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Article

A common pathogenic chain link of immune-mediated skin diseases in local disorders of immune-endocrine regulation

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Abstract: The goal of the study was to reveal a common pathogenic link of immune-mediated skin conditions such as disorders of interaction of adrenocorticotropic hormone and pro-inflammatory cytokines directly in the skin. 94 patients aged 18 to 45 years, of both sexes, with immune-mediated conditions, including atopic dermatitis, limited scleroderma, chronic spontaneous urticaria, and plaque psoriasis, were studied. A majority of patients, except for scleroderma, had atopic constitution with or without manifestation of respiratory allergic disease and food allergies. All patients also had various concomitant chronic conditions, primarily of cardiovascular and gastrointestinal systems. A patented modification of "skin window," when a chamber with saline is installed on the scarified skin area to accumulate exudate containing targeted molecules, corticotropin, and cytokines Interleukin-1β, Interleikin-18, Interleukin-6, and Tumor Necrosis Factor-α, is used. Determination of values of molecules is carried out using electro chemiluminescent immunoassay and other analyses. In all patients, the skin exudate adrenocorticotropic hormone value was significantly reduced compared to the control group, whereas the content of cytokines obtained from the "skin window" exceeded similar indicators in healthy individuals. A high degree of correlation between adrenocorticotropic hormone and IL-6 was registered. The forgotten "skin window" technology demonstrates a proper opportunity to acquire biological material from the skin for investigation of targeted molecules at the local level.

Keywords: skin window; skin chamber; skin exudate; ACTH; cytokines; inflammasomes; atopic comorbidity

1. Introduction

The skin, being the largest organ of the human body, is the longest site for the development of many immune-mediated skin diseases, for example, atopic dermatitis, scleroderma, psoriasis, various forms of urticaria and others [1]. Despite the different pathogenetic basis, all these conditions have a common link. Biomarkers of this link can be ACTH (adrenocorticotropic hormone), synthesized directly in the skin [2], and pro-inflammatory cytokines, some of which (IL-1β and IL-18) are of inflammasome origin [3–6].

Now we have a short excursion into the history of this technology and its scientific basics and rationale, how it was seen before us, and whether there is a need for it now. Among the methods of skin examination, the "skin window" stands out. It

has a long almost 70-year history. Initially, the method was proposed for acquiring neutrophils and macrophages adhered to glass at different time intervals [7]. In addition, the influence of Staphylococci on this process [8], the detection of neutropenic conditions [9], and its significance for the diagnosis of drug allergies [10] have been investigated. Subsequently, modifications were developed with the application of a fine-porous filter [11,12] and chambers [13] on the "skin window," which made it possible to examine white blood cells advancing inside the filter and obtain a suspension of cells in the chamber. The use of negative pressure on normal skin for up to 2 h allowed the generation of blisters containing skin exudate. This superficial standardized "skin window" was covered by a special camera in which skin exudate was accumulated [14]. In such properly collected standardized biological material, various biologically active molecules can be studied by modern methods, including omics technologies [15–21]. In the near future, using a technology like this [22,23], researchers will be able to make the skin invisible (total 'skin window') to study vessels, cells, and subcellular components.

Researchers of "skin window" cells and molecules, as well as classic skin allergic tests [24,25], are faced with the constant question concerning the level (local or systemic), which they affect and reflect. It is generally accepted that positive allergy tests indicate systemic sensitization, since the unique cytophilic nature of IgE is indisputable evidence of this [26]. It is also a well-known fact that sensitization to allergens in most atopies of other localizations can occur through the skin [26], therefore atopic dermatitis rarely proceeds as an isolated disease, and more often is accompanied by one or more atopies [27–29].

However, the inflammatory exudate obtained within 6 hours of chamber exposure should be attributed to the source of molecules, predominantly synthesized at the local level. Thus, in the study of the factors for maintenance, breakdown, and restoration of immunological tolerance in immune-mediated skin diseases, it is necessary to take into account the level where the event occurred and its relation to tolerance [26] as well as triple neuro-immune-endocrine regulation [30], the assembly and activation of inflammasomes as an early phase of inflammation [31], excessive cytokine production [1,32–34] and other processes.

