

STATE OF ENDOGENOUS INTOXICATION IN PATIENTS WITH ALOPECIA AREATA

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ABSTRACT

State of endogenous intoxication in patients with alopecia areata

Objective. To study the state of endogenous intoxication and the characteristics of the body mycobiota in patients with alopecia areata.

Materials and methods. A total of 42 patients with alopecia areata aged 7 to 34 years were examined. All patients underwent clinical, trichoscopic, biochemical, immunological and mycological investigations. The degree of endogenous intoxication was assessed using erythrocyte sorption capacity (ESC) and the level of medium-molecular-weight peptides (MMWP). Mycological examination of body biosubstrates was performed by culture-based methods. Specific IgG antibodies to *Candida albicans* and total IgE were determined by enzyme-linked immunosorbent assay. The control group consisted of 31 practically healthy individuals.

Results. Patients with alopecia areata showed signs of endogenous intoxication, characterized by a significant increase in erythrocyte sorption capacity to $39.5 \pm 0.4\%$ versus $26.8 \pm 0.3\%$ in the control group ($p < 0.001$), and in the level of medium-molecular-weight peptides to 0.37 ± 0.006 extinction units versus 0.24 ± 0.007 extinction units, respectively ($p < 0.05$). Fungi of the genus *Candida* were detected in 39 (92.8%) of 42 examined patients, predominantly in the intestine (69.2%). Among the isolated species, *Candida krusei* (43.6%), *Candida albicans* (28.2%), *Candida tropicalis* (23.1%) and *Candida glabrata* (12.8%) predominated. A significant increase in the level of specific IgG antibodies to *Candida* and total IgE was established, indicating the formation of mycogenic sensitization. Statistically significant correlations were identified between the indicators of endogenous intoxication and the level of colonization by *Candida* fungi.

Conclusions. In patients with alopecia areata, endogenous intoxication syndrome develops and is accompanied by disturbances of the body mycobiota and a high frequency of colonization by *Candida* fungi. The formation of *Candida*-associated intestinal dysbiosis and mycogenic sensitization may contribute to the maintenance of chronic inflammation and may participate in the pathogenesis of the disease. The obtained findings substantiate the need for a comprehensive assessment of mycobiota status and endogenous intoxication in patients with alopecia areata.

KEYWORDS: alopecia areata, focal alopecia, endogenous intoxication, mycobiota, *Candida*, *Candida*-associated dysbiosis, erythrocyte sorption capacity, medium-molecular-weight peptides, IgG, IgE.

INTRODUCTION

Alopecia areata (AA) is one of the most complex and clinically variable immune-inflammatory dermatoses [1, 2]. Despite the long history of research into this disease, issues related to early prediction of disease severity, factors contributing to chronicity and the selection of pathogenetically justified therapy remain unresolved [3].

According to current concepts, alopecia areata is an organ-specific autoimmune disease based on the collapse of hair follicle immune privilege and activation of cytotoxic T lymphocytes. IFN-gamma, IL-15, IL-2 and the JAK-STAT signaling pathway play leading roles in its pathogenesis [2, 4]. However, an exclusively immunological concept does not fully explain the pronounced clinical heterogeneity of the disease, differences in the rate of progression and variability of response to therapy [1, 3, 4].

In recent years, the concept of the gut-skin axis has been actively developing; according to this concept, the state of the microbiota and mycobiota has a substantial influence on the systemic immune response [5, 6]. Dysbiotic changes may promote activation of innate immunity, increased production of pro-inflammatory cytokines and maintenance of a chronic inflammatory process [7, 8].

Endogenous intoxication is one of the important pathogenetic factors. An increase in the level of medium-molecular-weight peptides and changes in erythrocyte sorption capacity reflect the accumulation of toxic metabolites and may contribute to the persistence of chronic inflammation [9, 10].

Objective

To assess the state of endogenous intoxication and the characteristics of the body mycobiota in patients with alopecia areata.

