

Vitiligo

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Abstract

Vitiligo is a common acquired pigmentation disorder characterized by depigmented macules and patches as a result of loss of functional cutaneous melanocytes. The condition affects 0.5 to 1% of population worldwide. Approximately 25% of affected patients have the onset of vitiligo before the age of 10 years. Genetic, immunological, and neurogenic factors may have a role to play in the pathogenesis. Typically, vitiligo presents as acquired amelanotic macules and patches that appear chalk or milk-white in color. Lesions often show homogenous depigmentation and are well demarcated. Lesions are often symmetrical and enlarge centrifugally in size with time. The most common location is the face, followed by the neck, lower limbs, trunk, and upper limbs. The clinical course is generally unpredictable. In children with skin type I and type II, no active treatment other than the use of camouflage cosmetics and sunscreens is usually recommended. Psychological support should be offered when necessary. If treatment is preferred for cosmetic reasons, a variety of treatment options are available. These include topical corticosteroids, topical calcineurin inhibitors, narrowband UltraViolet B phototherapy (nbUVB), and monochromatic excimer laser and light at 308nm.

Keywords: Vitiligo; Depigmentation; Topical corticosteroids; Topical calcineurin inhibitors

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Introduction

Vitiligo is a common acquired pigmentation disorder characterized by depigmented macules and patches as a result of loss of functional cutaneous melanocytes [1]. This condition can have considerable impact both psychologically and socially [2].

Prevalence

Vitiligo is estimated to affect 0.5 to 1% of population worldwide [3,4]. Approximately 25% of affected patients have the onset of vitiligo before the age of 10 years, 50% before the age of 20 years, and 95% before the age of 40 years [5]. The condition is rarely present at birth or seen in infancy [2,6]. There are no apparent differences in rates of occurrence according to race or skin type, although the condition is more noticeable in dark-skinned individuals [4,7]. The sex ratio is approximately equal, but females usually acquire the disease earlier than males [4,8,9]. Vitiligo is more common in atopic patients and patients with a personal or family history of autoimmune disease [5].

Etiopathogenesis

Genetic, immunological, and neurogenic factors may act alone or synergistically to trigger or perpetuate the loss of functional melanocytes from the basal layer of the epidermis [3,4]. It is estimated that 12 to 35% of affected patients in the pediatric age group have a positive family history of vitiligo [10]. The disease has a polygenic mode of inheritance. Certain Human Leucocyte Antigens (HLA) such as HLA-A2, HLA-DR4, HLA-DR7, and HLA-Cw6, may contribute to the susceptibility

[6,8]. Inheritance may involve genes associated with regulation of autoimmunity, melanin biosynthesis, and response to oxidative stress [9]. The gene *NALP1* (*NLRP1*) on chromosome 17p13, encoding NACHT leucine-rich-repeat protein 1, predisposes individuals to vitiligo and various autoimmune diseases [2,4,11]. Other genes that may be responsible include *PTPN22* (B-cell signal transduction gene) and *FOXD3* (melanocyte developmental regulator gene) [11,12]. Vitiligo is often associated with other autoimmune diseases such as Hashimoto thyroiditis, Graves disease, diabetes mellitus, Addison's disease, and pernicious anemia [9,13-15]. The involvement of autoimmunity in the pathogenesis of vitiligo (especially in nonsegmental vitiligo) is supported by the demonstration of circulating autoantibodies to melanocytes in patients with vitiligo [3,9].

Oxidative stress may also have a role to play. Accumulation of free radicals toxic to melanocytes may lead to their destruction by dermal dendritic cells [9]. Alternatively, melanocytes might exhibit increased sensitivity to oxidative stress [5]. It has been shown that serum oxidants and oxidative stress indexes are higher and serum antioxidants are lower in patients with vitiligo [16].

Trauma and friction (Koebner phenomenon) may also be involved in the pathogenesis of the disease [1,4,10,17]. In this regard, affected patients with Koebner phenomenon have an earlier age of onset of disease and an increased body surface area involved [17]. These patients also have poorer response to treatment [17].

In segmental vitiligo, a neurogenic sympathetic disturbance might be responsible [4]. Certain chemical mediators released from nerve endings might cause decreased melanin production or cause destruction of melanocytes [3,9]. In this regard, elevated neuropeptide Y levels have been demonstrated in the skin of affected patients [9].