An alternative method of obtaining biological material from the skin is to take wound exudate [35,36], which allows the study of both cells [37] and molecules [38]. However, this method is difficult to standardize, inconvenient for researchers from the organizational viewpoint and the results depend on many factors. Sterile inflammation is related to an inflammatory process, which develops without infection, but can occur in necrosis, neutrophil extracellular traps (NETosis) [39], cardiometabolic NLRP3 activation [40], etc. The implementation of a "skin window" also results in sterile inflammation; however, its inflammatory mediators do not introduce a significant error in the studied parameters of skin exudate in healthy persons [12].

The skin has a complex functional organization, involving many specialized cells that restrict the body's internal media from the aggressive external environment [1]. Also, the skin is a target for many hormones, including ACTH, glucocorticoids, sex hormones, and thyroid hormones, and displays at least two important physiological barriers: the well-studied epidermal barrier [41–43] and the rarely mentioned skin histohematic one [44,45]. The epidermal barrier protects the skin and the entire human

body from external harmful factors. The skin histohematic barrier is the space between the capillary walls and the tissue fluid of the skin, where structural, metabolic, and immune homeostasis are regulated and intracutaneous processes occur at the local level. However, the skin affects the whole body, outside the skin histohematic barrier, functioning at a systemic level. Disorders in both barriers are significant for all immune-mediated diseases. Sensitization in atopic allergic pathologies such as atopic dermatitis [46–48] occurs due to epidermal barrier defects [49], including filaggrin gene mutations [50,51]. For the continuous entry of a large number of specialized cells and molecules of the allergen tolerance maintenance system into the skin [26], disorders of the skin histohematic barrier contribute to the breakdown of tolerance and exacerbation of allergic inflammation. This barrier is especially important to restrain the development of autoimmune skin diseases (scleroderma [52], psoriasis [53–56], spontaneous urticaria [57–59]), in which a breakdown of autotolerance is observed [26]. It is clear that skin barrier impairment matters very much [60].

The central hypothalamic-pituitary-adrenal (HPA) axis [61], whose key effector molecules are glucocorticoids, in particular cortisol, as well as cytokines, neurotransmitters and neuropeptides, plays an important role in maintaining cutaneous homeostasis, including response to psychological and physical stress [30]. In response to the stress factor, ACTH is produced in the hypophysis, which mediates the inflammatory response and stimulates the production of cortisol by the adrenal glands, which, acting on cells and tissues through the bloodstream, shows many functions, including anti-inflammatory action and regulation of homeostasis of the skin [61–64].

In response to the ongoing impact of environmental factors, in order to regulate homeostasis in the skin, a peripheral HPA axis is available. It was formed in the process of evolution, similar in hierarchical structure to the central axis. The peripheral axis acts locally, exerting short-distance effects on skin cells through the corresponding peripheral melanocortin receptors (MCR1-MCR5) [64]. Of all the hormones of the peripheral HPA axis, only ACTH activates all types of melanocortin receptors, exerting an anti-inflammatory effect, which is manifested in a decrease in the production of pro-inflammatory cytokines, an increase in the expression of anti-inflammatory cytokines, a decrease in phagocytic activity, etc. [61,63,64].

A common link in the pathogenesis of chronic inflammatory skin diseases is the imbalance of most cells of the immune system and many molecules at the local level due to the breakdown of immunological tolerance and the development of the inflammatory process through the inflammasome activation [6,26]. In particular, for the formation of active forms of IL-1β, IL-18 from pro-IL-1β and pro-IL-18 in the skin, the formation of inflammasome NLRP1, NLRP3, AIM2 and some others is necessary. An intensity of the inflammation in the skin depends on the regulation of inflammasome development [3,4,65]. After the “maturation” of IL-1β and IL-18 during the activation of inflammasomes, they are secreted into the extracellular space and mediate the recruitment of immune cells to the site of inflammation and their subsequent production of broadspectrum cytokines, such as IL-6 and TNF-α. As noted earlier, along with cytokines, the vital activity of skin immune system cells is also affected by hormones produced in the skin itself [2]. Locally secreted ACTH and cytokines are characterized by a short-standing, autocrine and paracrine action. That is why their study at the systemic level does not reflect the full picture of the hormonal-

cytokine activity in the skin. This fact determines the relevance of this study of the involvement of a number of key players in immune-mediated skin diseases at the local level.

