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The Role of Viruses in the Pathogenesis of Vitiligo (Hypothesis).

Luidmila G Gereykhanova*, Yulia G Melnikova, Kristina A Myzina and Konstantin M Lomonosov.

Department of Skin Venereal Diseases of Medical Faculty, I.M. Sechenov First Moscow State Medical University; 119991, Moscow, Russian Federation.

ABSTRACT

The review of a virus etiology of many diseases of the person including skin diseases is provided in article. Authors provide data on not virus, and also virus theory of a disease of vitiligo and the hypothesis of possible virus pathogenesis of this disease is made. Also own data of authors by results of inspection of 40 patients from vitiligo and healthy donors on a carriage at them such widespread viruses as are presented in article: cytomegalovirus, virus of a rubella, virus of chicken pox and shingles, virus of simple herpes of 1 and 2 types, virus Epstein-Barr, adenovirus, herpes of viruses of the type of 6 and 8 types.

Objective: to work out our own concept of the viral theory of vitiligo pathogenesis and carry out a comparative research of different viruses antibody levels in both vitiligo patients and healthy donors.

Methods: we have analyzed up-to-date scientific data concerning the role of viruses in human disease pathogenesis and conducted an examination of 40 patients with different forms of vitiligo to check their IgG antibody levels to such viruses as cytomegalovirus, rubella virus, varicella virus, herpes zoster virus, herpes simplex virus of type 1 and type 2, Epstein-Barr virus, adenovirus, human herpes virus of type 6 and type 8.

Results: we have worked out our own vitiligo pathogenesis theory, which lies in its similarity to virogeny. This hypothesis can also explain genetic predisposition to vitiligo by analogy with the viral genetic theory of human cancer by Lev Zilber. The findings of the conducted research on virus carrying did not demonstrate any significant statistical discrepancy in the levels of these viruses IgG antibodies among the patients with vitiligo and the healthy donors.

Conclusions: the important fact is that the number of people having different viruses and high antibody titre to them prevails in healthy donors than in vitiligo patients. Thus, we can suppose that vitiligo patients have a weaker immune response compared to healthy donors.

Keywords: viruses, virus pathogenesis of diseases of skin, viruses and vitiligo.

Corresponding author

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INTRODUCTION

Diskhromium skin are an actual problem of dermatology as their specific weight makes about 10%. One of representatives of this group of a dermatosis - the vitiligo which is characterized by the expressed cosmetic defect and injuring mentality of the patient [6, 11, 12, 14].

In recent years the considerable increase of cases of vitiligo among persons of working-age leading to self-isolation of patients is noted as gives the social importance to this dermatosis [1, 3, 6, 14].

So far many parties of an etiology and pathogenesis of vitiligo remain unsolved. It should be noted that most of researchers adheres to nevrogenny, endocrine and immune theories of developing of vitiligo. So, consider that violations of nervous system are fundamental in pathogenesis of this illness, considering frequent emergence of a depigmentation of skin after psychological stresses [5, 14].

Vitiligo is often combined with diseases of endocrine glands that formed the basis to assume about a certain influence of the last on process of a melanogenic [9, 12, 14, 16]. The association between the clinical course of vitiligo and functional activity of a thyroid gland was revealed that was confirmed by high absorption of radioactive iodine a thyroid gland [9, 14].

LITERATURE REVIEW

In recent years the question of immune violations at sick vitiligo's is widely discussed [1, 4, 14, 21]. It was noted that vitiligo is quite often combined with various autoimmune diseases. Besides, at such patients fix the circulating organospetsific antibodies and antibodies of melanotsit [14, 17]. At the level of a bazalis layer of epidermis adjournment of C3 component of a complement and accumulation of cells of Langergans is defined that confirms the autoimmune mechanism of a depigmentation [9, 15]. There is a set of the theories directed to explaining the mechanism of development of vitiligo and each of them has the convincing scientific arguments both for and against.

