

Review Article

Vitiligo in Children and Adults: A Narrative Review

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Abstract

Vitiligo is a chronic acquired depigmentary disorder of the skin and rarely of the mucous membranes with similar reported prevalence among children and adults. It is caused by melanocyte destruction and has a multifactorial pathogenesis with autoimmunity playing a central role in the disease onset.

There are two main types of vitiligo according to the degree of the surface area being affected, segmental and non-segmental namely. Due to the relatively high prevalence of associated autoimmune disorders especially in non-segmental vitiligo, further investigations should be performed as necessary. Care of vitiligo includes various agents (topical and systemic) and different surgical techniques. The decision for each treatment depends on different parameters, with the extent and location of skin involvement, the duration and stability of the lesions and patient's adherence being the most important. The most widely used first line treatment medications for vitiligo remain the medium-potency topical corticosteroids and topical calcineurin inhibitors. Light therapies are the most extensively studied treatments for vitiligo. They have been administered in various types and regimens and mostly in combination with topical corticosteroids, vitamin D analogues, azathioprine and others. The majorities of combination therapies has both demonstrated increased repigmentation and have been proven to be the most efficacious.

INTRODUCTION

Vitiligo is a chronic acquired depigmentary disorder of the skin and rarely of the mucous membranes with similar reported prevalence among children and adults [1,2]. The prevalence of the disease varies across countries and both lifestyle and socioeconomic factors may affect it. According to a recent review by Kruger and colleagues [2], the prevalence of vitiligo in children worldwide is estimated to be between 0.01 and 2.16%. Similar proportions have been reported for adults in the general population (0.06-2.28%). A slight female preponderance has been traditionally noted, which could also indicate the greater impact of psychosocial and cosmetic issues on females [3,4].

ETIOLOGY-PATHOGENESIS

Vitiligo is caused by melanocyte destruction and has a multifactorial pathogenesis. Several theories have been proposed such as autoimmune, genetic, autolytic, viral and neural, which are probably interrelated, with autoimmunity being the central player in this interaction [5,6,7].

Antibodies against melanocytes have been detected in patients with vitiligo, whereas dendritic cells consistent with antigen-presenting cells in recent lesions and mature T cells in older lesions have been observed on skin biopsies [4].

In addition, vitiligo is often seen in the setting of other coexisting autoimmune disorders, such as thyroiditis

(Hashimoto), pernicious anemia, rheumatoid arthritis, Addison's disease, Diabetes Mellitus type I, Systemic Lupus Erythematosus and alopecia areata, which further supports the autoimmune theory [1,6].

This autoimmunity seems to be related to several environmental and genetic factors which may well contribute to the development of the disease. The main environmental triggering factors which have been identified are trauma, stress, drugs, infections, chemical exposure, sunlight and nutritional components [3,5,8]. However, the exact mechanism of how the initial triggering event leads to the activation of the immune system cascade is yet to be fully understood. It has been suggested that a combination of the factors described previously with melanocyte defects activate various innate immune system proteins and cytokines. This process initially leads to the attraction and activation of dendritic cells, which present melanocyte-specific antigens to T-cells and ultimately to the IFN- γ -induced CD8+T-cells-mediated destruction of melanocytes [9]. Furthermore, animal studies have demonstrated the appearance of autoantibodies before the onset of pigment loss [10,11]. Cytokines may play an important role in the pathogenesis of vitiligo as well. For example, increased levels of IL-6, an inhibitor of melanocyte proliferation, have been observed in the affected skin of patients with vitiligo and were correlated with disease severity and duration. Moreover, IL-17 seems to counteract factors associated with the function and life duration of melanocytes [12].

Other cytokines which have been found to play a role are interferon (IFN)-gamma which is an initiator of apoptosis and tumor necrosis factor (TNF)-alpha which is an inhibitor of melanocyte proliferation and initiator of apoptosis [12].

Several genes have been implicated in the pathogenesis of vitiligo which are characterised by incomplete penetrance and genetic heterogeneity [8]. Genome-wide association studies have identified numerous susceptibility loci encoding for immune system components, involving both the innate and the adaptive immune system. In particular, associations have been observed with Human Leukocyte Antigen genes (e.g., HLA-A*02:01), immunoregulatory genes (e.g., CD44, CD80), melanocyte related genes (e.g., TYR, ZMIZ1) and apoptotic and cytotoxic genes (e.g., RERE) [8].