MATERIALS AND METHODS

A total of 42 patients with alopecia areata aged 7 to 34 years were examined. There were 19 males (45.2%) and 23 females (54.8%).

According to clinical forms of the disease, the patients were distributed as follows: focal alopecia was diagnosed in 22 (52.4%) patients, subtotal alopecia in 8 (19.1%), total alopecia in 7 (16.6%) and universal alopecia in 5 (11.9%) patients. According to disease duration, patients were distributed as follows: up to 1 year in 9 (21.4%) patients, from 1 to 5 years in 14 (33.3%) and more than 5 years in 19 (45.2%) patients.

All patients underwent clinical, trichoscopic, biochemical, immunological, mycological, and statistical investigations. Mycological examination of body biosubstrates (oral mucosa, skin and intestinal contents) was performed by culture-based methods using Sabouraud media and chromogenic nutrient media. Specific IgG antibodies to *Candida albicans* and total IgE were determined in blood serum by enzyme-linked immunosorbent assay using commercial test systems (Vector-Best, Russia).

The degree of endogenous intoxication was assessed using erythrocyte sorption capacity (ESC) and the level of medium-molecular-weight peptides (MMWP). ESC was determined by the method of A.A. Togaybayev et al. (1988), and the MMWP level was determined by the method of N.I. Gabrielyan et al. (1981) [11, 12].

The control group consisted of 31 practically healthy individuals of corresponding age.

All patients were examined by related specialists: an internist, an endocrinologist and an infectious disease specialist.

RESULTS

The results of biochemical blood testing in patients with alopecia areata indicated the development of endogenous intoxication syndrome. This was manifested by a significant increase in erythrocyte sorption capacity (ESC) and the level of medium-molecular-weight peptides (MMWP) compared with the indicators of the control group.

The mean ESC value in patients with AA was $39.5 \pm 0.4\%$, whereas in the control group this indicator was $26.8 \pm 0.3\%$ ($p < 0.001$), corresponding to a 1.5-fold increase. The MMWP level was also significantly higher and amounted to 0.37 ± 0.006 extinction units versus 0.24 ± 0.007 extinction units in the control group ($p < 0.05$) (Table 1).

Table 1. Indicators of endogenous intoxication in patients with AA (M ± m)

Groups	Erythrocyte sorption capacity (%)	Medium-molecular-weight peptides (extinction units)
Main group of patients with AA N=42	$39.5 \pm 0.4^*$	$0.37 \pm 0.006^{**}$
Control group N=31	26.8 ± 0.3	0.24 ± 0.007

Note: significance of differences compared with the control group: * - $p < 0.001$; ** - $p < 0.05$.

These data indicate the accumulation of toxic metabolites in the bodies of patients, which may support chronic inflammation and immune disturbances [9, 10, 13].

Mycological characteristics of the examined patients

According to the results of mycological examination, fungi of the genus *Candida* were detected in 39 of 42 examined patients, which accounted for 92.8% of cases. In the control group, *Candida* fungi were detected in only 2 (6.5%) examined individuals. The obtained results are consistent with current concepts regarding the role of the intestinal mycobiota and *Candida* fungi in the formation of immune imbalance and chronic inflammation [7, 8, 14].

Candida fungi were most often isolated from intestinal contents, in 27 (69.2%) patients. They were detected on the oral mucosa in 12 (30.7%) patients and on the scalp skin in only 1 (2.6%) patient. Simultaneous detection of *Candida* fungi in the intestine and oral cavity was noted in 11 (28.2%) patients (Table 2).

Table 2. Detection rate of *Candida* fungi in body biosubstrates of patients with AA

Groups	Skin	Oral mucosa	Intestine
Main group N=39	1 (2.6%)	12 (30.7%)	27 (69.2%)*
Control group N=31	0	1 (3.2%)	1 (3.2%)

Note: * - significance of differences compared with healthy individuals ($p < 0.05$).

Among the identified species, the following were most common: *Candida krusei* in 17 (43.6%) patients; *Candida albicans* in 11 (28.2%); *Candida tropicalis* in 9 (23.1%); and *Candida glabrata* in 5 (12.8%).