The most popular and reasonable theories: neurogenetic (neuroendocrine), autoimmune (immune), autodestruktion (self-damage), theory of biochemical violations (oxidative stress), genetic.

According to data of literature [4, 5, 9], at sick vitiligo's development of autoimmune process is possible as a result of insufficiency of the T-cellular system of immunity leading to education autoantitet the melanincontaining structures arising owing to destruction of melanotsit. Sick vitiligo's had attempts of identification of special antibodies by means of immunofluorescent methods that allowed to suggest about existence of two types of this dermatosis: autoimmune and not autoimmune [4, 7].

It is specified that at sick vitiligo's considerable deviations in total of T-lymphocytes, and also their subpopulations are noted [2, 6]. Besides, increase of keeping of natural killers and T-suppressors which expressiveness of level was in direct dependence on prescription of skin process is noted.

It is specified that in epidermis of the depigmented skin decrease of the activity or a total disappearance of melanocyte is observed [5, 9, 10].

And it is result of immunological reactions at which the important place is taken by Langerhans cells. It is necessary to emphasize that Langerhans cells, having superficial receptors for IgG3 b-complement Fc-fragment, contain the anti-genes coded by genes of the immune answer and, therefore, exercise immunological "supervision" [2, 3, 6, 8, 9].

Along with immune system the system of anti-genes of a histological compatibility (HLA) which predetermines functioning of various cellular elements including melanotsit participates in maintenance of a homeostasis of an organism.

Search and testing of special pathogenesis markers which could serve as rather strict criteria of differentiation within one "a nosological range" of independent kliniko-genetic options is considered as an important scientific and practical task [2, 9, 14] now.

It is necessary to emphasize that the majority of the found associations of anti-genes of HLA concern diseases with the general signs, namely: with not clear etiology, lack of simple model of inheritance and existence of immunological violations. In this regard they are considered as diseases multifactorial of which clinical polymorphism and genetic heterogeneity, a big role of factors of external environment, an incomplete penetrance of genes are characteristic [5, 6, 11, 12].

Messages on research of the HLA system at sick vitiligo's are very small. Initial researches about distribution of anti-genes of a histological compatibility at sick vitiligo's indicated increase of relative risk for such anti-genes as HLA-A1, HLA-A2, HLA-A31 and HLA-B13 [1, 5, 7].

M. Minayev and co-authors [1, 5] when carrying out HLA typing at 135 patients aged from 8 till 68 years established statistically reliable increase of frequency of an anti-gene of HLA-A2 at 70,4%, and also HLA-B18 anti-gene at 18,5% against 10,7% in group of comparison (group of comparison 1085 healthy faces represented).

Ten of B.H. [2, 7] specified that for sick vitiligo's the general are such antigens of a histological compatibility as HLA-A9 (χ_2 = 12,5), HLA-A19 (χ_2 = 19,4), HLA-B18 (χ2=14,7), HLA-B21 (χ_2 = 13,0) and HLA-CW4 (χ_2 = 18,5) which in various gaplotipa cause emergence of certain clinical forms and options of a current of the specified dermatosis. Besides, the author established: at these patients changes from separate indicators of cellular and humoral links of immunity come to light. Depending on duration and clinical forms of a dermatosis, and expressiveness of immunological violations is predetermined by such anti-genes of a histological compatibility as HLA-A9 and HLA-B21.

Y. Zhao and coauthors [7, 10] carried out by a microcytotoxic method a histological compatibility of anti-genes of a histological compatibility of loci And yes In at 95 patients and 100 healthy people. It was noted that at a universal (vulgar) form of vitiligo the frequency of such anti-genes as HLA - A10 increases; A30+31; HLA-B13 and B15, at a focal form - HLA-A2; A30+31; at akrofatsialny – HLA-B13, B15 and B40. Authors specify: the autosomic-prepotent type of inheritance of vitiligo is characterized by increase of anti-genes: HLA-A30+31 and HLA-A2/V40, while autosomic-recessive - HLA-A30+31/B13 haploid type.