Patients with vitiligo usually are susceptible to Koebner phenomenon which is the development of depigmented skin lesions after skin irritation (eg exposure to sunlight) or trauma. This may be explained by melanocytorrhagy which is a defective adhesion of melanocytes in the epidermis and can cause destruction of melanocytes [11].

Oxidant stress may also play a role in the pathogenetic pathways of the disease, with free radicals and nitric oxide being toxic to melanocytes [7].

Contact allergens such as paraphenylenediamine, which can be found in hair dyes, can be linked to this oxidant stress pathway [4]. Chronic stress may also be implicated in the mechanism of melanogenesis. Stress may suppress the activation of the cutaneous "HPA axis" through glucocorticoids and, thereby, reduce melanogenesis. The exact pathophysiological pathways however are not fully understood [13].

A recent systematic review and meta-analysis revealed an association between low 25-hydroxyvitamin D levels and vitiligo in adults. Although the observed heterogeneity was significantly high, the study might indicate the importance of measuring 25(OH)D levels in patients with vitiligo. The association between the two conditions might be explained by the hypothesis that low serum 25 (OH)D concentration directly increases the risk of autoimmune disease. However, further studies are necessary to demonstrate this possible relationship [14].

CLINICAL PRESENTATION

Vitiligo lesions are characterized by depigmented mainly or hypopigmented macules or patches with well demarcated borders which progress to centrifugal enlargement over time.

The classification of vitiligo is based on the involved skin area and can be divided in two major categories: segmental and non segmental [1].

Segmental is more common in childhood than adulthood and accounts for 10-15% of all vitiligo types [1]. This type usually involves a specific dermatomal or quasi-dermatomal area with band-shaped distribution and sometimes follows the Blaschko lines [6]. Patients with segmental vitiligo most frequently have impaired follicular melanocyte reservoir (poliosis) which causes patches of white hair [15] and may have perihalo nevi as an adjunct [16].

Non segmental vitiligo includes specific types, such as acrofacial, mucosal, generalized, universal, mixed and focal.

Generalized vitiligo(vitiligo vulgaris) is the commonest type and involves all the areas of the body usually with symmetric lesions. Several halo nevi, hair loss of pigmentation (poliosis), Koebner phenomenon are common findings and this is usual consistent with positive family history [1]. The untreated lesions usually extend over time and this rarely leads to another type of non-segmental vitiligo, the universal type, involving more than 80% of surface area [4,6].

The acrofacial type does not usually affect children and mostly involves facial orificies, distal fingers, while mucosal type affects oral or genital mucosae and sometimes is part of generalized vitiligo [1].

Focal vitiligo presents either as a solitary or multiple macules in a specific area. Trichrome vitiligo is a vitiligo variant characterized by hypopigmented, depigmented lesions and normal skin areas which coexist forming a trichrome pattern [15].

Other variants include vitiligo minor, follicular vitiligo and punctuate vitiligo [1]. Mixed form accounts for both segmental and nonsegmental cases and it is rarely observed.

VITILIGO ASSOCIATED DISORDERS. LABORATORY INVESTIGATIONS

Due to the relatively high prevalence of associated autoimmune disorders especially in non-segmental vitiligo, investigations need to be performed including full blood cell count, TSH, T3, fT4, serum thyroid autoantibodies (Anti-Tg, Anti-Tpo) and antinuclear antibodies. (ANA) for detecting anaemia, thyroid disorder [1,15] and ANA-positive photosensitivity respectively [1]. Kakourou et al., showed that Hashimoto's thyroiditis is 2.5 times more frequent among children and adolescents with vitiligo than in a healthy age- and sex-matched population and it usually follows the onset of vitiligo [17] while Iacovelli et al., showed that 16% of patients with non-segmental vitiligo had thyroid alterations [18]. Several studies indicate a strong relationship between a positive family history of vitiligo and autoimmune/endocrine abnormalities (Autoimmune polyendocrinopathy- candidiasis-ectodermal dystrophy (APECED), leukotrichia and earlier disease onset .This may be the result of a mutation in the AIRE gene [19].

