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VITILIGO: MODERN VIEWS ON ETIOLOGY, PATHOGENESIS AND THERAPY METHODS

Latipov Ikhtiyor Ikromovich,
Bukhara State Medical Institute,
Republican Specialized Scientific and Practical Medical Center for Dermatology and Cosmetology Bukhara branch
ikhtiyorlatipov@gmail.com

Kholov Bahriddin Bakhtiyorovich,
Bukhara State Medical Institute,
Republican Specialized Scientific and Practical Medical Center for Dermatology and Cosmetology Bukhara branch.
baxamed_0848@mail.ru

Annotation
Vitiligo is classified as an autoimmune hypomelanosis. The prevalence is 0.5%. In etiology, the main factor is the genetic defect of the enzymatic system melanogenesis. The article is of a review nature, it highlights modern data on the pathogenesis, classification and treatment of vitiligo. Existing methods of treatment, on average, have moderate efficiency. The main ones can be considered ultraviolet therapy, laser therapy, use of topical corticosteroids and calcineurin inhibitors.

Keywords: vitiligo; etiology; pathogenesis; classification; treatment.

Introduction

Vitiligo is the most common depigmentation disorder where the selective destruction of functioning melanocytes causes depigmentation of the skin, hair and mucosal surfaces. It affects approximately 0.5% to 1% of the population (1), with an average age of onset at about 24 years, its prevalence appears to be equal between men and women and there is no difference in the rate of occurrence according to skin type or race. Several etiological factors have been suggested for which the most compelling evidence involves a combination of environmental, genetic and immunological factors interacting to contribute to autoimmune melanocyte destruction. Vitiligo is a common skin disorder characterized by depigmented white patches in the skin due to loss of melanocytes. It remains unclear what causes damage or death to the melanocytes, there are many potential pathophysiological theories involving

autoimmune, neural, autocytotoxic, biochemical, oxidative stress, melanocytorrhagy, and decreased melanocyte survival hypotheses (2). Autoimmune theory is more prominent in generalized vitiligo, which is considered a complex disorder involving combined pathogenic effects of multiple susceptibility genes and unknown environmental factors that lead to autoimmune destruction of melanocytes (3).

Melanocytes are classified as epidermal dendritic cells, located between basal keratinocytes, on average their number is 1:10 in relation to all basal cells. Melanocyte, connecting with 36 keratinocytes, form- cuts the epidermal melanin unit, in which the synthesis, transfer and accumulation of the pigment proceeds. Melanocytes interact with keratinocytes via adhesion molecules (E-cadherins and integrins), while keratinocytes are controlled function, proliferation, migration of melanocytes by se-Cretion of growth factors - the main growth factor of fibroblasts (bFGF), epidermal growth factor (EGF), endothelins, hormonal monos, including melanocyte-stimulating hormone (MSH); cytokines, including tumor necrosis factor (TNF); interlaki- new (IL) and interferons (IFN).

Melanocytes of the skin originate from the neural tube of the fetus, after closure of which a group of cells migrates in the dorsolateral direction to form the neural crest. These cells are are precursors of many structural elements, including number of skin melanocytes. Melanocytes enter the skin and hair follicles during the 3rd month of intrauterine development. Control of triggering melanocyte differentiation and mechanisms their migrations have not been studied enough, but an important role of c-KIT, tyrosine kinase receptor, transcription factors MITF, PAX3 and Sox10. All melanocytes contain tyrosinase and melanin is processed, but only skin melanocytes are capable of transfer melanin to other cells, so they are considered as unicellular glands (secretory melanocytes). Like in all secretory cells, in melanocytes there is an endoplasmatic reticulum and Golgi complex. Tyrosinase and others enzymes are formed in the granular endoplasmic reticulum and are delivered to the small vesicles that make up the mela-

noses. The development of these organelles goes through four stages: stage I is characterized by the presence of an unorganized matrix; stage II - the orderliness of the secretory matrix, however, melanin not yet available; in stage III, melanin enters the melanosomes; in stage IV they accumulate pigment. In stages I and II, melano-soma are found only in melanocytes, in stages III and IV they can be found in various cell types, mainly in keratinocytes.