H.D. Chen and coauthors [3, 13] conducted research of anti-genes of a histological compatibility 2 classes at 91 sick vitiligo's, having found out high association of a dermatosis with HLA-DR B1, and having determined certain consistent patterns with a clinical form and a hereditary comorbidity on vitiligo, having made at the same time the conclusion about the high importance of immune-genetic mechanisms in development of a disease.

R. Orozco-Topete and coauthors [5, 6] specified that anti-genes 2 classes of a histological compatibility are characteristic of autoimmune diseases and carried out a compatibility at 71 sick vitiligo's and 47 patients with diseases of a thyroid gland, at the same time having revealed reliable increase of such anti-genes as HLA-DR4 and HLA-DR14 in both groups of patients that is the convincing proof of a community of pathogenetic mechanisms of the specified diseases.

Thus, the conducted researches devoted to immunogenetic markers testify to a certain hereditary conditionality of vitiligo. Apparently, the specified anti-genes of a histological compatibility cause independently or in a combination with anti-genes of other loci of the HLA system determination to the specified dermatosis. It is possible to assume that not only anti-genes of system of a histological compatibility, but also other anti-genes of the HLA system, along with factors of external environment, can promote development of vitiligo that quite often has family character.

It would be desirable to stop on the problems connected with antioxidant properties of skin at sick vitiligo's [5, 12, 18] as clinical supervision indicate a possibility of an aggravation of skin process after ultra-violet radiation when isomorphic reaction of Kebner can be shown [6]. Apparently, studying of a problem of a photopatronage at sick vitiligo's will have prospect and in respect of medical actions.

Functioning of melanotsit is defined by activity and the maintenance of a tyrosine, tyrosineelements, ions of copper, zinc, molecular oxygen [8, 9, 14].

So, A. Sh. Vaisov [9] at research by a neutron and activation method of structure of minerals at sick vitiligo's revealed decrease in content of zinc and copper in the depigmented skin and increase them in blood and urine, and at most of patients of change of an exchange of minerals are combined with dysfunction of a thyroid gland, the digestive channel, and also with a helminthic invasion, giardiasis, etc. [2, 8, 14].

H.K. Shadyev and coauthors [28] specified that he at all children of vitiligo is followed by an intestinal dysbiosis, the expressed reduction of quantity of anaerobe bacterias, increase in quantity of opportunistic microorganisms, especially lactosonegative colibacilli, a protea and Candida mushrooms, and these changes are aggravated with increase in prescription of a disease. The conducted researches allowed to develop the scheme of treatment of sick vitiligo's taking into account degree of activity of the main pathological process and a condition of acid-forming function of a stomach [2].

Along with a functional condition of the digestive channel at sick vitiligo's violations of farmako-metabolizing function of a liver [3], system of a hemostasis [18], microcirculation [16] come to light that, naturally, has to be considered when developing methods of therapy of this dermatosis. Chemical, in particular phenolic connections, can cause the phenomena hypo – and skin depigmentation, in such cases they and have professional character [4, 13].

The most recognized and put into practice is the classification of vitiligo offered Mosher D.B. and co-authors. [5], according to which distinguish the localized and generalized forms of a dermatosis. Treat localized focal (existence of the depigmented center in one area), seminary (existence of the depigmented spots on the course of nervous trunks) and mucous (existence of the depigmented spots only on mucous membranes). Generalized forms are presented universal (a full depigmentation of the general cover), vulgar (randomly located depigmentation sites on all skin) and akrofatsialny (the depigmented spots settle down mainly on face skin and extremities) by dermatosis forms. The so-called syndrome of Sutton representing the depigmented spot around a pigmentary nevus, and different quantity is especially allocated.

