Section A -Research paper

"MICROINFLAMMATION" AND "MICROFIBROSIS" IN THE PATHOGENESIS OF ANDROGENETIC ALOPECIA.

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Summary :

The article presents the results of the study of "microinflammation" and "microfibrosis" in the pathogenesis of androgenetic alopecia. We examined 85 males with androgenetic alopecia aged 18 to 41 years. In a study of 85 people, 20 (23.5%) patients with androgenetic alopecia had the demodex folliculorim mite, and 51 (60%) patients with androgenetic alopecia had Propionibacterium spp.

The conducted studies have proved the great role of "Propionibacterium spp" and "Demodex folliculorum" in the formation of an inflammatory infiltrate around the hair follicles, parameters of extracellular matrix activity - in "microfibrosis" in the pathogenesis of androgenetic alopecia.

Today, hair loss is becoming a common complaint of patients in dermatological clinics and is about 8% of the total population of people with dermatological pathology. One of the most common causes of hair loss is androgenic alopecia, which dramatically reduces the quality of life, since appearance occupies a significant place and, if not observed, can lead to

psychological maladaptation. It has been proven that dihydrotestosterone, penetrating follicle cells, launches a cascade of reactions that lead to higher cytokine products, mainly TGF β β and 2 (1,2,3). Cytokines contribute to the onset of the vehlen phase and the generation of aging signals for hair papilla cells (11). As a result, dystrophy of hair follicles occurs and, as a result, degradation of hair follicles. The regression of hair follicles is also due to the fact that the vessels of the capillary hair channel of the scalp in predisposed persons show increased sensitivity to androgenes, in particular to dihydrotestosterone, as well as to enzyme 5a-reduktase. As a result, a vascular spasm occurs, the power of the hair follicle is impaired, and as a result, baldness (Gevorgyan M.A. et al. 2017) (4.5.6).

It should be noted that recently there has been an increase in diseases caused by opportunistic flora, which can be associated both with an imbalance between macro and microorganism, and within the bacterial association. Volosy follicle is a microorgan that has not only its own system for regulating the hair growth cycle, but is subject to various exogenous factors. It is known that the normal microflora of the skin of the scalp is represented by staphylococci, propion bacteria and yeast of the genus Malassezia, which are in symbiosis with macroorganism, forming a stable ecosystem, however, the transformation of some saprophytic forms into pathogens leads to the development of dermatoses.

Presumably, perifollicular inflammation can be the cause of some cases of androgenic alopecia according to the masculine type, which to some extent do not respond to minoxidyl. The inflammatory process is probably the initiator of the local change in hormone metabolism in the event of androgenic alopecia. Extensive studies have been conducted on the likely role of Demodex folliculorum as an agent causing a inflammatory process. Penetrating into the greasy glands of hair follicles, the demodex causes an immune response and inflammation of the surrounding tissues. Thanks to a long intrusion, the parasite depletes the hair follicle and shifts the hair cycle from anagen to the telogen (7.8.9).

So, in 1992, Jaworsky in research showed that inflammatory infiltrate in the upper third of hair follicles, represented by activated T cells and macrophages, is associated with thickening of the hair shells and an increase in the pool of collagen. In 1993, Whithing demonstrated that in 40% of cases of androgentic alopecia in men, perifollicular inflammation and fibrosis are detected. Further world research was aimed at delimiting the term "microphevation" with androgentic alopecia and classical inflammation during scar alopecia (2000 Mahe).

This suggests that some representatives of the transit flora, such as Propionibacterium sp.; Staphylococcus sp.; Malassezia ovalis may be involved in this complex inflammatory process. The presence of porphyrins produced by Propionibacterium sp. in a sawnoid duct is observed in 58% of patients with androgen alopecia who are able to induce the production of the chemotactic factor of the (C5), being a possible cofactor of initial inflammatory stress in hair follicles. Propionibacterium sp. synthesizes many enzymes that destroy the off-cell matrix (gialuronatliase) and the orohovite shell (endoglycoceramidase, silidase), heat shock proteins that activate the congenital immune system, and other enzymes involved in metaborilism. Porphyrins released from Propionibacterium sp. activated by ultraviolet light with the formation of active forms of oxygen, which, in turn, can contribute to the inflammation of follicles through a cascade of a compliment.