Despite a long history, "skin window" technology in new modifications brings an obvious novelty to skin research, as it makes it possible to study cells and molecules directly, and compare the course of immunological processes at the systemic and local levels. Such an approach allows obtaining skin biological material easily and conveniently that should inspire our respect for our predecessors in immunology.

The aim of the research is to determine the values of the adrenocorticotropic hormone and cytokines IL-1β, IL-18, IL-6, and TNF-α in the cell-free fraction of the "skin window" exudates in atopic dermatitis, plaque psoriasis, limited scleroderma, and chronic spontaneous urticaria.

2. Materials and methods

Persons, including 19 patients with atopic dermatitis with mild to moderate symptom severity [66], 24 patients with limited scleroderma [52], 26 patients with chronic spontaneous urticaria [57], and 25 patients with plaque psoriasis [67] aged 18 to 45 years, of both sexes, were examined. They were under observation in the inpatient department of the State Autonomous Healthcare Institution Novokuznetsk City Hospital No. 1, LLC Media-Service (Novokuznetsk, Russia), and Municipal Student Hospital (Tomsk, Russia). All diagnoses were established by generalists and specialists related to the kind of pathology (dermatologists, allergists, and rheumatologists). A majority of patients, except for scleroderma, had atopic constitution with or.

The middle third of the palmar surface of the patient's forearm is disinfected with 70° alcohol. The marked 1 × 1 cm area on the epidermis upper layers is then scarified to the shiny layer using a sterile scalpel. An affected surface had to acquire a characteristic sheen. Place a 1 mL plastic chamber pre-filled with a saline solution or medium 199 containing a broad-spectrum antibiotic on the scarified area. The chamber is fixed on a scarified area of the skin by means of an adhesive plaster. Circular bandaging of the forearm with adhesive plaster tape provides the most reliable fixation of the chamber. In the wound from scarification, the process of exudation begins, and the exudate of aseptic inflammation gradually accumulates (see right). After 6 hours, the chamber is removed, and its contents are pipetted and transferred to the test tube. Next, centrifugation is carried out. After this procedure a volume of 5 μL is taken by an automatic pipette from the top of the centrifuged liquid (supernatant) and transferred to another test tube. The supernatant is used to determine targeted molecule values by enzyme-linked immunoassay reagent kits using a standard technique. Standardization of values of the studied molecules is carried out by protein using a microbiuretic test. The results are standardized in accordance with a common protein value.

Without manifestation of respiratory allergic disease and food allergies. Signs and syndromes of food allergies were predominant among allergic comorbidities. All patients also had various concomitant chronic conditions, primarily of cardiovascular and gastrointestinal systems. The control group consisted of 25 healthy volunteer

donors aged 20–35 years. All persons signed voluntary informed consent to participate in the study and were also aware of the possible associated risk. The material for the study of ACTH and cytokines in the skin was the cell-free fraction of the exudate of the "skin window", obtained from 1 mL chambers installed on the initially non-lesion then on the scarified area of the skin pre-filled with a sterile 0.9% sodium chloride solution (see **Figure 1**). The procedure was performed according to a patented medical technology [68].