Vitiligo can affect the melanocytes of all structures, such as the eyes (uveal tract and retinal pigment epithelium) and the auditory system (inner ear) which may result in ocular and hearing disorders [20,21].

Alopecia areata is another comorbidity, implicated in similar mechanisms of autoimmunity. Both diseases are characterized by a mechanism of increased cellular stress and development of reactive oxygen species which contribute to the innate immune pathways [22].

Vitiligo like lesions has also been described in patients with malignant melanoma. This fact may be explained by the T-cell mediated immunological reaction after the development of impaired malignant melanocytes which leads to auto antibodies formation and the development of depigmented lesions [23].

DIAGNOSIS-DIFFERENTIAL DIAGNOSIS

The diagnosis of vitiligo is primarily clinical. The key finding which can differentiate this disorder from other similar skin entities is that vitiligo lesions are characterized by complete loss of pigmentation with usually marked borders, sometimes hyperpigmented with the texture of healthy skin. No itching is present.

Biopsy studies usually reveal the absence of melanocytes at the centre of the lesion and signs of inflammation peripherally [1].

The differential diagnosis varies widely. Congenital lesions can be early diagnosed; achromic nevus is usually apparent after birth and increases in size during child's development; albinism is also apparent at birth and piebaldism is usually located on the forehead, upper trunk and shins.

Post-inflammatory hypopigmentation, tinea versicolor, pityriasis alba, and pityriasis versicolor result in an incomplete loss of pigmentation and the use of Wood's light can easily distinguish them from vitiligo.

Asymptomatic tuberous sclerosis with Ash-leaf spots as the primary sign may also be initially perceived as vitiligo. Mycosis fungoides, lichen sclerosis, chemical leukoderma and Waardenburg syndrome should be considered in the differential diagnosis as well.

TREATMENT

Care of vitiligo includes various agents (topical and systemic) and different surgical techniques. The decision for each treatment depends on different parameters, with the extent and location of skin involvement, the duration and stability of the lesions and patient's adherence being the most important [6,23].

Patients with less than 20% of total body surface area affected can be treated with topical therapy, while those with greater extent of lesions (> 20% of total body surface area) need to receive additional therapies in order to achieve clinical improvement [24].

The aim of treatment is to reactivate pigment cells leading to re-pigmentation and to inhibit the mechanism of depigmentation and it involves anti-inflammatory agents such as corticosteroids and immunomodulators, and phototherapy, such as PUVA and 308nm excimer laser which can promote melanocytes migration [6]. Patients need to be informed in detail about the treatment options and the possible adverse effects of each treatment and be aware of the duration of therapy required in order to observe any signs of improvement. The psychological impact of the disease should always be considered as quality of life may sometimes be significantly impaired. Consultations with a psychologist/psychiatrist are warranted upon onset of treatment, especially in cases with lesions of great extent [1,24].

A recent Cochrane review published in 2015 included 96 randomized controlled trials which compared all types of interventions used in the management of vitiligo [25] and they are briefly discussed in the following sections along with evidence from published guidelines

TOPICAL CORTICOSTEROIDS

The most widely used first line treatment medications for vitiligo are the medium-potency topical corticosteroids. Facial and neck lesions tend to be more responsive to treatment with topical corticosteroids than those on the trunk, distal extremities and bony prominences [6,24]. Dark skin and recent lesions are also good prognostic factors for the efficacy of topical corticosteroids [26]. The effect of topical corticosteroids on repigmentation either as monotherapy or as combination therapy has been examined in 12 studies. In the study by Akdeniz and colleagues, patients on betamethasone plus calcipotriol plus NB-UVB were more likely to achieve repigmentation compared to NB-UVB only [27]. Similarly, topical hydrocortisone plus laser significantly improved pigmentation compared to laser treatment alone in adult patients [28]. No statistically significant differences were observed in studies comparing betamethasone with calcipotriol or betamethasone plus calcipotriol [29].

The reported adverse effects of topical corticosteroids mainly involved atrophy, teleangiectasia, hypertrichosis, striae [24,25].