Recently as the agents responsible for development of many diseases of skin, a number of viruses is considered. In particular, as the etiological agent of the Kaposha's sarcoma (KS) it is recognized herpes-virus the person of the 8th type (NNV-8), its high degree is proved to association with idiopathic and the CK [7] immunosuppressive type. Are suggested that along with bacteria, development of psoriasis can be connected also with a virus of papilloma of the person. It is established that the frequency of detection of VPCh-5 on skin of psoriatic plaques more than twofold surpasses that in samples probably of healthy skin [11]. More than fivefold increase of a caption of stromal antibodies to VPCh-5 and VPCh-8 at patients with psoriasis in comparison to healthy people is noted that indirectly testifies in favor of participation of VPCh and some microbic agents in pathogenesis of local immune skin violations at psoriasis [1]. The role of a cytomegalovirus is supposed as red flat depriving of a cofactor in development [2].

Bypassed this direction and vitiligo. In many large guides to skin diseases at the description of vitiligo one of estimated pathophysiological mechanisms of developing of this disease notes influence of viruses [3]. Though this received by various researchers, as well as their opinions are very inconsistent. As the agents responsible for vitiligo, many viruses, including a cytomegalovirus (TsMV), a virus Epstein-Barra, and the human immunodeficiency virus (HIV) [8, 10] are considered. So, in 1996 Grimes et al. [9] identified existence of DNA of TsMV both in depigmented, and in the intact sites of skin at 38% (still 21% of patients had an uncertain result) patients about vitiligo and lack of DNA of TsMV in group of control donors. On the basis of the conducted researches, authors assumed a possible starting role of a cytomegalovirus infection at part of patients with genetically caused susceptibility that can cause destruction of melanotsit at vitiligo by means of start of aberrantly immune reactions. On the contrary, the researchers conducted by Akar A. et al., 2002 [6] and Toker S. C. et al., 2007 [12] the results received by Grimes did not confirm and authors came to a conclusion about an improbable role of cytomegaloviruses in pathogenesis of vitiligo.

The virus hypothesis of vitiligo of doctor Iversona [10] who assumed similarity of symptoms of vitiligo is interesting: a persistention, communication with nervous fibers, complexity of elimination with symptoms the caused herpes virus or retroviruses which can cause death of melanotsit at vitiligo both direct impact on nuclear DNA, and action on DNA in the course of formation of melanotsit, and also forcing immune system it is wrong to influence melanocytes in the course of attack to the viruses which are released from the nervous

terminations, and the general nerve ganglions in a spinal cord can explain existence of the symmetric nervous terminations.

In turn, analyzing the available scientific data we, also assumed possible similarity of a course of a disease with a virogeniya. Virogeniya or integrative type of interaction of a virus with a cage is characterized by embedding (integration) of virus DNA in the form of a pro-virus in a chromosome of a cage and their further joint replication. At the same time the integrated genome of a virus is replicated and functions as a cage genome component. The integrative type of interaction is characteristic of oncogenic viruses and some infectious viruses as DNA-genomic (for example, HBV), and RNA-genomic (for example, HIV). Integration with a genome of a cage requires existence of a ring form of two-chained DNA of a virus. DNA-genomic viruses in a ring form are attached to cellular DNA in the place of a homology of nucleotide sequences and built in a certain site of a chromosome with the participation of a number of enzymes - of restriction enzymes, endonucleases, ligases. DNA of a virus integrated into a chromosome of a cage is called a pro-virus. It is replicated as a part of a chromosome and passes into a genome of daughter cells, i.e. the condition of a virogeniya is inherited. However, under the influence of some physical or chemical facts the pro-virus can be excluded from a chromosome of a cage and pass into an autonomous state with development of productive type of interaction with a cage [4].

Additional genetic information of a pro-virus at a virogeniye reports to a cage new properties that can be the cause of a blasttransformation, and also developments of autoimmune and chronic diseases. Saving virus genetic information in the form of a pro-virus as a part of a cellular genome and transfer to its posterity is the cornerstone of a persistention of viruses in an organism and developments of latent viral infections [4].