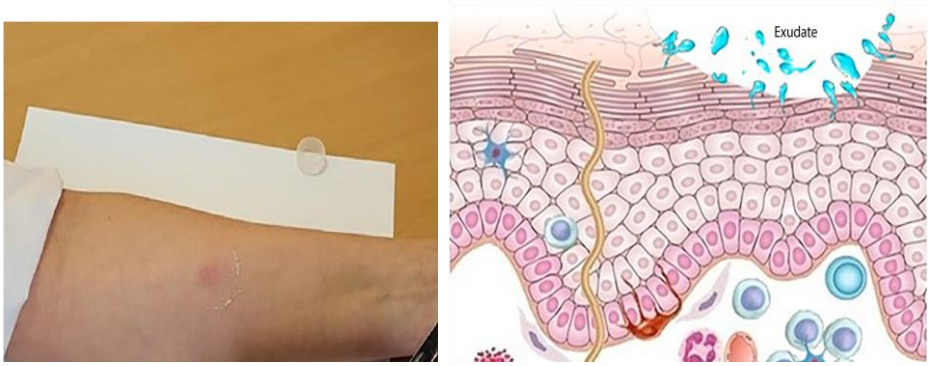

Figure 1. Skin window technology.

The ACTH level was measured by electrochemiluminescent immunoassay technology using a Cobas e411 (rack) automatic analyzer (Roche Diagnostics GmbH, Germany). The IL-1β, IL-18, IL-6, and TNF-α values were determined by a solid-phase enzyme-linked immunosorbent assay using reagents from Vector-Best (Novosibirsk, Russia). Statistical processing of the study results was carried out using the statistical programs of the SPSS group. Testing the hypothesis of data distribution for normality with the calculation of the asymmetry and excess coefficients showed that the obtained indicators did not obey the normal distribution law. Accordingly, nonparametric statistical methods for data processing were then used. The indicator values were presented in the form of medians and quartiles. To assess all available data samples for statistical significance, the non-parametric Mann-Whitney criterion known as U (comparable to critical U) as well as *p* Value were calculated. To specify the correlation, the Spearman's calculation was used. The platform "Highcharts.com" was exploited for the visualization of statistical data according to a noncommercial plan.

3. Result

The values of ACTH, IL-1β, IL-18, IL-6, and TNF-α in the cell-free fraction of the "skin window" exudates obtained as a result of the study in atopic dermatitis, scleroderma, urticaria and psoriasis in comparison with the control group are presented in **Table 1**.

Table 1. Values of ACTH and cytokines IL-1β, IL-18, IL-6, and TNF-α in the "skin window" exudates in atopic dermatitis, limited scleroderma, chronic spontaneous urticaria, plaque psoriasis, and healthy individuals, Me (Q1–Q3).

Groups		**"Skin window" exudates ACTH and cytokines values**				
		ACTH (pg/mL)	**IL-1β (pg/mL)**	**IL-18 (pg/mL)**	**IL-6 (pg/mL)**	**TNF-α (pg/mL)**
Atopic dermatitis (n = 19)	1	3.41 (2.71–4.63) *P*3, *P*5	21.66 (15.2341.17) *P*5	1148 (523.3–1238) *P*2, *P*5	512.8 (450.1600.7) *P*5	5.63 (4.61–10.91) *P*5
Scleroderma (n = 24)	2	3.84 (3.44–4.72) *P*3, *P*5	12.51 (9.96–15.82) *P*5	490.7 390.2–620.9 *P*1, *P*3–*P*5	573.2 (420.1–600.3) *P*5	4.25 (2.55–5.51) *P*5
Urticaria (n = 26)	3	5.01 (4.39–5.83) *P*1, *P*2, *P*4, *P*5	15.01 (12.58–22.24) *P*5	854.4 (645.1–1194) *P*2, *P*5	598.5 (475.7–600.1) *P*5	4.95 (3.07–8.23) *P*5
Psoriasis (n = 25)	4	3.01 (2.71–3.61) *P*3, *P*5	14.58 (10.06–17.76) *P*5	871.2 (635.1–1160) *P*2, *P*5	582.5 (456.1–600.2) *P*5	5.5 (4.1–6.3) *P*5
Control (n = 25)	5	6.24 (5.59–6.81)	7.21 (4.62–9.66)	270.8 (213.7548.2)	271.1 (173.3303.3)	1.7 (1.0–2.5)

Note: Me—median, Q1—the first quartile, Q3— the third quartile; *P*1–*P*5—statistical validity of the difference ($p < 0.05$) in relation to other pathologies marked by sequence number.

