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## CORRELATION ANALYSIS OF HORMONE-IMMUNE INTERACTIONS IN PATIENTS WITH DEMODICOSIS

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**Annotation.** *The paper finds and specifies scientific data on the status and relationship of hormonal and immune systems in demodicosis as well as defines their role in the disease pathogenesis. We have proved reliable correlations between the level of circulating hormones in blood and the key indices of cellular and humoral immunity in demodicosis. We have also discovered a disorder of normal relationships and the emergence of new correlations between hormonal and immunological parameters.*

**Keywords:** *demodocosis, cellular immunity, humoral immunity, correlation analysis, hormonal system, reliable relationship.*

**Topicality.** The important role of Demodex mites in the development of acne and acne-like dermatitis that are characterized by an expressed polymorphism of clinical manifestations, due to the development of inflammatory and noninflammatory lesions on the skin areas rich in sebaceous glands has been actively discussed during the recent decades [1, 17].

The pathogenesis of demodicosis has not been sufficiently studied. Uncontrolled reproduction of Demodex mites is explained by some authors as due to the weakening of the immune mechanisms and endocrine disorders [2]. A number of studies have shown that demodicosis occurs and persists against the background of pathological conditions caused by central hyperandrogenism [3]. A number of researchers believe that the presence of these parasites in the sebaceous hair follicles of the facial skin is the main cause of rosacea [4; 5; 16]. At the same time, demodicosis is sometimes believed to be an independent disease, but in the International Classification of Diseases X demodicosis is not presented as a separate nosologic form that reflects the idea of only provocative actions of the mite in the development of acne-like dermatoses [6; 7].

The skin is actively involved in the metabolism of steroid hormones, and most of the functions of the skin (the intercellular lipid synthesis, hair growth, mitotic activity of the epidermis) are influenced by androgens [16]. Under the influence of the enzyme 5-reductase testosterone turns into its more active metabolite — dihydrotestosterone. Increased androgen and enzyme activity in the puberty leads to the fact that inactive sebaceous glands start producing sebum. Secretion of fat depends on many factors: the ambient temperature, the patient's age, menstrual cycle, biological rhythm [8; 9].

The pathogenesis of demodicosis includes an increased production and changes in the composition of sebum, due to the peculiarities of metabolism and function of the sebaceous glands controlled by androgens [10]. Such changes during the puberty are due to an increased sensitivity of androgen receptors of the sebaceous glands to male sex hormones, often under normal physiological composition and levels of androgens in blood [16]. However, in some patients demodicosis occurs and persists on the background of pathological conditions caused by central hyperandrogenism [11]. Many re-

searchers emphasize that sustainable progress of demodicosis can support background diseases, its persistence after the puberty is possible under the influence of additional trigger factors [18] that are important to detect during the examination. At the same time, the algorithms of examinations of adolescents with demodicosis is insufficiently covered in the literature.

Most authors indicate that the prevalence of demodicosis among young people is about 90% in boys and 80% in girls aged under 21 years [12]. The incidence peak of the disease was observed in 14–16 year-old girls and 16–17 year-old boys [13]. Demodicosis development leads to a severe psychological trauma that deranges the social adaptation of teenagers. In numerous special psychological studies many authors note that 38% of 13–16 year-old adolescents have psychological disorders due to demodicosis [16].

We know that the overstrain of regulation systems can lead to a depletion of the host defenses, reducing its functionality. A prolonged exposure to any parasitic infestation, including demodicosis, as a stress factor, may lead to activation of hormonal regulation while maintaining the adaptive capacity of the body can be a pathogenetic basis of various functional disorders and injuries at lower adaptive capacity [14; 17].

Adapting to different destructive factors occurs at all levels of the body, but its mechanism is mainly manifested by changes in the hypothalamic-pituitary-adrenal system [15]; however the adaptation and adaptive response of the body in parasitic invasions including demodicosis have not been studied. Therefore, we must further study the role of hormone-immune regulatory system with demodicosis in terms of forming the economic and parasitic relationships, deepening the knowledge of the demodicosis pathogenesis as well as substantiate the therapy and increase the treatment efficacy.

**Objective.** To evaluate the changes and to analyze the hormonal and immunological relationships based on gender and functional state of the liver in patients with demodicosis.

**Materials and methods.** To perform the tasks we examined 109 patients with demodicosis aged 20 to 60 years (63 men and 46 women) who were on outpatient examination and treatment. For comparison and control we examined 20 healthy individuals of corresponding sex and age. Diagnosis "demodicosis" in all patients of the group and its absence in the control group was confirmed according to diagnostic criteria based on the totality of clinical, clinical and laboratory parameters and of laboratory tests for demodicosis. Criteria for inclusion: the experimental group included patients with reliably diagnosed "demodicosis" in the acute stage, ranging from 14 to 30 days after obtaining their informed consent.

