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Research Progress on Vitiligo and Its Comorbidities

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Abstract: ***Vitiligo is a chronic acquired depigmentation skin disease, the pathogenesis of vitiligo is not clear, previously, clinicians usually regarded vitiligo as a simple skin disease, but more and more research evidence shows that vitiligo patients are more likely to have autoimmune diseases, psychological diseases and other diseases than the general population. Therefore, this article classifies vitiligo and related diseases, and elaborates its possible pathogenesis, to provide a basis for further research on vitiligo and its comorbidities.***

Keywords: Vitiligo, Comorbidities, Research progress, Review**.**

1. Introduction

Vitiligo is a chronic acquired depigmented skin disease that affects 0.5-2% of the world's population [1] and affects the skin, mucous membranes, and hair follicles, It is considered to be the most common pigment disorder. At present, the pathogenesis of vitiligo is not clear, and various theories including autoimmune response, oxidative stress, melanocyte theory, neurochemical factor theory, and genetic theory [2,3] are still controversial. Still, autoimmune theory is widely recognized by the public. Clinically, vitiligo is mainly divided into two categories: segmental vitiligo and non-segmental vitiligo [4]. Segmental vitiligo is characterized by unilateral, asymmetrically distributed white patches that match a part of the skin and may appear in childhood, whereas nonsegmental vitiligo is more prevalent and appears as symmetrically distributed depigmented patches.

Current treatment for vitiligo depends on the type and extent of the disease and the timing of onset, with continued use of topical high-potency corticosteroids and topical calcineurin inhibitors recommended in stable non-segmental vitiligo involving less than 10% of the body surface, narrow-band (NB)-UVB phototherapy for diffuse disease, targeted local therapy (high-potency corticosteroids and calcineurin inhibitors) or phototherapy and surgery for stable segmental vitiligo, Autotransplantation of healthy melanocytes into depigmented areas [5,6,7], early detection and prompt treatment improve prognosis and disease progression. However, after suffering from vitiligo, patients rarely have special discomfort except for appearance changes, and the treatment period is long and the cost is high, so it is easy for patients to ignore the importance of treatment.

However, there is growing evidence that vitiligo is not just a skin disease, but due to its unique pathogenic mechanism, vitiligo patients are more likely to develop other diseases such as autoimmune diseases and mental illnesses than the general population. Therefore, this article classifies vitiligo and its related diseases, and expounds its possible pathogenesis, to provide a basis for further research on vitiligo and its comorbidities. In many susceptible sites to vitiligo, associated gene and DNA sequence variants can be found. Among the proteins involved in immune regulation, some play a role in apoptosis, while the other can regulate melanocytes.1 Autoimmune diseases.

2. Autoimmune Diseases

Available evidence suggests that both innate and adaptive immunity are involved in the pathogenesis of vitiligo. Early activation of innate immune cells by endogenous or exogenous stress signals released by melanocytes and keratinocytes, leading to subsequent activation of adaptive immune responses, both humoral and cell-mediated, leads to targeted autoimmune destruction of melanocytes [8], either in the presence of autoantibodies against melanocyte antigens in the serum of patients with vitiligo or in lymphocytes during the active phase of vitiligo [9,10] The aggregation of predominant cells and the detection of interleukin (IL)-1β, interferon (IFN)-γ, and transforming growth factor (TGF)-β in vitiligo patients [11] indicate that the pathogenesis of vitiligo is related to autoimmunity. The risk of vitiligo is related to whether the patient and his relatives have autoimmune diseases, such as: type I diabetes, autoimmune thyroiditis, lupus erythematosus, rheumatoid arthritis, alopecia areata, autoimmune gastritis, etc., and people who often suffer from the above immune diseases are at greater risk of vitiligo.

2.1 Thyroid Disease

Among all the autoimmune diseases associated with vitiligo, thyroid disease is one of the most common and widely studied diseases [12], it is undeniable that the autoimmune background is common among diseases, and some scholars have proposed that a large number of reactive oxygen species can destroy melanocytes and thyroid cells [13], and the target molecules thyroxine and melanin have a common origin: tyrosine[14], and genetic colocalization between vitiligo and thyroid autoantibodies has also been identified [15], and vitiligo tends to precede the onset of thyroid lesions in patients with a positive family history of these conditions and lack of other associated autoimmune or inflammatory lesions [16]. Therefore, clinicians should be aware of the increased risk of autoimmune thyroid disease in patients with vitiligo.