The results presented in the table show that the ACTH value in the "skin window" exudates in groups of patients with atopic dermatitis, psoriasis and scleroderma is almost two times lower than the values of the control group ($p < 0.05$). In chronic urticaria, a statistically significant ($p < 0.05$) decrease in the ACTH value at the local level (i.e., in the skin) is also observed compared to control. However, the ACTH value in urticaria was reliably ($p < 0.05$) higher than those in other skin pathologies. The concentrations of all cytokines were found to be increased in comparison with the control. The highest value was registered for IL-18 in atopic dermatitis, while the content of this cytokine was not too enhanced in scleroderma.

Since such studies have not been conducted in other laboratories, it is possible to make a positive comparison with the data of pro-inflammatory cytokine concentrations obtained in wound exudate [37,69]. There were significantly increased values of IL-1, IL-6, and TNF-α in both acute and chronic wounds [70]. The same pro-inflammatory cytokines, IL-1, IL-6, and TNF-a, were revealed to be present in essentially higher concentrations in wound fluid, especially in nonhealing ulcers [71]. However, high concentrations of cytokines reflect the wound inflammatory process itself, rather than any disease in the body, which confirms that the use of wound exudate to investigate pathology through the skin is not a proper way.

The correlation analysis revealed a negative correlation between parameters obtained from skin exudate (see **Table 2**). In the table, moderate and strong degrees of associations are displayed. In three cases, a high-strength correlation between ACTH and IL-6 in atopic dermatitis, psoriasis, and chronic urticaria is revealed, as captured in **Figures 2–4**.

Table 2. Spearman's rank correlation of skin exudate parameters in atopic dermatitis, limited scleroderma, chronic spontaneous urticaria, plaque psoriasis, and healthy individuals.

Groups	Correlation pairs	Coefficient ρ	*P*-value
Atopic dermatitis (*n* = 18)	ACTH: IL-6	−0.782	< 0.01
	ACTH: TNF-α	−0.479	< 0.05
Scleroderma (*n* = 24)	ACTH: IL-6	−0.683	< 0.01
	ACTH: IL-18	−0.498	< 0.05
Urticaria (*n* = 26)	ACTH: IL-6	−0.729	< 0.01
	ACTH: IL-18	−0.661	< 0.01
Psoriasis (*n* = 24)	ACTH: IL-6	−0.769	< 0.01
	ACTH: IL-18	−0.544	< 0.01
Control (*n* = 24)	ACTH: IL-6	−0.446	< 0.05
	ACTH: TNF-α	−0.539	< 0.01

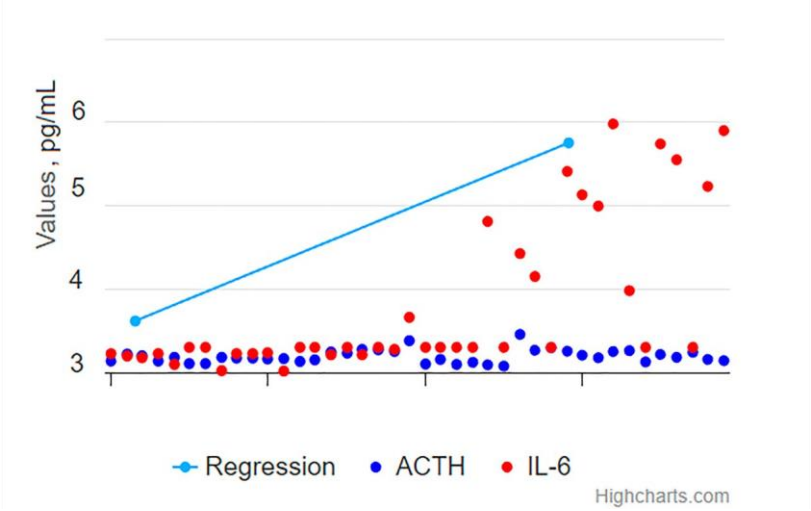

Figure 2. A high strength correlation ($\rho = -0.78$, $p < 0.01$) between ACTH and IL-6 skin exudate values in atopic dermatitis.

