected skin biopsies of the AA patients [28].

The results of our work showed that the serum level of IL-2 in patients with AA is significantly higher compared to control individuals. Similar results were also obtained by Barahmani et al. [8] and Tembhre et al. [9]. Wherein, Tabara et al. [12], studying the content of various pro-inflammatory cytokines in the peripheral blood of children with AA, demonstrated that blood level of IL-2 in sick children was within normal limits despite the changes in IFN-γ, IL-6, IL-15 and IL-17 concentration.

Our results also revealed that serum level of IL-2 depends on the severity and clinical type of alopecia. The positive correlation between IL-2 blood concentration and SALT score was also observed. Thus, we have shown that the more severe AA is associated with higher serum level of IL-2. Kasumagić-Halilovic et al. [11] also checked the relation between serum IL-2 and AA clinical course. However, the results showed that the IL-2 level does not depend on the AA duration, clinical type and severity. At the same time, Gautam et al. [10] demonstrated that blood IL-2 concentration in patients with extensive AA is significantly higher than in patients with localized AA. Moreover, the authors showed a strong positive correlation between IL-2 and SALT score ($r = 0.673$).

IL-17A is one of the most famous members of IL-17 lymphokines family produced by Th17 cells. Its involving in the response to external pathogens invasion as well as in the development of autoimmune tissue injury has been shown [29]. Recently, Tanemura et al. have identified the presence of $CD4^+IL\text{-}17A^+$ Th17 cells around the hair follicles of scalp dermis in patients with AA [4].

Our results have shown a close association between IL-17A serum level and AA development, which has been revealed in many previous studies [10, 13, 14], including the study of alopecia areata in children [12]. Also, the association between IL-17A serum amount and AA severity and clinical type was detected in our work. In addition, it was shown that the blood concentration of IL-17A in patients with alopecia positively correlates with the SALT score and level of serum IL-2. Thus, our results showed that the blood amount of IL-17A is higher in those patients with alopecia, in whom this disease is more severe.

Morsy et al. [15] found a significant negative correlation between serum IL-17A level and SALT index in AA patients. However, before the treatment, there was no significant correlation between IL-17A and SALT score. The results of the study by El-Morsy et al. [30] showed that the concentration of IL-17A in the blood correlates with the age of AA patients and the age of disease onset. At the same time, the correlation between IL-17A and clinical manifestations of AA (SALT score, severity, clinical subtype) was non-significant.

Atwa et al. [14] showed that serum level of IL-17A in AA patients with S3-S5 severity as well as in AA patients with multiple and totalis subtype is significantly higher compared to patients with S1 severity and single alopecia, respectively. In addition, Gautam et al. [10] found that the blood level of IL-17A in patients with AA is positively correlated with AA severity, SALT score ($r = 0.416$) and blood level of IL-2 ($r = 0.359$).

IL-10 is known to be a lymphokine with potent anti-inflammatory properties. The dysfunction of IL-10 is linked with an increased risk of various autoimmune conditions [31]. It has been shown that IL-10 pathway within Treg cells is necessary for inhibition of Th17 cell-mediated inflammation [32]. Moreover, Hamed et al. [6] revealed the deficiency of FOXP3+CD39+ T regulatory cells in affected skin of patients with AA.

We have not established the association of IL-10 serum level with AA development, severity and clinical type. Although a weak, but significant negative correlation between IL-10 and SALT score was identified. At the same time, the blood amount of this cytokine in AA patients was not correlated with the level of IL-2 and IL-17A.

Most studies also did not reveal the relation between IL-10 blood level and AA occurrence [8, 9]. Only Gautam et al. [10] showed that the serum concentration of IL-10 in patients with AA is significantly higher than in relatively healthy people. However, the link between IL-10 and the AA severity, SALT score and serum levels of other cytokines in patients with AA was not revealed.

There are limitations in our work that should be mentioned. Only the small number of cytokines have been evaluated in blood serum of AA patients. While the blood level of other cytokines such as IL-6, IL-12, IL-15, IL-22, IFN-γ etc. have not been detected. Patients with S4 and S5 alopecia severity, as well as patients with totalis, universalis and ophiasis form of disease were not enrolled in our study. In addition, the effect of treatment on the serum levels of various cytokines in patients with AA has not been studied.

CONCLUSIONS

Thus, it was revealed that levels of IL-2 and IL-17A in blood serum is associated with AA. In addition, it was shown that the blood levels of IL-2 and IL-17A are intercorrelated and depend on the severity and clinical type of AA. There was no link between the serum IL-10 concentration and AA development and clinical course.

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Conflict of interest:

The Authors declare no conflict of interest.

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