Childhood vitiligo: the effect of narrow-band ultraviolet B phototherapy

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Received 30 January 2019
Accepted 19 March 2019
Published 11 June 2021

Journal of Current Medical Research and Practice
2021, 6:99–103

Vitiligo is an idiopathic acquired disorder characterized by depigmented macules or patches and affects ~0.5–2% of the worldwide population, without any predilection in terms of sex or ethnicity. It usually begins in childhood or young adulthood. Many etiologic hypotheses have been postulated for vitiligo, including biochemical, neural, and autoimmune mechanisms. The most compelling of these suggests a combination of genetic and immunologic factors that interact and result in an autoimmune melanocyte destruction. Phototherapy using narrow-band ultraviolet B (NB-UVB) with wave length 311–313 nm is considered the treatment of choice in vitiligo, even in childhood. The choice of NB-UVB phototherapy for the treatment of vitiligo has been reported since 1997. Previous studies showed that NB-UVB is a safe treatment for vitiligo in children. NB-UVB is considered more effective and better tolerated than psoralen plus ultraviolet A and shows more stable results.

Keywords:
Childhood vitiligo, NB-UVB, NB-UVB phototherapy, phototherapy, phototherapy in childhood vitiligo, vitiligo

J Curr Med Res Pract 6:99–103

2357-0121

Introduction

Vitiligo is an acquired disease, possibly autoimmune by nature, sometimes with a clear hereditary component, which is characterized by clearly circumscribed, milky white spots on the skin and/or mucous membranes [1]. Vitiligo is the most prevalent pigmentary disorder [2], irrespective of age, race, ethnic origin, or skin color [3]. It is reported that 1–2% of the world's population is affected [4].

Clinical pictures

Patients present with one to several amelanotic macules or patches that appear chalk white or milk white in color [2] surrounded by a normal or a hyperpigmented border. Very rarely, the patches may have a red, inflammatory border [5]. The lesions are usually well demarcated, but the margins may be scalloped [2].

The patches are of various sizes and configurations. The hairs in the vitiliginous areas may become white. Vitiligo lesions are especially marked in dark-skinned individuals [6,7].

Lesions may enlarge at an unpredictable rate and can appear on anybody site, including mucous membranes [8].

The most commonly affected sites are the face, upper part of the chest, dorsal aspect of the hands, axillae, and groin. There is a tendency for the skin around orifices to be affected (the eyes, nose, mouth, ears, nipples, umbilicus, penis, vulva, and anus). Lesions also appear at areas of trauma, so vitiligo favors the elbows and knees [5].

Ocular abnormalities are increased in patients with vitiligo, including iritis and retinal pigmentary abnormalities. Overall, 8% of patients with idiopathic uveitis have vitiligo or poliosis [9].

Vitiligo in childhood

The first study of childhood vitiligo was conducted by Halder *et al.* [10]. They concluded that childhood vitiligo is a distinct subset of vitiligo, with high incidence of segmental type, family history of autoimmune or endocrine disease, early or premature graying, increased autoantibodies, and poor response to topical psoralen plus ultraviolet A (PUVA).

Other studies reported that children and adolescents with vitiligo demonstrate increased frequency of Hashimoto's thyroiditis. Considering the fact that vitiligo usually precedes autoimmune thyroiditis, a possible early diagnosis of the latter is possible. It is therefore recommended that children and adolescents with nonsegmental vitiligo undergo annual screening for

antibodies against thyroperoxidase, antithyroglobulin antibodies, and thyroid-stimulating hormone [11].

Histopathology

The most prominent feature in vitiligo is the alteration of melanocytes at the dermal–epidermal junction [12]. It shows loss of melanocytes and melanin in the white patches, and inconstant lymphonuclear infiltrate in the advancing margins of lesions [6].