Note: Here and in other graphs, IL-6 values are shown reduced by a factor of 100.

A high degree of correlation between ACTH, a HPA hormone, and cytokine IL-6, well-known as a strong proinflammatory as well as anti-inflammatory factor, corresponds to the involvement of both in immune-endocrine imbalance in atopic dermatitis [61]. The imbalance is caused by such factors as HPA axis dysregulation, stress, atopic sensitization, and mutations in the filaggrin gene [1,33,48,51]. The scatter plot shows the peculiarity of the distribution of ACTH and IL-6 values in atopic dermatitis. Since IL-6 increases in monotonic ACTH dynamics, the dispersal of IL-6 grows up. The regression line goes up sharply.

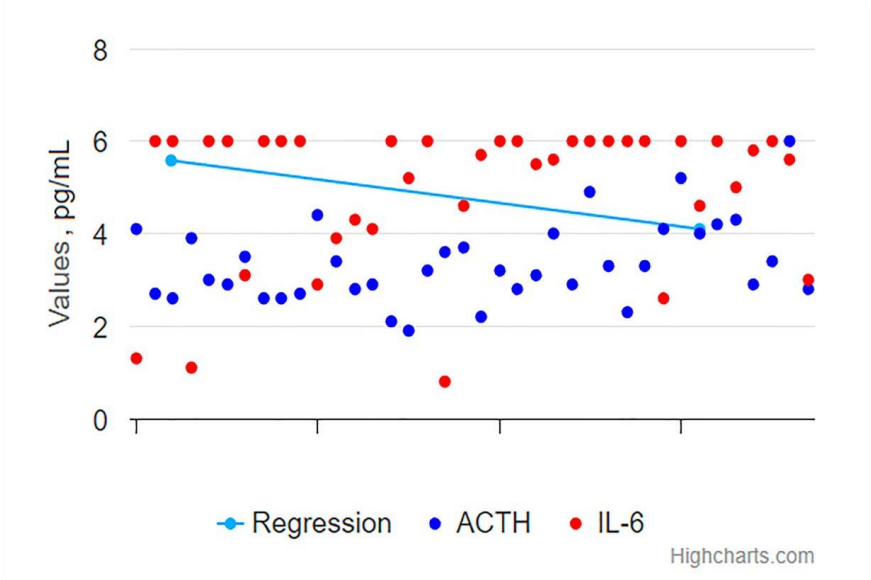

Figure 3. A high strength correlation ($\rho = -0.77$, $p < 0.01$) between ACTH and IL-6 skin exudate values in plaque psoriasis.

Stress, immune-neuroendocrine imbalance, mutation in filaggrin gene, and any unknown factors play a role in pathogenesis of psoriasis. A high strength correlation between ACTH and IL-6 highlights only a small proportion of pathogenic disorders in psoriasis [53,72,73]. A scatter plot demonstrates the monotonic distribution of ACTH and IL-6 values in the disease. Taking into account the presence of a common link of pathogenesis of immune-mediated skin conditions, a short joining pathogenic schema will be described below.