Histopathology

Histologically, melanocytes are absent in established lesions [1,5]. A superficial dermal lymphocytic/mononuclear infiltrate may be seen in the advancing margin of vitiligo, especially in early lesions [1,9].

Clinical Manifestations

Typically, vitiligo presents as acquired amelanotic macules and patches that appear chalk or milk-white in color [9,13]. Lesions often show homogenous depigmentation and are well demarcated [4]. Pinpoint depigmentation may precede patchy depigmentation in

rapidly progressing disease [4]. A hyperpigmented rim at the interface of depigmented and normally pigmented skin may be seen after sun exposure [4,8]. Lesions are often symmetrical, spread centrifugally, and increase in size with time [8,9]. New lesions may also appear. The most common location is the face, followed by the neck, lower limbs (Figure 1), trunk, and upper limbs [5,18]. The back is relatively spared [5]. Rarely, the hair, buccal mucosa, and gingiva may also be affected [5]. Typically, lesions of vitiligo are asymptomatic but itch has been reported [8,13].

Vitiligo is classified into subtypes based on the pattern and extent of involvement. Generalized vitiligo, also known as vitiligo vulgaris, is the most common type and accounts for approximately 80% of cases [5]. Lesions are widely and usually symmetrically distributed [9]. Universal vitiligo refers to vitiligo with involvement of more than 80% of the body and is very rare [1,8]. Focal vitiligo presents as a solitary macule or a few macules in a localized area and not in a dermatomal pattern [19]. Segmental vitiligo represents unilateral macules in a dermatomal pattern [19]. In most patients, one unique segment is involved [7]. This type of vitiligo is less likely associated with autoimmune diseases [9,18]. Segmental vitiligo is more common in children than in adults and accounts for 4 to 19% of cases in the pediatric age group [19]. Acrofacial vitiligo affects periorificial areas and digits [19]. Mucosal vitiligo involves mucous membranes [9]. Confetti vitiligo presents as numerous small macules with variable distribution patterns. Trichrome vitiligo is characterized by both hypopigmented and hyperpigmented macules in addition to normally pigmented skin [6,19]. Quadrichrome vitiligo has additional marginal or perifollicular hyperpigmentation [8].

Diagnosis

The diagnosis is mainly clinical, based on the findings of acquired, well-demarcated white macules and patches that tend to enlarge [1]. Wood's lamp accentuates the lesion and may be of benefit in the diagnosis (e.g. to differentiate from tinea versicolor or pityriasis alba), especially in fair skin individuals [8,20]. A skin biopsy is usually not necessary except when the diagnosis is in doubt. The use of dopa stain for tyrosinase or Fontatana-Masson stain for melanin can be used to confirm the diagnosis [6].

Laboratory Studies

Because of the associations with autoimmune diseases, screening with a thyroid-stimulating hormone, antithyroglobulin antibody, antithyroid peroxidase antibody, complete blood count, fasting blood

glucose or HgbA_{1c}, and antinuclear antibody is often recommended in children with active vitiligo [5,11].

Differential Diagnosis

The differential diagnosis includes pityriasis alba, tinea versicolor, hypomelanosis of Ito, nevus depigmentosus, tuberous sclerosis, nevus anemicus, achromic nevus, oculocutaneous albinism, idiopathic guttate hypomelanosis, progressive macular hypomelanosis, lichen sclerosis, piebaldism, and postinflammatory, chemical-induced, or drug-induced hypopigmentation [1,4,19]. The distinctive features of each condition allow a relatively straightforward differentiation from vitiligo.

Complications

Affected areas are hypersensitive to ultraviolet light and are at risk for sunburn. In addition, vitiligo can be cosmetically and psychologically devastating, resulting in a lower self-esteem, poor body image, social anxiety, peer rejection, insomnia, depression, obsession, hypochondria, and stigmatisation [2,3,6]. The psychological impact is greater in dark-skinned individuals, females, and when visible areas are involved [19]. The disease has an adverse effect on the quality of life of affected patients [21].

Prognosis

The clinical course is generally unpredictable [1]. Most patients, except those with segmental vitiligo, experience slow progression of the disease through the appearance of new lesions or enlargement of existing lesions [22]. There may be periods of relative inactivity which may last for months to years [3]. In segmental vitiligo, lesions tend to progress rapidly at onset and show a more stable course thereafter [3,23]. In the majority of cases, vitiligo is a chronic persistent disorder [13,20]. Spontaneous repigmentation is uncommon and the repigmentation is usually incomplete [19,22].