The inflammatory process also develops due to the reaction of keratinocytes to chemical stress, pollutants, UV radiation, and even mechanical stress. Not only radical forms of NO oxygen, prostaglandins and histamine are developed, but also stored intracellularly by IL-1a. This phase of inflammation often leads to remodeling of the tissue in which collagenases, such as matrix metal prostheinases (MMP-9 MMP-8) play a leading role. Thus, it is assumed that collagenases contribute to the so-called « perifollicular fibrosis » by « preparation » fabric matrix and basal membranes for macrophages and T-cell adhesion. Another factor, such as monocytic chemotoxic protein (MCP-1), makes a huge contribution to organ fibrosis in the experimental inflammation model. Since it was discovered that MCP-1, along with other chemokines, is expressed in man's hair follicles in vitro, as well as in eckrin ducts of greasy glands in vivo, their active participation in the progression of perifollicular fibrosis during androgenic alopecia (12.13) has been proven.

Purpose of the study: To study the factors « microinflammation » and «microfibrosis » in the pathogenesis of androgenic alopecia.

Research materials and methods: 85 males with androgenic alopecia aged 18 to 41 were examined. The distribution of patients with androgenic alopecia, depending on the duration of the pathological process, showed that the main number of people seeking consultation with dermatologist are patients with a duration of the disease from 1 year to 5 years - 51.6%, as well as up to 1 year – 24.8% and from 5 to 10 years – 23.6%. The results of hormonal testing for testosterone showed its increase in blood concentration in only 4% of patients with

androgenic alopecia. Patients noted stressful situations (62%), chronic nose and throat diseases (43%), and hormonal drugs (28%). The control group consisted of 20 healthy people, representative by gender and age. All patients with androgenic alopecia were given a video-dermatoscopic examination of the skin of the scalp using the Aramo-SG (Korea) with lenses X60 and X200, and the Trichoscience diagnostic program. The main detail of the study is a phototrichogram, which allows you to differentiate androgenic alopecia from other forms of alopecia.

According to the clinical specific classification (BASP) androgenic alopecia in 36 (42.3%) patients, type C2-C3 was recorded, in which hair loss was noted in the frontal and temporal areas of the scalp. In 26 (30.5%) patients with androgenic alopecia, the M3 type was observed, in which pronounced bald spots were observed in the frontal-temen region, and in 23 (27.2%) patients registered U1, in which the fusion of the bald head of the frontal and parietal regions was noted, only the intact hair of the occipital region of the scalp remained. A characteristic feature of the phototrichogram of patients with androgenic hair loss, carried out in the parietal zone, was an increased amount of velus hair and thin hair (more than 45%).

A study of the phases of anagen and telogen in male patients with androgenic alopecia showed a highly reliable decrease in the amount of hair in the anagen phase and an increase in the amount of hair in the telogen stage in the parietal region, while the ratio of the phases of growth and peace in the occipital regions was not reliable with the type C2-C3 and was reliably reduced with the types M3 and U1. So, in patients of type C2-C3 androgenic alopecia (tab.1) the amount of hair in the growth stage in the parietal region was 58.4 ± 3.1%, type M3 - 41.7 ± 1.1%, type U1 - 32.1 ± 0.8%, while in the control group this indicator was 87.1 ± 4.3%. In parallel, the amount of hair at the rest stage increased from 41.6 ± 1.8% with a type C2-C3, 58.3 ± 2.4% with a type M3 to 67.9 ± 2.0 with a type U1.

Table 1.