Emergence and growth of spots of vitiligo can have analogy of a virogeniya since nature of emergence and growth of spots of vitiligo very much resembles formation of negative colonies of viruses in culture of cages superficially. Perhaps, there is a virus which provokes emergence and growth of the centers of a depigmentation. Also, as well as vitiligo, a pro-virus is induced by various, often unlike inductors among which can be an ultraviolet, some mutagens, antibiotics, etc. This hypothesis can explain as well genetic predisposition to vitiligo by analogy with the veresokina theory of cancer of the person Lev Zilber who considered that the healthy cell can mutate under the influence of certain viruses. DNA of an onkovirus is built in DNA of a cage and changes its genetic properties. The cage begins to share uncontrolledly and descends "bad qualities" to newborn "children".

So far a lot of things in an etiology and pathogenesis of vitiligo remain to unknown that, naturally, affects treatment of this category of patients.

In literature there are messages on application of various means for the purpose of stimulation of a melanogenesis. These are preparations of copper [3, 4], iron [19], extract of a placenta [10], dopegit [16], steroid hormones [3, 5, 6], and also local and system antioxidant therapy [6]. The preparation "Melagenin" and its modification "Melagenin-Plus" [3, 9] which use is carried out by infrared radiation of the vitiliginozny centers, and also usual greasing of sites of a depigmentation is especially allocated.

In recent years there were separate messages on efficiency of application of a kaltsipotriol for sick vitiligo's [2, 4], and even in combination with photochemotherapy [3, 8].

Especially it is necessary to stop on photochemotherapy of patients from vitiligo which is carried out everywhere and which has certain results [13].

Now the photochemotherapy mechanism, mainly, is studied and is characterized by photochemical reaction between molecules of the photosensitizing means which are excited by long-wave ultraviolet rays and molecules targets (keratinotsita, melanotsita).

The specified photochemical reaction is capable to interfere with replication of threads of DNA, and, therefore, slows down proliferative processes in cages of a basal layer and Langergans's cells that has the pathogenetic importance at treatment of sick vitiligos [9, 13, 18]. So, A. Sh. Vaisov [9] showed that carrying out photochemotherapy at sick vitiligos leads to stimulation of activity of the melanotsit which are settling down

mainly in a border area of the depigmented centers and around hair follicles and also reduction of quantity of cells of Langergans.

Application of photochemotherapy showed: not all sites of skin equally react to the carried-out treatment as PUVA-therapy leads to a repigmentation first of all of the centers of defeats on a face, a neck, and worst of all sites on brushes and feet will respond to treatment. Y. I. Koshevenko [14] notes that fresh spots give in to a repigmentation quicker, than the old centers, and an important clinical sign is existence on the depigmented spots of the decoloured hair which, as a rule, complicate a repigmentation.

In the conditions of the increased natural insolation carrying out photochemotherapy has the restrictions [13] in view of what the combined methods allowing to reduce a total dose of ultra-violet radiation when PUVA-therapy is combined with use of extract of a placenta [10], T-aktivinom [12], kaltsipotrioly [18] are developed. At treatment of sick vitiligo's application not only PUVA-therapies, but also in general the ultra-violet radiation stimulating melanogenesis [2, 4] is possible. Despite positive influence of ultraviolet rays, sick vitiligo's can have owing to radiation kelloidny hems [2] and their regeneration in a cancer of skin [5].

Quite interesting messages concern "Khellin-therapy" [5, 7] at the children having vitiligo when the preparation was applied locally in the form of 5% of ointment, and also in combination with photochemotherapy. So, S. Valkova [6, 7] used KUVA-therapy (Khellin+UVA) at treatment of 34 sick vitiligo's and within 2-26 months gained good effect at 20-90% of observed patients.