The biosynthesis of melanin is a rather complex process. The main amino acid in the production of melanin is tyrosine or hydroxyphenylalanine. In melanosomes, tyrosine is converted to DOPA (dihydroxyphenylalanine), and then oxidized to DOPA-

quinone. The copper-containing enzyme tyrosinase plays a regulatory role playing a role in the process of biosynthesis. mRNA tyrosinase levels and enzymes are about the same in dark and white skin.

At the stage of DOPA-quinone, the process proceeds through several pathways and three types of melanin are formed: eumelanin: dark brown white or black; with a cyclic structure; insoluble

rimy; pheomelanin: red or yellow; contains sulfur; non-cyclic structure; soluble in solutions of alkalis and trichrum: intense red; with abundant sulfur content; otherwise similar to melanin.

In the skin, a mixed type is usually observed, but in individuals with dark eumelanin predominates in the skin. Eumelanin is responsible for hair color, while pheomelanin and trichrome melanin characteristic of blondes and redheads. Depending on the failure of melanogenesis in the skin

allocate:

• Complete absence of pigment - amelanosis;

• Decrease in melanogenesis - hypomelanosis with diffuse or

localized hypopigmentation.

During vitiligo, it is customary to distinguish stages of progression processes, which are a kind of predictors of the effect effectiveness of therapy: so for the stages of preclinical and initial manifestations are characterized by a favorable prognosis, while pro the diagnosis of the stage of a detailed clinical picture is considered unfavorable pleasant.

• The preclinical stage is characterized by a deficiency in the system melanocyte growth factor. In the foci, there is a decrease expression of c-KIT receptors on melanocytes and a decrease in

keratinocyte-driven cytokines that are important for life activity and activity of melanocytic cells (granulocytic) macrophage colony stimulating factor, bFGF, SCF).

• In the initial stage (possibly reversible) a decrease in the amount of melanin in melanocytes.

• Late stage (practically irreversible) melanocytes are destroyed. Sometimes deeply located melanocytes moose follicles are also destroyed, but most often they remain relatively stable and are potential source for cell migration.

Vitiligo classification

Clinically distinguished [3]:

• Non-segmental vitiligo (NSV): generalized, acrofacial, universal, mucous membranes (with the presence of more than one lesion) and rare variants;

• Segmental vitiligo (SV): uni-, bi- or multi-segment;
• Mixed vitiligo: a combination of non-segmental and segmental option;
• Unclassified vitiligo: focal, vitiligo mucous membranes (in the presence of a single focus
defeat).

Unclassified vitiligo is only considered in in the event that long-term observation of the patient does not allow it is possible to attribute this form to segmental or non-segmental type. The segmental form is characterized by a rapid onset, progressive course, and involvement of the hair follicle. Different clinical forms have different prognosis depending on carrying the effectiveness of treatment (least favorable for acrofacial vitiligo) and different tactics of managing patients (specificity - with localization on the eyelids and mucous membranes).

The clinical picture in vitiligo is represented by foci hypopigmentation: at the beginning of the process they may be pinkish color, later milky white. In typical cases, pre-property localization - skin, less often mucous membranes. The spots have a different size and shape, but always with clear graprostrate. Quite often there is a positive symptom of Koebner. In some cases, the appearance of white spots may be accompanied by itching, erythema and peeling of the skin.

Diagnosis of vitiligo is usually not difficultions, the volume of surveys directly depends on the established the diagnosis. Patients with vitiligo should be tested for antithyroglobulin antibodies (anti-TPO), thyroid stimulating hormone (TSH) and other tests as needed to assess function thyroid gland (for example, anti-TSHR antibodies in case of over- Graves' climb). Additional laboratory tests and consultations of related specialists are advisable when there are burdened history of autoimmune diseases or suspicion of the presence of autoimmune syndromes in the patient. In case of difficulty in making a diagnosis, patients are biopsy from foci bordering on unaffected skin (characteristic lack of melanocytes and melanin in the basal layer, according to on the edge of the affected area, islands of lichenoidth lymphocytic infiltrate). It is also recommended to study studies that allow a differential diagnosis with other hypomelanoses or dermatoses, in the clinical picture which have foci of depigmentation (mycological, immunonological, genetic).