Some scholars [17] analyzed the prevalence of six thyroid diseases in vitiligo patients from 1968 to 2018, including subclinical hyperthyroidism, overt hyperthyroidism, subclinical hypothyroidism, overt hypothyroidism, Graves' disease, and Hashimoto's thyroiditis, and concluded that the prevalence of subclinical hypothyroidism was the highest, and the prevalence of subclinical hyperthyroidism and Graves' disease was the lowest. The correlation between the

prevalence of thyroid dysfunction and anti-TPO antibody titers in patients with NSV (nonsegmental vitiligo) is higher than that of the general population [18]. Another study of 37 patients with vitiligo [19] showed that the prevalence of TD, ATD, anti-thyroid peroxidase autoantibodies, and anti-thyroglobulin antibodies was 15.7%, 1.9, 16.8%, and 11.4%, respectively, in all patients with vitiligo, significantly higher than in healthy controls. Colucci et al. [20] found that the levels of thyroid hormone antibodies (THAbs), triiodothyronine, and thyroxine were extremely high in vitiligo patients, and proposed that THAbs may be a "bridge to a vicious circle" between melanocytes and the thyroid system.

2.2 Alopecia Areata

Vitiligo and alopecia areata are autoimmune-mediated skin diseases, both of which significantly affect patients' quality of life, mental health, etc. In a retrospective study of 1098 patients with vitiligo, alopecia areata was the second most common autoimmune disease associated with vitiligo, occurring in 3.8 percent of patients with vitiligo [21]. Oxidative stress and genetically predisposed autoimmunity are a co-pathogenesis of alopecia areata and vitiligo [22]. Elevated serum levels of oxidative stress markers IFN-γ, IL-1β, and IL-6 were seen during the progression of both diseases [23], and affected the bulb follicle in early growth and epidermal melanocytes in the basal layer of vitiligo in AA, respectively [24]. Clinical studies have shown that oral Janus kinase inhibitors are effective in both AA and vitiligo [25], so we believe that the two share a common pathogenesis, but further research is needed.

2.3 Diabetes

Diabetes mellitus is often associated with a variety of skin diseases, and type 1 diabetes is a recognized autoimmune disease characterized by targeted destruction of B cells that endocrine insulin in the pancreatic islets [26]. Among them, vitiligo is more common in type 1 diabetes. Some scholars believe that vitiligo and type 1 diabetes are both T cell-mediated immune diseases [27], and when patients have immune dysfunction, on the one hand[28],, it leads to the loss of B-cell antigen tolerance and the destruction of pancreatic islets, which in turn causes lymphocyte infiltration, resulting in an increase in blood glucose in the body, and on the other hand [29]. Causes damage to melanocytes, resulting in the release of antigenic substances, the formation of anti-melanocyte antibodies, and the inhibition of melanin production, which leads to the production of vitiligo. At the same time, the increase in autoantibodies in patients with vitiligo also supports the hypothesis of an autoimmune etiology [30,31]. Chang et al. [32] concluded that there was a significant association between vitiligo and type 1 diabetes mellitus through a systematic review of 15,657 vitiligo patients, which may be related to the similar T cell-mediated disruption of both diseases and proposed that type 2 diabetes mellitus may also be associated with vitiligo.

Recently, it has been found that the incidence of vitiligo in patients with type 2 diabetes has increased, and some scholars have selected 600 patients with type 2 diabetes and healthy adult volunteers without type 2 diabetes to measure fasting and postprandial blood glucose levels, and through medical statistical analysis, it is concluded that vitiligo is seen in 12% of patients with type 2 diabetes and 6% of healthy control groups. Therefore, vitiligo has also been found to occur in patients with type 2 diabetes, but the specific mechanism remains unclear and further research is needed [33].