Many studies have shown similar efficacy between topical corticosteroids and topical calcineurin inhibitors but patients with extrafacial vitiligo seem to respond better on topical calcineurin inhibitors [30-32]. Short term treatment with TCS is considered as safe and effective though [24].

SYSTEMIC CORTICOSTEROIDS

In cases of progressive or generalized vitiligo, oral corticosteroids have been used in order to control the disease. Oral mini pulses (OMP) of moderate doses of dexamethasone or methylprednisolone have been used intermittently, demonstrating a good effect and minimizing the adverse effects of continuous corticosteroid use. In cases of early onset disease, relapses are common [33,24]. Combinations of OMP with UVB have been also used with satisfying results [40].

TOPICAL CALCINEURIN INHIBITORS

The role of calcineurin inhibitors is immunosuppressive and anti-inflammatory [33]. Suppression of inflammatory pathways during depigmentation can have a positive impact in the mechanism of melanogenesis. In randomized controlled trials (RCTs) of calcineurin inhibitors monotherapy, the proportions of patients achieving 75% repigmentation was similar compared to patients receiving topical steroids.

The comparisons included tacrolimus 0.1% ointment twice daily for 6 months versus 0.05% fluticasone, pimecrolimus 1% ointment for 3 months vs mometasone 0.1%, 0.03% tacrolimus plus 0.01% mometasone vs 0.01% mometasone alone [32,34,35]. Likewise, no statistically significant difference was observed between 0.03% tacrolimus and superoxide dismutase and catalase creams [36] and between 0.1% tacrolimus and 1% pimecrolimus [37]. Topical calcineurin inhibitors have also been assessed in combination with other interventions (UVB, monochromatic excimer light). Non statistically significant benefits have been observed [38].

Overall, data from small RCTs and observational studies suggest that monotherapy with TCIs seems to be effective and

well-tolerated [39]. Regarding the daily dose and duration of treatment with topical calcineurin inhibitors, twice daily applications tend to exhibit better outcomes than once daily applications, whereas long term treatment (more than two months) seems to be more effective. However, further studies are needed to support these findings [37,40].

Similarly to topical corticosteroids, facial and neck lesions tend to respond better to treatment with TCIs [37]. Adverse events that have been reported are pruritus, erythema and burning sensation [24,25,39].

VITAMIN D

Vitamin D analogues such as calcipotriol (a synthetic Vitamin D3 analogue) have been mainly administered as combination therapy in the majority of RCTs. They are useful for patients refractory to treatment with topical corticosteroids and also for decreasing the dose of corticosteroids so as to avoid the adverse effects of long-term use [33]. In the RCT by Koumaran and colleagues, none of the participants receiving calcipotriol achieved greater than 75% repigmentation [41]. The addition of Vitamin D to various treatment modalities did not confer statistically significant benefit in the majority of trials [24,25].

ORAL AND TOPICAL ANTIOXIDANTS

Antioxidants are most frequently used in combination with phototherapy. Limited data are currently available with respect to pseudocatalase, vitamin E, vitamin C, ubiquinone, lipoic acid, Polypodiumleucotomos, catalase/superoxide dismutase combination, and Ginkgo biloba. Vitamin E oral supplementation combined with UVB or topical calcineurin inhibitors did not have a statistically significant benefit [42,43].

In a double-blind, placebo- controlled trial, the combination of lipoic acid, vitamins E, C and NB-UVB were superior to placebo in terms of repigmentation and oxidative stress [44].

PHOTOTHERAPY

Light therapies are the most extensively studied treatments for vitiligo. They have been administered in various types and regimens (UVA, PUVA, NB-UVB, excimer laser 308nm) and mostly in combination with topical corticosteroids, vitamin D analogues, azathioprine and others. The majority of trials have demonstrated increased repigmentation. Psoralens have been used along with long-wave UVA radiation (PUVA). Psoralens can be administered as oral or topical treatment and precede the UVA radiation. The mechanism of action entails induction of melanogenesis and migration of melanocytes [24].