The ratio of hair in the stages of anagen and telogen on the scalp in male patients with androgen alopecia

Hair Follicle Cycle Phases (%)		control group (n=20)	Types of androgenic alopecia		
			C2-C3 (n=36)	M3 (n=26)	U1 (n=23)
parietal area	anagen	87,1±4,3	58,4±3,1***	41,7±1,1***	32,1±0,8***
	telogen	12,9±1,9	41,6±1,8***	58,3±2,4***	67,9±2,0***
Occipital zone	anogen	85,4±3,9	81,7±1,1	79,2±3,2	72,1±1,8***
	telogen	14,6±2,3	18,3±2,4	20,8±1,4*	27,9±2,5***

Note: * - differences regarding the data of the control group are significant (* - P < 0.05, - P < 0.01, * - P < 0.001)

Results and discussion: In our study of 85 people, 20 (23.5%) patients with androgen alopecia recorded the tick demodex folicularum, which is a mandatory human octoparasite and lives in saline-hairy units and has immunoactive lipase, which may be responsible for inflammation induction. Subsequently, prolonged invasion by the demodex of hair follicle causes an immune response, depletion of hair follicle and, ultimately, a shift in the cycle of the hair cycle from the anagen phase to the telogen. And so, in 15% of patients with androgenic alopecia, 1-3 « Demodex folliculorum » was noted in sight, in 30% - from 3 to 5, in 55% - more than 5.While the persons of the control group did not have 80% of the presence of this type of tick, and only 10% - from 1-3, in 10% - from 3-5 in the field of view (tab.2).

Table 2.

« Demodex folliculorum » in patients with androgenic alopecia

Activity «Demodex folliculorum », in sight

Activity «Demodex folliculorum», in slide	Control group (n=20)	Group of patients with androgen alopecia (n = 20)
0	16 (80%)	-
1-3	2 (10%)	3 (15%)
3-5	2 (10%)	6 (30%)
More than 5	-	11 (55%)

From 85 people in 51 (60%) patients with androgenic alopecia . was registered Propionibacterium spp, which produce extracellular coprophyrins and contribute to the formation of biofilm with S.aureus express on the surface. This leads to an inflammatory process. Formed bacterial biofilms show great resistance to antibiotics, off-cell enzymes (for example, produced by neighboring bacteria) and adaptive immune response.

Table 3.

« Propionibacterium spp. » in patients with androgenic alopecia

Activity «Propionibacterium spp». КОЕ/см2	Control group (n=20)	Group of patients with androgen alopecia (n = 51)
10-21	14 (70%)	-
22-35	5 (25%)	4 (7,8%)
36-50	1 (5%)	19 (37,3%)
More than 51	-	28 (54,9%)

In our study, in patients with androgenic alopecia, in 7.8% of cases, « Propionibacterium spp » from 22-35 KOE / cm2 was microscopically noted, in 37.3% - 36-50 KOE / cm2, in 54.9% - more than 51 KOE / cm2. Similar studies in

the individuals of the control group showed the presence of « Propionibacterium spp » in 70% of cases from 10-21 KOE / cm2, in 25% - 22-35 KOE / cm2, in 5% - 36-50 KOE/cm2 (tab 3).

Jinghong Huang, Yuping Ran used light microscopy to monitor hair root morphology. Morphological observations were also carried out in positive samples using scanning electron microscopy and translucent electron microscopy. The high-performance sequencing method was used to identify fungal microecology of hair roots in different areas. In addition, using PCR, a comparison of the Malassezia fungal load in different groups and on the skin of the head was checked. Hair root fungi observed using optical microscopy are mainly Malassezia yeast. The positive Malassezia in the hair loss group (60%) was higher than in the control group (40%). Malassezia's detection efficiency with scanning electron microscopy was higher than with light microscopy. Malassezia had a positive correlation with the frequency of androgen alopecia (20).

Demodex Ticks has immunoactive lipase, which may be responsible for inflammation induction. or, possibly, prolonged demodex of hair follicle causes an immune response, depletion of hair follicle and, ultimately, shear of the cycle of the hair cycle from the anagen phase to the telogen (21.22).

Studies of the following scientists showed that when examining 54 patients with androgenic alopecia, they showed that in 53 of 54 cases, the demodex was found in the skin of the scalp: Europeans - 40 (+), 32 (-) for demodex, African-Americans - 9 (+), 9 (-), Hispanics - all 5 (+ and Asian cases - all 4). A total of 87.3% of cases with androgenic alopecia were positive for the demodex (23.24).