2.4 Lupus Erythematosus

Patients with vitiligo have a higher prevalence and risk of lupus erythematosus in different populations, which may indicate a similar pathogenesis. Choi et al. [34] conducted a large-scale cross-sectional study and showed an increased risk of lupus erythematosus in 86,210 patients with vitiligo. Although no definite mechanism is known, several studies have identified potential isolated genes, particularly SLEV1, AIS1, and AIS2 on chromosomes 17p13, 1p, and 7q [35,36]. Considering that phototherapy is an effective treatment for vitiligo, timely screening of patients with vitiligo for lupus erythematosus is necessary because photosensitivity can exacerbate lupus erythematosus [36,37].

3. Mental Illness

3.1 Sexual Dysfunction

Although vitiligo is generally asymptomatic, local or systemic depigmentation greatly affects the appearance and causes great inconvenience to the patient's normal social activities and mental health [38,39]. The skin plays an important role in sexual function, and skin lesions can adversely affect sexual function, especially in patients with genital involvement. More than 50% of patients with vitiligo experience problems interacting with the opposite sex, and most feel that their sex life has been affected [40], while vitiligo is not life-threatening or physically incapacitating, it can greatly affect the patient's sexual function [41]. Studies have shown that patients with vitiligo are at greater risk of sexual dysfunction, that female patients are more correlated, and that sexual dysfunction may be more closely associated with female patients, but there is no clear evidence that fertility is affected in patients with vitiligo [42]. It can be seen that whether it is the appearance of depigmented plaques in the genital area or other factors, the quality of sexual life of vitiligo patients has decreased significantly.

These studies suggest that clinicians should be aware of the potential risk of sexual dysfunction in the treatment of vitiligo, pay attention to the quality of life and mental health of patients, actively popularize the relevant knowledge of vitiligo among the family members and sexual partners of vitiligo patients, and supplement it with psychological counseling, to reduce the psychological burden of patients and improve the quality of sexual life as much as possible.

3.2 Anxiety and Depression

Vitiligo is known to have a serious impact on mental health. Quality of life scores for people with vitiligo reflect a higher level of burden compared to healthy people. Morrison et al. [43] demonstrated that patients with vitiligo have a compromised quality of life and that psychosocial illness is more prevalent in patients with vitiligo than with diseases

such as acne, alopecia areata, and atopic dermatitis [44], and that quality of life impairment is even comparable to that of non-skin diseases such as chronic lung disease, arthritis, and cancer [45].

Depression and anxiety are the most common psychosocial comorbidities. Wang et al. [46] showed that the prevalence of clinical depression in patients with vitiligo was 8%, and the prevalence of depressive symptoms increased to 33%, which was 4.96 times that of the general population. Kussainova et al. [47] showed that the overall incidence of anxiety in patients with vitiligo was 35.8%, and the incidence was significantly higher in women. In addition, vitiligo patients often have a negative mood that affects the people around them, and studies [48] have shown that parents of children with vitiligo have a reduced quality of life and a higher risk of depression and anxiety.

To sum up, vitiligo will undoubtedly increase the psychological burden of patients, cause psychological problems such as anxiety and depression, and at the same time, mental and psychological stress will further aggravate the progression of vitiligo, thus creating a vicious circle. Therefore, in addition to providing appropriate psychological counseling and health education to patients, it is also necessary for clinicians to regularly complete the assessment of quality of life and psychological state.

4. Melanocyte-related Diseases

4.1 Ocular Abnormalities

Vitiligo is associated with a variety of eye anomalies. According to the melanocyte theory, melanocytes in the skin, mucous membranes, and hair follicles are unable to maintain normal skin color due to various reasons such as autoimmune damage, defects in the internal structure and function of melanocytes, excessive free radicals causing melanocyte metabolism, or neurochemical damage to melanocytes, resulting in abnormal melanocyte function and inability to maintain normal skin color, which in turn leads to the evolution of vitiligo [49]. Melanocytes are also present in the retinal pigment epithelium and the choroid of the eye, and melanocytes in the retinal pigment epithelium are essential for the metabolism of the extra rod and retinoids, as well as for photoprotection of the retina, and in the choroid, which contribute to eye pigmentation and UV protection [50,51]. When these melanocytes are damaged and the production of melanin is reduced, it can lead to eye abnormalities and even visual impairment.