Management

In children with skin type I and type II, no active treatment is necessary other than the use of camouflage cosmetics including fake tanning products [24]. The use of sunscreens is advisable to reduce the risk of sunburn [20]. Psychological support should be offered when necessary.

If treatment is preferred for cosmetic reasons, a variety of treatment options are available. The therapeutic effect of all the treatment modalities used varies greatly from one patient to another and treatment must be individualized. In general, the best treatment response is seen in younger patients, recent disease onset, darker skin types, and head and neck lesions [7,25]. Acral lesions usually respond poorly to treatment [7].

Topical corticosteroids and calcineurin inhibitors (tacrolimus and pimecrolimus) are the treatment of choice for those with localized disease [19,23,26]. Potent or very potent topical corticosteroids may arrest the attack on melanocytes by the immune system and can repigment vitiligo [2,20]. Topical corticosteroids are chosen because of their relative low cost and ease of application [26]. The success rate ranges from 45 to 60% in childhood vitiligo [24]. Compared with adults, children are at higher risk of local and systemic side effects. Local adverse events include skin atrophy, telangiectasia, striae, decreased adipose tissue, rosacea, hypertrichosis, folliculitis, and perioral dermatitis. Systemic adverse events include Cushing syndrome, adrenal suppression, cataracts, glaucoma, osteopenia/osteoporosis, and growth retardation. As such, treatment with potent or very potent topical



Figure 1: Vitiligo presenting as well-demarcated depigmented patches on the dorsum of the left foot of a 10-year-old girl.

corticosteroids should ideally not exceed two months [19,20]. The addition of topical calcipotriene to the corticosteroid regimen once a day can enhance efficacy and reduce the risk of skin atrophy [11,24,25]. Judicious use of a short course of oral prednisone should be considered for patients with rapidly progressing vitiligo.

Topical tacrolimus and pimecrolimus block the action of calcineurin, thereby downgrading the transcription of genes encoding pro-inflammatory cytokines which are involved in the pathogenesis of vitiligo [22]. In addition, these compounds stimulate melanocytes and melanoblasts proliferation [23]. Topical calcineurin inhibitors are effective in repigmentation of vitiligo [19,22]. Randomized, double-blind, placebo-controlled trials showed that tacrolimus offers similar results compared to topical corticosteroids in the treatment of childhood vitiligo [27,28]. Tacrolimus has a slightly better response rate compared to pimecrolimus [26]. Topical calcineurin inhibitors have a better safety profile compared to topical corticosteroids and are generally preferred for lesions on the face, neck, genitalia, and intertriginous areas [4,11]. Stinging/burning, pruritus, irritation, and erythema may occur in some patients. Topical calcineurin inhibitors have been given a black box warning by the Food and Drug Administration (FDA) for a potential cancer risk based on animal studies and case reports, although most dermatologic and pediatric societies have dismissed this concern [19].

Narrowband Ultraviolet B (nbUVB) phototherapy is currently the phototherapy of choice and should be considered in those who have widespread vitiligo or those with localized vitiligo associated with a significant impact on the quality of life who do not respond to treatment with topical corticosteroids and calcineurin inhibitors [7,20,25,29]. It has been shown that nbUVB phototherapy is superior to UVA phototherapy [1,25]. nbUVB induces tyrosinase which is crucial to melanin production [25]. Patients treated with nbUVB do not need to take oral psoralen or apply psoralen and they do not have to wear protective sunglasses [20]. Side effects include burning, pruritus, erythema, desquamation, xerosis, blistering, and ulceration [25]. Monochromatic excimer laser and light at 308nm allow for the targeted treatment of specific lesions and have fewer side effects [1,11,24,25]. Monochromatic excimer laser and light have similar efficacy and have better outcomes compared to nbUVB phototherapy [30-32].

Surgical therapies may be considered for adults with stable (no progression for 6 to 12 months) vitiligo who do not respond to medical therapies [16]. Such therapies are not recommended for children [20].

Depigmentation therapy involves the use of monobenzyl ether of hydroquinone [24]. This is mainly reserved for adult patients with extensive disease unresponsive to traditional therapies. Possible adverse events include skin irritation, burning sensation, pruritus, and eczema [23].

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