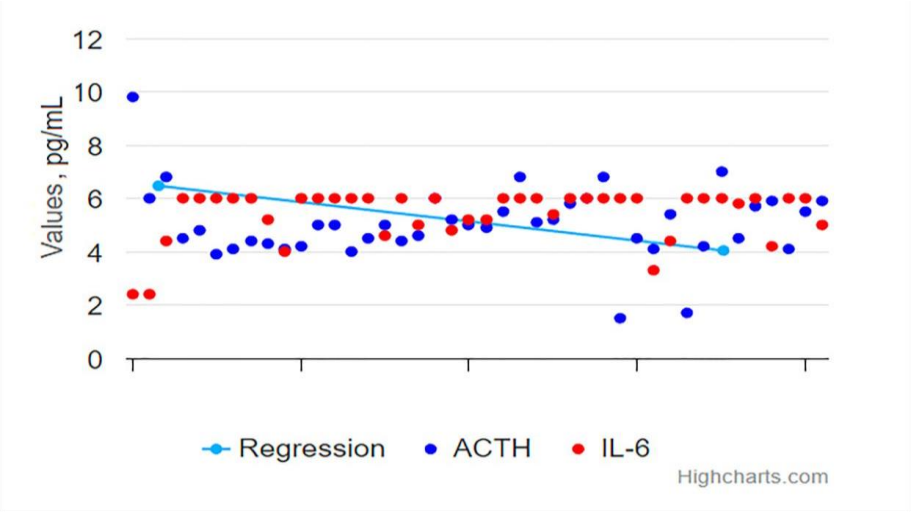

Figure 4. A high strength correlation ($\rho = -0.73$, $p < 0.01$) between ACTH and IL-6 skin exudate values in chronic spontaneous utricaria.

A high degree of revealed correlation in chronic urticaria reflects a deep dependence of this pathology on stress, imbalance of HLA axis, a long and repeated over-activation of mast cells and eosinophils, and hepatic disorders. IL-6 plays rather a positive role, affecting HLA and upregulating the release of ACTH [57,59,74]. A scatter plot shows the monotonic distribution of ACTH and IL-6 values in urticaria.

4. Discussion

Three immune-mediated skin diseases, including atopic dermatitis, psoriasis, and chronic urticaria, are characterized by patients' high exposure to stress and dysregulation of the immune system and HPA axis [61]. Ambivalent cytokine IL-6 is simultaneously a pro-inflammatory and anti-inflammatory factor, which can modulate the HPA axis to release ACTH, which, in turn, upregulates cortisol, a main anti-stress hormone. A high degree of correlation between ACTH and IL-6 may be due to the need for regulatory systems of the body to restore the disturbed balance [75,76].

The study showed that, in particular, patients with atopic dermatitis have a higher concentration of pro-inflammatory cytokines and lower ACTH in the "skin window" than healthy donors. ACTH stimulates the secretion of hormones by the adrenal glands, primarily the powerful anti-inflammatory hormone cortisol [2]. In turn, cortisol reduces ACTH production by the pituitary gland through a negative feedback mechanism. It means that a decrease in ACTH secretion by the pituitary gland can be both the cause of a less active cortisol release and a consequent high cortisol-producing adrenal function.

The first option seems to be more probable. In patients with atopic dermatitis, higher production of pro-inflammatory cytokines in the skin may be associated with insufficient control over inflammation by the adrenal glands, since a decrease in ACTH secretion entails inhibition of cortisol production. This assumption is indirectly supported by the inverse correlation between the synthesis of pro-inflammatory cytokines (IL-1β and IL-18) and the concentration of ACTH in the exudate of the "skin window." It can be explained by the anti-inflammatory effect of ACTH through cortisol. If the level of ACTH was due to the influence of the level of secretion of the adrenal hormone cortisol, one would probably find a one-way correlation between the concentration of ACTH and secreted values of pro-inflammatory cytokines, since cortisol has an anti-inflammatory effect. Moreover, according to the principle of negative feedback, cortisol also reduces the secretion of ACTH. Further studies aimed at comparing ACTH, cortisol and cytokine concentrations at the local level ("skin window" exudate) and the level of the whole body are necessary to confirm or reject this hypothesis. Concomitant diseases, especially those of the cardiovascular system, can be of great importance for ACTH. In addition, the presence of one disease from the "atopic march" group significantly increases the chances of other concomitant diseases of atopic genesis [77,78]. It is known that 2/3 of patients with atopic dermatitis develop allergic rhinitis, and 1/2 develop bronchial asthma and food allergy [29,48].