It should be noted that the highest frequency of *Candida* detection was observed in patients with the progressive stage of the disease. At the same time, the colonization level often exceeded 10^3 CFU/g, which may indicate disruption of intestinal microbial balance. Clinically, these changes were accompanied by complaints of gastrointestinal discomfort, periodic abdominal bloating and a tendency to constipation.

When clinical forms of the disease were analyzed, *Candida* fungi were most often detected in patients with focal alopecia, in 19 of 39 examined patients (48.7%).

Immunological indicators

The enzyme-linked immunosorbent assay results showed a significant increase in the level of specific IgG antibodies to *Candida* fungi and total IgE in patients with AA compared with healthy individuals.

The concentration of IgG to *Candida* was 1.4 ± 0.05 pg/mL versus 0.06 ± 0.008 pg/mL in the control group ($p < 0.05$). The total IgE level was increased more than threefold and amounted to 150.7 ± 1.2 IU/mL versus 47.2 ± 1.7 IU/mL in healthy individuals ($p < 0.05$).

Increased levels of specific IgG antibodies to *Candida* and total IgE indicate the formation of mycogenic sensitization of the body [15, 16].

Table 3. Indicators of specific IgG antibodies to *Candida* and total IgE in patients with AA

Indicator	Patients with AA N=42	Healthy control group N=31
IgG to <i>Candida</i> , pg/mL	$1.4 \pm 0.05^*$	0.06 ± 0.008
IgE, IU/mL	$150.7 \pm 1.2^*$	47.2 ± 1.7

Note: * - significance of differences compared with healthy control individuals ($p < 0.05$).

Correlation analysis

The performed correlation analysis revealed statistically significant relationships between indicators of endogenous intoxication, immunological parameters and the level of colonization by *Candida* fungi.

A direct correlation was established between the level of specific IgG and the presence of *Candida tropicalis* ($r = +0.8$) and *Candida glabrata* ($r = +0.4$). An inverse correlation was found for *Candida albicans* ($r = -0.3$).

In addition, indicators of endogenous intoxication were associated with the level of colonization by *Candida* fungi. For individual fungal species, both direct and inverse statistically significant correlations with ESC and MMWP were observed ($p < 0.05$), confirming the involvement of the mycobiota in the formation of endotoxemia in patients with alopecia areata.

DISCUSSION

The obtained results indicate that patients with alopecia areata show signs of endogenous intoxication accompanied by changes in the body mycobiota and a high frequency of colonization by *Candida* fungi.

Increased ESC and MMWP indicators reflect accumulation of metabolic products and impaired detoxification processes.

At the same time, the high frequency of detection of *Candida* fungi, predominantly in the intestine, as well as increased levels of specific IgG and total IgE, may indicate the formation of chronic mycogenic sensitization.

The identified correlations between indicators of endogenous intoxication and colonization by *Candida* fungi allow us to suggest the involvement of *Candida*-associated intestinal dysbiosis in the pathogenesis of alopecia areata [7, 8, 14-16].

CONCLUSIONS

1. In patients with alopecia areata, signs of endogenous intoxication were identified, characterized by a significant increase in erythrocyte sorption capacity and the level of medium-molecular-weight peptides.
2. *Candida* fungi were detected in 92.8% of examined patients, predominantly in the intestine, indicating a high prevalence of mycobiota disturbances in this category of patients and the development of *Candida*-associated intestinal dysbiosis.
3. Patients with alopecia areata showed a significant increase in the levels of specific IgG antibodies to *Candida* and total IgE, indicating the formation of mycogenic sensitization.
4. Statistically significant correlations were established between indicators of endogenous intoxication and colonization by *Candida* fungi, which makes it possible to consider mycobiota disturbances as one of the factors involved in the pathogenesis of the disease.
5. The obtained data substantiate the advisability of a comprehensive assessment of mycobiota status and endogenous intoxication in patients with alopecia areata in order to optimize therapeutic and preventive measures.

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