The clinical examination was conducted on patients by using a conventional technique that included some data of carefully collected history, subjective and objective data, laboratory findings (blood count, urinalysis, blood chemistry, analysis of stool for helminth eggs and protozoa, immune status) and instrumental study (fluoroscopy or chest radiography, electrocardiography, ultrasound of internal organs).

Statistical analysis of the results of research was carried out using the software package "STATISTICA" for Windows (Stat Soft Inc, USA) on a computer with processor Pentium II Celeron 850 PPGA. In some cases the method of statistical analysis

using criterion  $\chi^2$  (2x2 contingency tables) was applied. Assuming that the average value of many of the studied parameters were within normal limits we applied a more informative way for such cases — the analysis of the incidence of disorders in values. A disorder was considered a deviation from the value from the average normal values which equals 2 (standard deviation).

**Results.** The study involved 109 patients with demodicosis aged 20 to 60 years (average age  $37,7 \pm 0,18$  years). There were 63 (57.7%) men and 46 (42.2%) women. To eliminate mixed helminth infestations, all patients were examined for antibodies to the antigens of ascarides, lamblia, opisthorchiasis and trichinella using ELISA. All the patients observed were taken feces samples on helminth eggs — see the section "Materials and Methods".

The duration of demodicosis on the day of examination, according to the information obtained from the patients ranged from several months to 2-15 years or more, in most cases the patients were not sure about the start of infestations.

The examination of patients with demodicosis was conducted by a detailed survey and a thorough checking up. It allowed revealing even minor symptoms that do not immediately attract attention, and patients did not think them to be important.

The history of stages of secondary sexual characteristics obtained from the patients did not allow an accurate assessment of the sequence and timing of their occurrence. However, a number of the patients, without being pretty sure, reported that the debut of puberty in them manifested with sexual body hair, which indicates hyperandrogenism starting with the puberty.

The male patients did not show an irregular sequence of secondary sex characteristics development in their history (development of external genitalia, pubic body hair, that in the armpits, hair growth on the face, Adam's apple, voice mutation).

While being examined before the treatment, the patients complained a lot about itching, burning, tightening skin, reducing the elasticity and softness, feeling some drilling into the skin or parasites crawling under it and so on. All the patients complained about increased sebaceous excretions.

During the clinical examination 30.4% (14 people) of patients were diagnosed with progressing hirsutism 39.1% (18 people) with android body type and 15.2% (7 people) with excessive height. The examination did not reveal any pronounced signs of virilization of external genitalia.

17.4% (8 persons) of patients had a combination of atrophic stretch marks and excessive body hair. 23.9% (11 people) of patients had no signs of hypertrichosis or hirsutism but they had stretch marks, and 19.6% (9 people) of girls with hirsutism or hypertrichosis had no stretch marks. These data suggest a variety of dishormonal manifestations of demodicosis in patients. The largest group consisted of patients with combined clinical forms of androgen dermatopathies — 76.0% (35 people). 32.6% (15 people) had hirsutism, 10.8% (5 people) — signs of alopecia by male pattern, 4.6% (10 people). —follicular hyperkeratosis on the extensor surfaces of the extremities.

While examining the men we found some signs of androgenetic alopecia in up to 95% of them.

Due to the preconceived idea about the role of the liver in the metabolism of hormones, the existence of a functional relationship between the pituitary gland and the liver, and taking into account data on the development of the hypothalamic-pituitary dysfunction in the liver, the patients were divided into 2 groups: the 1<sup>st</sup> group included the patients without manifestations of functional disorders of the hepato-biliary system, and the 2<sup>nd</sup> one consisted of patients with liver dysfunction (LD).

Moderate changes in blood gonadotrophin hormones rate and pronounced changes in the content of sex hormones indicate some disorders of pituitary-gonadal relations in demodicosis. A significant increase in estradiol and the testosterone decline in men, a decrease in estradiol and their testosterone increase in women without marked changes in the content of LH and FSH and clinical manifestations of impaired sexual function may be the outcome of disorders in the degradation of estradiol, testosterone aromatization and their mutual transformation observed during the liver dysfunction. The quantitative evaluation of identified quality ratios of the content of gonadotropin and sex steroid hormones in the blood by pair correlations showed that the functional relationship between these hormones in patients with demodicosis changed significantly. The structure of relationships in patients with demodicosis both men and women differed from the controls and was different in patients without LD and those with LD. In men without LD the correlation of hormones decreased significantly and the structure of the relationships changed. Among the relationships, which were found in the control group, only one remained reliable- the testosterone-estradiol. Instead of other correlations, present in healthy men, patients with demodicosis without LD had a "new" one-LH-estradiol. In patients with LD there were no reliable correlations.