In the presented research, a majority of patients except those with scleroderma had an atopic constitution, which was manifested in the form of at least one additional atopic disease (allergic rhinitis, allergic conjunctivitis, bronchial asthma, or food allergies) and frequently a respiratory allergic disease with food allergies. Also, most family histories showed the presence of atopic conditions.

Thus, based on the results obtained, as well as on the scientific literature data, it can be concluded that the decrease in ACTH production at the level of the "shock organ" leads to dysregulation between the endocrine and immune systems in the skin. As a result, this is manifested by the corresponding clinical picture. In addition to

classical cytokines and such subsets of T cells as type 2 helper T cells (Th2) and type 22 helper T cells (Th22), which have an important role in the development of chronic inflammatory skin diseases [79], reduced ACTH production directly at the local level can contribute to the pathogenesis of these diseases. The peripheral HPA axis, which has intracrine, autocrine and paracrine effects on skin cells, exhibits its anti-inflammatory effect in response to the ongoing exposure to the environmental factors, through the production of hormones and their interaction with melanocortin receptors (MCR1-MCR5), thereby regulating skin homeostasis [63]. Insufficient release of ACTH at the local level probably cannot fully inhibit inflammatory processes, resulting in impaired control over the immune system of the skin.

Excessive production of local inflammatory cytokines IL-1β and IL-18 may be the result of inflammasome activation in skin cells such as macrophages, dendritic cells, keratinocytes, fibroblasts, which play a key role of containers as future inflammasomes [3,4,54,56]. Additional overproduction of IL-6 and TNF-α demonstrates a specific activity of these pro-inflammatory cytokines in the further development and aggravation of the chronic inflammatory process in the skin due to their high cytotoxicity.

In general, the findings obtained are unique and may serve as an example of a completely new approach in research of the regulation of the immune system at the local level. If neuro molecule would be included in research program, this could provide a better and complete understanding of the most diverse pathological processes in the skin [26].

5. Conclusions

1) In such immune-mediated skin diseases as atopic dermatitis, urticaria, psoriasis, and scleroderma, there is a significant decrease in the ACTH value in the “skin window” exudates in comparison with the control group.
2) The decreased ACTH production at the local level indicates a disruption of the endocrine regulation of skin cells and skin-associated lymphoid tissue, which reduces their anti-inflammatory potential and increases the pro-inflammatory activity of the immune system in the skin.
3) In most immune-mediated skin conditions, there is an essential increase in all proinflammatory indicators in the “shock organ”: IL-1β, IL-18, IL-6, and TNF-α, which corresponds to the inflammatory nature of these skin diseases, whereas immunological tolerance breakdown, inflammasomes, and cytokines initiate this inflammation.
4) The forgotten technology of the “skin window” allows obtaining biological material that is skin exudates, being adequate and convenient for studying skin pathologies.

Author contributions: Conceptualization, DZ, VK and OU; methodology, OU; software, AK; validation, AK; formal analysis, MM, AD and YK; investigation, DZ; resources, DZ; data curation, AK; writing—original draft preparation, VK; writing—review and editing, NK; visualization, AK; supervision, DZ, VK and OU; project

administration, PI. All authors have read and agreed to the published version of the manuscript.

Ethical approval: The study was conducted in accordance with the Declaration of Helsinki, and approved by the Ethics Committee of Russian Continuous Postgraduate Education Academy, Novokuznetsk branch (Protocol 4, Sept 2, 2024). Written informed consent was obtained from all patients involved in the study, and written informed consent has been obtained from the patients to publish this paper.

Conflict of interest: The authors declare no conflict of interest.

Abbreviation

IL-β	Interleukin-1β
IL-18	Interleikin-18
IL-6	Interleukin-6
TNF-α	Tumor Necrosis Factor-α
ACTH	adrenocorticotropic hormone
HPA axis	hypothalamic-pituitary-adrenal axis
MCR1-MCR	melanocortin receptors
NLRP3	an inflammasome
Th2	type 2 helper T cell
Th22	type 22 helper T cell

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