A cross-sectional study by Genedy et al. [52] showed a significantly higher prevalence of ocular anomalies in patients with vitiligo, but no significant difference in visual acuity, possibly because ocular melanocytes are not directly involved in detecting or transmitting visual information. However, there have also been reports of vision loss due to vitiligo comorbidities, such as Dertlioğlu et al. [53], who found that 9 out of 49 patients with vitiligo (18.4%) had normal-tension glaucoma, while the control group showed no signs of glaucoma. In the absence of treatment, glaucoma can lead to permanent vision loss as it is a chronic, progressive neuropathy that damages the optic nerve. Prabha et al. [54] identified a variety of ocular anomalies in patients with vitiligo and suggested that periorbital depigmentation was associated with ocular anomalies. Chen et al. [55] used cumulative incidence and Cox proportional hazards models to study the risk of retinal detachment (RD) in vitiligo patients. Subgroup analyses showed that the incidence of RD in the vitiligo cohort was significantly higher than that in the non-vitiligo cohort, and patients with vitiligo treated with phototherapy, systemic corticosteroids, or immunosuppressants were at greater risk of developing RD.

4.2 Auditory Abnormalities

In the auditory system, melanocytes are distributed in the vascular striae and spiral ligaments of the cochlea, which are necessary for the maintenance of cochlear potential, which plays an important role in normal hearing [56], and oxidative stress is considered one of the most important factors in sensorineural hearing loss (SNHL) [57]. Oxidative stress plays a crucial role in triggering vitiligo and melanocyte destruction. When skin melanocytes are exposed to ultraviolet (UV) radiation and chemical pollutants, they are more likely to produce excess reactive oxygen species (ROS) in response to stress and fail to remove them in time, which causes changes in the body's oxidative and antioxidant balance [58], and both endogenous and exogenous stress can trigger the excessive formation of ROS. Another important mechanism of oxidative stress leading to the pathogenesis of vitiligo is the loss of melanocyte dendrites, resulting in the inability of melanin to transfer to keratinocytes, resulting in the loss of melanocyte function [59]. Based on the available evidence, melanocytes are both triggers and victims of oxidative stress, but there is no doubt that melanocytes in vitiligo patients are more susceptible to oxidative stress. A retrospective study was conducted by scholars and found that SNHL occurred in 0.61% of vitiligo patients and 0.29% of control groups. After adjusting for relevant influencing factors such as gender and age, it was found that there was still a significant association between vitiligo and SNHL, and the risk of SNHL was 2.2 times higher than that of the control group. Therefore, it is concluded that it plays an important role in the early prevention of SNHL in patients with vitiligo [60].

Therefore, vitiligo patients are also at higher risk of hearing abnormalities in the ears than the general population. As a result, many scholars have studied the relationship between vitiligo and hearing impairment, but the results have varied. A recent systematic review showed a 6.02-fold increased risk of sensorineural hearing loss in patients with vitiligo compared with controls [61]. However, Lien et al. [62] performed a similar analysis to examine hearing loss by assessing the pure-tone threshold. According to their findings, vitiligo patients only have a significant increase in the pure tone threshold at high frequencies, but not at low and medium frequencies, considering that most of the sounds in daily life are low and medium frequencies, and hearing loss in high-frequency areas is not sensitive to ordinary people, therefore, the authors believe that the hearing loss of vitiligo patients has no significant impact on daily life.

The destruction of melanocytes in patients with vitiligo indeed affects melanocytes with a common embryological origin, and ultimately the function of the organs in which they are located.

However, the small sample size and different evaluation indicators led to conflicting results between these studies. Further large-scale studies are needed to elucidate the disease burden and associated pathogenesis of ocular and auditory abnormalities in patients with vitiligo [63]. Based on the above findings, we recommend regular evaluation of patients with vitiligo to detect ocular and auditory abnormalities and treat these conditions at an early stage.

5. Summary

Previously, clinicians often thought of vitiligo as a simple skin disease, but there is growing evidence that people with vitiligo are more likely to develop other diseases such as autoimmune diseases and mental illness than the general population. Although the pathogenesis of vitiligo and its comorbidities is not well understood, further research is needed. However, the available evidence suggests that vitiligo is at risk of comorbidities with other diseases, so when dealing with vitiligo patients, dermatologists should consider vitiligo-related diseases and screen and identify them in advance if necessary, to improve the patient's quality of life as much as possible and avoid worse conditions.

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