PUVA seems to be associated with more short and long term risks compared to NB-UVB. [1,24]. Oral PUVA is contraindicated for children under 12 years of age because of the retinal side effects[24,33]. Topical PUVA is generally well tolerated and it requires small cumulative UVA doses and less phototherapy sessions. Adverse effects include blistering formation and peripheral hyperpigmentation. Inadequate response has been noted in active extensive vitiligo [24,45].

NB-UVB is the treatment of choice for active and widespread vitiligo because it does not only promote repigmentation but also, has an impact on the stabilization of the lesions [1,24].

Targeted phototherapy, such as excimer laser 308 nm is indicated for localized vitiligo and there is some evidence that it is more effective with topical interventions [6,24]. It is not used for more extensive types because it cannot prevent the spread of the lesions. Excimer laser and topical CNI were found superior to excimer laser monotherapy in a meta-analysis of four studies with regards to treatment success of vitiligo [46] The combination of topical vitamin D3 analogues and excimer laser did not confer a statistically significant benefit compared to excimer laser monotherapy in a meta-analysis of three studies (two RCTs showed no statistical significance, whereas one demonstrated statistically significant improvement only for the primary outcome) [46-49]. The combination of topical corticosteroids with excimer laser was only assessed in one study, suggesting a better effect compared to excimer laser alone [46,28]. One RCT compared azathioprine (low-dose) in combination with PUVA, to PUVA monotherapy and showed that combination therapy resulted in higher repigmentation after 4 months of treatment [50].

Despite the beneficial effects of phototherapy, there are some risks that require lifelong follow-up of the patients. It is widely understood that chronic exposure to UV irradiation leads to photoaging, immunosuppression and may ultimately result in photocarcinogenesis [51]. More long-term studies are warranted in order to estimate the exact risk of phototherapies.

SURGERY

Surgical procedures are used for the replacement of impaired melanocytes by those from a normal donor site. These procedures are used only after failure of the other treatment options. The majority of patients with vitiligo, however, are not suitable for surgery. Patients with stable segmental or focal vitiligo should be considered for surgical treatment, whereas patients with non- segmental vitiligo could be operated only after 6 months of inactive disease. Patients with Koebner phenomenon are not eligible for surgery [24].

Vitiligo is described as stable when the lesions remain the same for 2 or more years with or without signs of repigmentation, though some of these lesions may be still active and therefore, resistant to surgery. The unilateral form of vitiligo is also characterized as stable. Moreover, the positive mini grafting test is used to define stable vitiligo, when 4-5 mini grafts implantation at sites of lesions causes repigmentation [23]. Many techniques have been used and some of them require general anaesthesia. Methods include punch- grafting, epidermal blister grafting, ultrathin epidermal sheet grafting, cellular grafts and transplants of melanocytes.

DEPIGMENTATION

Depigmentation is useful for dark skin color adults with extensive or resistant to treatment vitiligo. It is not recommended for children because they lack the ability to understand and comply with the long-term consequences. It has a permanent effect and sun protection needs to be lifelong [33].

Monobenzone ethyl ester (MBEH) cream is an agent which is used for depigmentation. Possible adverse effects include irritation, burning sensation and dermatitis. Switched ruby

laser monotherapy or combined with methoxyphenol is another option for depigmentation [24].

CAMOUFLAGE

There are several cosmetic agents that are additionally used in order to decrease the psychosocial impact of the disease and improve quality of life. Self-tanning agents, dyes, whitening lotions, tinted cover creams, tattoos are some of them and they can be applied to conceal the areas of depigmentation [52,53].

OTHERS

Systemic immunosuppressants have also been investigated in a few studies, such as cyclophosphamide, cyclosporine and anti-TNF- α [24].

Recent studies have also shown the beneficial effect of topical prostaglandin-based formulations (latanoprost) in combination with NV-UVB in vitiligo [54,55]. Further studies are needed to confirm the efficacy of these treatments.

The combined use of ablative fractional CO₂ laser followed by UVB [56] or sunlight [57] may also be alternative treatments for refractory non-segmental stable vitiligo. These studies suggest satisfactory efficacy and safety of these therapies.

In summary, the available evidence suggests that combination therapy is the most efficacious option in the treatment of vitiligo. The relative benefits of combination regimens are yet to be established with additional studies.

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