A study of the concentration of matrix metal prostheinase inhibitors (TIMP1) as a pathogenetic factor of microfibrosis in patients with androgenic alopecia showed a reliable decrease in its level compared to the same indicators of the control group. So, with C2-C3 type, the concentration of TIMP1 was 2.01 ± 0.18 pg / ml ($P < 0.001$), with M3 type - 1.49 ± 0.022 pg / ml (P 1TA/ml ($P < 0.001$).

Table 4.

The concentration of tissue activity of testosterone and the inhibitors of matrix metalproteinasein the blood of male patients with androgen alopecia.

Biological molecule (pg/ml)	Control group (n=20)	types of androgenic alopecia		
		C2-C3 (n=36)	M3 (n=26)	U1 (n=23)
Matrix Metal Proteinase Inhibitors (TIMP)	3,7±0,09	2,01±0,18***	1,49±0,022***	0,88+0,054***

Note * - differences regarding the data of the control group are significant (* - $P < 0.05$, *** - $P < 0.001$) Biological molecules (pg / ml)

A study of the concentration of matrix metal proteinase inhibitors (TIMP1) in patients with androgenic alopecia showed a reliable decrease in its level compared to the same indicators of the control group. So, with an M3 type, the concentration of TIMP1 was 2.01 ± 0.18 pg / ml ($P < 0.001$), with C2-C3 type - 1.49 ± 0.022 pg / ml (/ml ($P < 0.001$). In the control group, the same indicator was 3.7 ± 0.09pg / ml (tab. 4).

In our study, the reliably low TIMP1 rates for androgen alopecia are associated on one side, apparently with the observed oxidative stress in the extracellular matrix and the inflammatory process, in which the selection of active forms of oxygen occurs in parallel with a decrease in the level of TIMP1 and, accordingly, an increase in the level of matrix metal proteinase. On the other hand, an increase in the receptor sensitivity of cell membranes to steroids, occurring with an increase in the level of heat shock proteins, is accompanied by a change in the level of growth factors, as a result of which there is a decrease in the concentration of their inhibitors – TIMP1, and, as a result, an increase in matrix metal proteinase that changes the metabolism of the connective tissue of hair follicles and subsequently leads to atrophy of the latter.

The study of the activity of matrix metal proteinase was studied by many scientists. In particular, French scientists have found that cytokine and EGF-induced activation of MMP-9 (10) in the lower epithelial department of human hair follicles is the main mechanism by which hair follicle can be injected, observed during alopecia. California scientists have found that the β-catenin independent wnt path stimulates the polarization of newly attached T cells on the surface of the base membrane, while the transmission of signals of the β-catenin-dependent wnt path regulates the expression of MMP. In the absence of a wnt

signal, T cells cannot activate the expression of the MMP and, therefore, cannot cross the base membrane and penetrate inflammatory tissue. Therefore, the manipulation of wnt T-cell signal transmission can later be used as a control of the activity of matrix metal proteinase and the inflammatory process (25).

In another study, 37% of cases of androgenic alopecia had a certain degree of inflammation and fibrosis. Whiting in histopathological research showed that there is perifollicular lymphogistiocytic inflammation in 30% of cases of androgenic alopecia and in 10% of control entities, in addition, in another study of Whiting et al., Only 55% men with androgenic alopecia and microinflammation responded to minoxidil. It was less than the percentage of patients (77%) without signs of inflammation.

Therefore, it is entirely possible that perifollicular microinflammation can cause some cases of male-type androgenic alopecia that do not respond to the (18.19). In Young JW, Conte ET studies, one of the most important factors in the etiology of androgen alopecia is various inflammation activators. Fifty percent of the scalp samples of patients with androgenic alopecia had inflammatory infiltrate from mononuclear cells and lymphocytes. In the Abell study, 70% of patients and 30% of control entities had inflammation and perifollicular fibrosis (14.15.16.17).

Conclusions: The studies have proven a large role in «Propionibacterium spp» and « Demodex folliculorum » in the formation of inflammatory infiltrate around hair follicles, the activity parameters of the extracellular matrix in « microfibrosis» in pathogenesis of androgenetic alopecia. Given the above data, in the treatment of androgenic alopecia, it is necessary to sanitize the microbial flora of the scalp and apply measures that reduce the formation of atrophy around hair follicles.

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