Taking into account a possibility of development of carcinogenesis methods of microphotochemotherapy of vitiligo [4, 9] when ultraviolet rays of V (UFV) on the device "Bioskin" in the range of 300-320 nanometers with a diameter of radiation of 1 cm are used are developed now.

Clinical physicians continue to discuss the question concerning methods of surgical treatment of sick vitiligo's [4, 5] though, considering isomorphic reaction of Kebner to subject travmatization skin is very problematic.

Today the most widespread method of treatment of sick vitiligo's is the photochemotherapy in spite of the fact that it is capable to lead to various undesirable effects which elimination is possible through reduction of a total dose of ultra-violet radiation and consequently, by development of new methods of complex PUVA-therapy taking into account pathogenetic mechanisms of developing of vitiligo, especially conditions of immunogenetic factors at this dermatosis that eventually will allow to allocate certain groups of patients for the purpose of their subsequent, differentiated correction.

RESULTS

In the work we conducted examination of 40 patients with various forms of vitiligo on presence of class IgG antibodies at them to such viruses as: cytomegalovirus (Anti-CMV-IgG), virus of a rubella (Anti-Rubella-IgG), virus of chicken pox and shingles (Anti-VZV-IgG), virus of simple herpes of 1 and 2 types (Anti-HSV-IgG), virus Epstein-Burra (Anti-EBV-IgG-VCA), adenovirus (Anti-Adenovirus-IgG), herpes virus of the types of the 6th IgG type (Anti-HHV6-IgG), herpes virus of the 8 types (Anti-HHV-8-IgG).

The control group included the equal number (40 people) of rather healthy donors who do not have the vitiligo similar to patients to vitiligo in gender and age.

As a result of the conducted researches we did not reveal any significant statistical differences on the level of maintenance of antibodies of the class IgG to above to the listed viruses between patients with vitiligo and healthy donors (Table 1).

Table 1. Average values of maintenance of antibodies of the class IgG

Viruses	Vitiligo (n=40)	Donors (n=40)	Norm
anti - CMV IgG E/ml	89,25	114	‹ 6,0
anti - Rubella IgG E/ml	20,23	9,80	‹ 5,0

анти-VZV IgG E/ml	823,26	1024	‹150
anti - HSV IgG E/ml	25,05	30,70	‹ 0,9
anti-EBV IgG-VCA (капс. бел.) E/ml	159,45	134,73	‹ 20
anti-Adenovirus IgG E/ml	2,96	2,77	‹ 0,8

Only the fact that the number of the persons which had contact with various viruses and having a high caption of antibodies to them, are more in group of healthy donors attracts attention, than at patients with vitiligo is (Table 2).

Table 2. The number of patients with positive value of maintenance of antibodies of the class IgG to various viruses.

Viruses	Vitiligo (n=40)	Donors (n=40)
anti-CMV IgG E/ml	29 (72,5%)	37 (92,5%)
anti-Rubella IgG E/ml	24 (60%)	36 (90%)
анти-VZV IgG E/ml	40 (100%)	40 (100%)
anti-HSV IgG E/ml.	37 (92,5%)	40 (100%)
anti-EBV IgG-VCA E/ml	36 (90%)	28 (70%)
anti-Adenovirus IgG E/ml	36 (90%)	40 (100%)
anti-HHV-6 IgG E/ml.	13 (32,5%)	10 (25%)
anti-HHV-8 IgG E/ml	3 (7,5%)	4 (10%)

CONCLUSION

And considering that in the course of the life all these patients and donors were in more or less equal vital conditions (climatic zones, living conditions, existence of the accompanying pathology etc.) it is possible to assume about weaker immune answer at patients with vitiligo, in comparison with healthy donors. But for more reasoned confirmation of this assumption it is expedient to conduct research at these patients of cellular and humoral antiviral immunity (system of interferon, NK-lymphocytes, In - and T-lymphocytes) that we also are going to make in our further works.

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