The treatment of vitiligo is a rather complex problem. cottage for both doctors and patients. The unreliability of existing methods, a significant negative impact of the disease on quality of life creates certain difficulties. After diagnosis and counseling, it is necessary to evaluate the ratio of the possible effectiveness of therapy and its safety,

with in this case, the patient must be informed about all possible treatment options, prognosis and potential risk of recurrence. Most patients need psychological counseling. This aspect should not be neglected.

Theoretically, the best results can be obtained at the preclinical stage, when melanocytes are preserved in the foci and an immune-mediated inflammatory response however, it is impossible to diagnose it clinically, as there is no characteristic depigmentation yet. At the same time, by prescribing a general therapy (phototherapy methods, systemic therapy), it is possible to influence the beginning process and slow down its development.

Therapeutic measures for advanced clinical picture are aimed at the regeneration of melanocytes from the hair follicle or interfollicular progenitors. Forecast treatment depends on the duration of the disease and the clinical forms. Although in any case the efficiency does not exceed 30–70%. Numerous treatments for vitiligo are just confirm that there is no effective therapeutic approach. At the stage of development of patient management tactics comorbidities should be taken into account, in particular autoimmune. Please note that some treatments vitiligo are used “off-label”. All methods of therapy can be divided into drug (local and systemic preparations), phototherapy and surgical.

Medical treatment of a limited amount of light living lesions with corticosteroids usually leads to repigmentations in 10–50% of patients. You can use the continuous application: 1-2 times a day for 6-8 weeks, after which interval of several weeks to minimize the risk of side effects, while using topical corticosteroids (TCS) of medium strength [4, 5]. Treatment of TCS can be carried out according to an intermittent technique, when tea preparations of high or very high degree of activity: applications are carried out 1 time per day for 2 weeks after blowing two-week break. In the absence of side effects effects spend 4-6 repeated courses. Best Results (75%) repigmentations are noted on the skin of the face and neck [6], in patients with dark skin [7]. Acral foci respond poorly to corticosteroid therapy. Local side effects (atrophy, telangiectasias, hypertrichosis, folliculitis and striae) are highly active corticosteroids limit their use, this preference should be given to such as mometasone furoate and methylprednisolone aceponate, which are largely degrees are devoid of these side effects.

In the treatment of patients with limited forms of vitiligo in cases of lack of effect from the use of topical glucocorticoids ticosteroids alternative means are topical calcineurin inhibitors [8, 9]. There is data on the comparison my effectiveness of TCS and calcineurin inhibitors (tacrolimus and pimecrolimus) [10, 11], however, when used in short term, the former are more effective. High effectiveness is noted with combined

use topical calcineurin inhibitors and UV irradiation (UVB 311 nm) or an excimer laser, which, apparently, is explained their synergistic action [12, 13].

Sunscreen is a must, as with intense strong insolation, the contrast between healthy and damaged female skin and foci are even more visualized. Besides,the use of sunscreen reduces the risk of new foci and the development of skin cancer in areas of depigmentation. One of the alternative methods can be considered the use of the use of special masking cosmetics, which allow you to effectively hide the foci of depigmentation. Modern dermocosmetics designed for vitiligo are quite resistant to external factors (temperature, moisture, sweat, etc.), and keep effect for a long time, which is very convenient for everyday use. It is possible to use lotions (creams, oils) for artificial tanning or auto bronzers (usually with digital droxyacetone) and other coloring preparations (walnut oil), which can be attributed to alternative camouflage common methods.