In women without LD the level of hormone relationships also declined and their structure changed. The connection LH-estradiol remained stable like in healthy women, although the level of their relationship was lower than the normal one. The bonds between LH-progesterone, estradiol and testosterone got disintegrated. There were two "new" pairs instead, — LH-FSH and FSH- estradiol. The bond LH-estradiol remained relatively high in patients with LD and a new correlation — FSH-testosterone appeared. There were no other correlations between gonadotropin and sex hormones in women with LD.

These data show that a decrease in strength and changes in the structure of correlations were more pronounced in men than in women who did not have clinical and laboratory findings for LD. The bonds in patients with LD underwent even more significant changes, indicating more pronounced hormonal disintegrations.

Heterogeneity of changes in hormone concentration in the blood of patients with demodicosis before the treatment is indicative of their adaptive-compensatory nature. The identified hormonal changes during demodicosis were caused probably not only by the presence of a parasite in the body, but also by a number of other reasons, including the pituitary-gonadal dysfunction and disorders in pituitary- hepatic bonds developing with increasing duration of the disease.

Currently, there are a lot of data showing hormonal and neuro-humoral control of the formation and functioning of immuno-competent cells, which are summarized in several monographs [16; 17].



In healthy people, all the hormones influence the immune response, and this influence is provided by the receptors on the immunocompetent cells to all the hormones with no exception [13].

To get a real idea of the role of the pituitary-gonadal system in the implementation of demodicosis influence on the formation of the immune response, we evaluated the complex of correlations between the rate of circulating hormones in the blood and immune basic values under chronic infestation action. In order to make the initial conditions as typical as possible, we performed a correlation analysis of hormonal and immunological parameters in men with demodicosis.

The information about correlations is presented in table 1


Table 1.


**The structure of the hormonally immunological connections in patients with demodicosis**

Hormone	Immunity											
	1						2					
	Tl	Ok	VI	IgA	IgM	IgG	Tl	Ok	VI	IgA	IgM	IgG
galactopoietic hormone						-0,66					00,50	
LH		-0,44		00,63	-0,62		00,46	-0,51				
FSH	-0,37	00,32							00,43			
estradiol			00,33		00,37							
testosterone											00,55	
progesterone	-0,31			00,34					00,30	00,34		

Note:

- 1 — patients with normal liver function;
- 2 — patients with liver dysfunction

 — reliable connection —  $1,0 \geq r \geq 0,42$  ( $P \leq 0,01$ )

 — moderate connection —  $0,42 \geq r \geq 0,30$  ( $P \leq 0,05$ )

It was established that the correlations of hormone- immunological parameters before the treatment of patients without clinical manifestations of LD (group 1) were characterized by the presence of 3 strong connections with the correlation coefficient more than 0.54, a less strong but reliable connection with the correlation coefficient more than 0.42 and less than 0.54 ( $P < 0.05$ ) and 6 moderate connections with the correlation coefficient below 0.42 and more than 0.30 ( $P > 0.05$ ). In total, the patients of group 1 had 4 reliable connections before the treatment, 3 pairs of which reflected the relationship between the pituitary hormones and immunoglobulins.

The patients with LD (group 2) had one strong and 4 less strong reliable connections, 4 of which reflected the relationship of pituitary hormones, and one — the relationship between testosterone and immunological parameters. There were also 2 moderate connections.

There were mainly positive connections between the hormones and immunological parameters which were indicative of some commonality of systems aimed at preserving defense reactions and homeostasis.

Apart from the quantitative changes there were also qualitative ones in system interconnections. Correlations between pituitary hormones and immunological parameters in patients of group 1 were reliably stronger than in the second group ( $x_2 = 6.23$   $P < 0.01$ ).

The presence of reliable connections between the pituitary hormones and the values of immunity in patients from the 1<sup>st</sup> and 2<sup>nd</sup> groups before the treatment allows us to consider it as one of the main mechanisms in the effects of tropic pituitary hormones on the immune response.

The papers of recent years found that tropic pituitary hormones can change the functional activity of immunocompetent cells, affecting these cells both indirectly through the peripheral gland hormones and directly too. This possibility is due to specific membrane receptors on these cells to almost all pituitary hormones. In addition, the regulatory action of galactopoietic hormone is determined by regulatory cells of the thymus [16].

Now it has been proved that sex hormones influence the immune system actively [17].

It has been established by experiments that the effects of sex steroid hormones on the immune system, like other hormones, are dose-dependent and depend on the type of hormones too. For instance, we know that estrogen and progesterone in physiological doses stimulate the function of B cells and phagocytic activity of macrophages and inhibit the function of T-suppressors [15]. The estrogens are believed to stimulate an antigen-dependent differentiation and cooperation of T- and B-lymphocytes. According to some researchers androgens do not cause such effects, and according to others the testosterone reduces suppressively the activity of T — and B cells [12].