Phototherapy in the form of narrow-band ultraviolet B with long 311 nm wave twice a week is the method of choice for widespread process [14]. This is also the second line method children after topical corticosteroids or calcineurin inhibitors. Evaluation of the effectiveness of therapy is carried out after 2 months, when the question of the expediency of its continuation is decided. The average course is 60-80 procedures. The advantages of narrow phototherapy compared with PUVA therapy include in better repigmentation, refusal to take photosensitivitors, reducing the risk of side effects, the possibility of using anxiety in children. However, patients with skin phototypes I–II and acral localization of vitiligo foci do not respond to such treatment. PUVA therapy can be used in the form of PUVA baths or systemically with the reception of a photosensitizer inside. Partial repigmentation is noted in 70-80% of patients, complete – only in 20% of patients. Relapse occurs in 75% of patients, usually 1-2 years after the main course. Duration PUVA therapy is at least 6 months before you can consider whether the effect is sufficient. For complete re-
skin pigmentation may require 12–24 months of continuous therapy [15, 16]. The extent of the positive effect depends from the clinical form and localization. Yes, good enough the clinical result is noted in 60% of patients with lesions of the face and neck; significantly less with skin lesions of the endnews. Patients with darker skin respond better. If a improvement does not occur within 6 months, treatment should be terminated. Otherwise, the patient taking 2 times a day week from 100 to 300 sessions, is at risk of actinic skin damage and cancer development. PUVA baths require lower doses of radiation. Local PUVA therapy is possible. Small affected areas can be treated with 0.3% ammifurin lotion (0.0006-0.005% photosensitizing cream) applied for 30-60 minutes before UV irradiation.

Laser techniques can become an alternative to ultraviolet therapy. Use of xenon chloride excimer a laser that generates radiation in the medium-wave ultraviolet range (wavelength 308 nm) is an effective method for the treatment of limited vitiligo, first of all, with acrofacial localization. The best results are noted with the combined use of an excimer laser. in combination with topical calcineurin inhibitors or TCS [17, 18]. Numerous studies have proven the effectiveness of not only the excimer laser, but excimer light with a radiation source with a wavelength between 306 and 310 nm with a peak at 308 nm [19].

Systemic medicine treatment (betamethasone, dexamethasone) is used in the form of pulse therapy: periodic administration of glucocorticosteroid drugs to enhance the therapeutic effect against the background of sufficient safety (break when taking corticosteroids reduces the risk of side effects
effects) [20]. Systemic glucocorticosteroids can stop increase the activity of the disease, but do not give stable repigmentation [21]. Efficacy data available (88%) dexamethasone 10 mg daily on 2 consecutive days per week up to 24 weeks [22]. Possible short-term use of dexamethasone in dose of 7.5 mg per day, and then 5 mg in combination with phototherapy [23]. The use of cyclophosphamide at a dose of 50 mg 2 times a day has a certain effectiveness, but numerous side effects in the form of alopecia, cytopenia, have limited research in this direction [24]. Single studies on study of the effectiveness of cyclosporine showed insufficient efficacy when used at a dose of 6 mg / kg daily, which in combined with the side effects of the drug is not promising [24]. The occurrence of cellular oxidative stress during progression of vitiligo is the basis for local or systemic antioxidants (pseudocatalase, vitamin E, vitamin C, ubiquinone, lipoic acid, ginkgo biloba [25]. This group of drugs is most often used in combinations with phototherapy methods.

The surgical approach to the treatment of vitiligo is the most new. Surgical repigmentation gives the best results in patients with stable vitiligo. There are a number of methods but the most promising today is epidermal transplantation using finely perforated grafts, as well as the transfer of a pure culture of melanocytes or mixed epidermal cultures on the prepared site [26]. The greatest efficiency of these techniques is observed with stable (lack of progression for 6 months to 2 years) segmental vitiligo [27]. For non-segmental vitiligo best results are obtained in combination with phototherapy or other methods, mainly systemic effects.

Thus, vitiligo is currently considered as a multifactorial disease with a certain contribution to development of genetic and environmental components. Insufficient the study of the etiology and pathogenesis of the disease determines the unreliability of existing methods. Given the pronounced negative impact of dermatosis on the

quality of life of patients, their social adaptation is necessary for most patients psychologist consultation. The overall effectiveness of the treatment of vitiligo does not exceed 80%, while the recurrence of the process can be 75%. TCS and calcineurin inhibitors are among the most effective methods to date predominantly in combination with phototherapy (UVB 311 nm and excimer laser). The feasibility of using systemic corticosteroids and PUVA therapy should be considered through the prism of the safety of methods with the expected low effect. Cellular technologies are promising methods, but research in this direction has not yet been confirmed by the evidence base.

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