Considering the controversy of published data, the difference in the immunological effects of various hormones of pituitary-gonadal system and the lack of relevant research on demodicosis, we carried out a correlation analysis between the concentration of hormones of the pituitary-gonadal system in the blood and parameters of cellular and humoral immunity in men and women with demodicosis without clinical manifestations of LD.

The data on correlations between hormonal and immunological parameters are shown in Fig. 1.

It has been established that the structure of interconnections in men before the treatment was characterized by the presence of 3 significant correlation pairs. There was no reliable connection with the peripheral hormones. The women had 4 reliable connections before the treatment, including 3 with LH and 1 with progesterone.

A comparative evaluation of the correlation analysis between men and women showed that the number of reliable hormonal and immunological connections women before the treatment was greater than in men. There was not any reliable connection between hormones and T- and B-lymphocytes in the men before treatment, and the women had a reliable connection between LH and progesterone and those of cellular and humoral immunity.

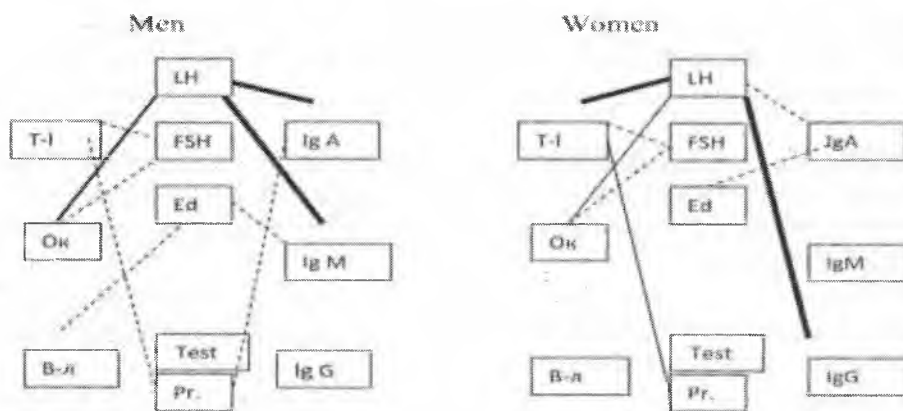


Fig. 1. The structure of the correlations between hormones of the pituitary-gonadal system and immune parameters in patients with demodicosis

Value:  
 strong connection —  $1,0 \geq r \geq 0,54$  ( $P \leq 0,01$ )      **—————**  
 less strong connection —  $0,54 \geq r \geq 0,42$  ( $P \leq 0,05$ )      **-----**  
 moderate connection —  $0,42 \geq r \geq 0,30$  ( $P \geq 0,05$ )      **.....**

These data show rather convincingly that the structure of relations between the pituitary-gonadal hormones and immunological parameters differ significantly by gender.

There is not any reliable connection between immunological parameters and progesterone in men, unlike women. There was not any connection with estradiol regardless of the gender.

These data conclude that a different degree of correlations was depended not only on the level of hormones and immunological parameters, but also on the type of sex hormones.

The lack of correlations between estradiol and immunological parameters shows that these mechanisms are not essential in regulating immunogenesis. It is suggested that sex steroids depending on the dose can cause both stimulating and inhibitory effect not only acting directly through the receptors of relevant cell populations, but also by changing the activity of the thymic epithelial cells.

Various fractions of estrogens are known to produce different effects. It is believed that estradiol is not directly involved in immunological process a lot, but it does not prevent its development. In excess, this hormone in the body inhibits the host immunosuppressor effect of testosterone.

**Conclusions.** Thus, evaluating the results of the analysis, the nature and characteristics of correlations between the pituitary hormones and those of peripheral endocrine glands with indices of cellular and humoral immunity shows that the changes in hormonal and immunological balance that occur in demodicosis alter the structure and level of interconnections which leads to inconsistencies in their functioning and disorders in interaction between the hormonal and immune systems, defining one of the main conditions of hormonal and immunological adaptation. The emergence of new

correlations in response to the invasion can give an answer to the question of mechanisms of hormonal-immunological changes and indicates the transition to a new level, which becomes a kind of norm for patients.

An imbalance between the hormonal and immunological parameters discovered during the studies, derangement of assistance between the endocrine and immune systems reflect the individual and gender features and they flow differently depending on the state of the liver and can (among other reasons) cause various defects in the regulation of physiological functions shaping the immune response of the host to the invading parasite, and therefore in the formation of relationships in the host-parasite system.

The identified patterns of changes and the nature of the dynamics of hormonal-immunological connections extend our knowledge of the pathogenesis of demodicosis, as well as create certain preconditions for the directional correlation of hormone-immune disorders and open up the prospects for improving pathogenetic treatment of demodicosis.

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