The peripheries of expanding lesions, which are hypopigmented rather than completely depigmented, still show a few dopa-positive melanocytes and some melanin granules in the basal layer. In the outer border of patches of vitiligo, melanocytes are often prominent and demonstrate long dendritic processes filled with melanin granules [12].

Specific staining procedures such as the Masson–Fontana method for melanin or dihydroxyphenyl alanine technique for tyrosinase generally show absence of melanocytes from vitiligo lesions [6]. Electron microscopy fails to identify melanocytic cells in vitiligo achromic patches. The melanocytes are degenerated and appear to be replaced by Langerhans cells. Moreover, the epidermis of areas around the margins of vitiligo shows abnormalities of keratinocytes [13].

Wood's lamp examination

Wood's lamp provides bright reflection of white patches and enhanced details on intermediate pigment tones (panel A), as compared with normal light (panel B) [14].

Clinical variants of vitiligo [15,16]

(1) Trichrome vitiligo: in addition to normally pigmented and amelanotic skin, there is also an intermediate, hypopigmented interface
(2) Quadrachrome vitiligo: there is a fourth, hyperpigmented band, which may develop during repigmentation
(3) Blue vitiligo: vitiligo macules at the sites of postinflammatory hypermelanosis
(4) Inflammatory vitiligo: the depigmented macule is surrounded by a raised, erythematous border, and sun exposure may cause the whole macule to become erythematous
(5) Confetti vitiligo: patients develop several hundred small macules (≤2 mm) with variable distribution patterns.

Differential diagnosis

Pityriasis alba

This is a common, benign, localized form of hypopigmentation, more commonly seen in children than in adults, with unclearly bordered hypopigmented maculae and pityriasis-like desquamation on their surface. The disease begins with an erythematous plaque with elevated edges, and desquamation occurs after several weeks. The changes are localized on the head, neck, and upper limbs [17].

Piebaldism or albinism

It is a rare depigmented disorder owing to a mutation of c-kit proto-oncogene affecting the differentiation and migration of melanocytes. It is characterized by stable and circumscribed white patches with absence of melanocytes (autosomal dominant) present at birth, affecting the face (especially the central area with localized poliosis), sternal and abdominal zones, knees, and elbows [18].

Tuberous sclerosis

It is a autosomal dominant, multisystemic neurocutaneous syndrome, characterized by the formation of multiple hamartomas usually localized in the skin, brain, heart, kidney, liver, and lungs. The characteristic triad consists of deafness, mental retardation, and cutaneous angiofibromas, in only 29% of patients. It occurs at birth or during the first months of life in 97.2% of patients [19].

Depigmented lesions in leprosy

It shows anesthetic disturbance of sensibility [20].

Achromic nevus

It is a well-limited depigmented area, stable and evident at birth, in which melanocytes are either normal or reduced [20].

Postinflammatory leukoderma (e.g. after psoriasis or syphilis)

Patients have a history of pre-existing dermatosis [20].

Pityriasis versicolor

It is a superficial yeast infection that can lead to loss of pigment in darker-skinned individuals. It presents as light-colored macules typically on the upper trunk and chest, with a fine dry surface scale where mycologic examination reveals hyphae and spores [18].

Idiopathic guttate hypomelanosis

It presents with multiple small discrete white macules on the trunk or on sun-exposed areas of the limbs [20].

Progressive macular hypomelanosis

It is most common in African–American patients originating from tropical countries. It is characterized by ill-defined, nummular, nonscaly hypopigmented macules on the trunk, often confluent in and around the midline and rarely extending to the proximal extremities and head and neck [20].

Treatment of vitiligo

Although it is relatively resistant to most of the treatments, spontaneous repigmentation occurs in more than 1–25% of cases [5].

Sun protection of the vitiliginous areas with sunblocks is important [9] which helps prevent sunburn, and thus may lessen photodamage as well as the chance that a Koebner phenomenon will occur [2].

Cosmetic improvement can be achieved by camouflage products and self-tanning dyes [9]. The newer self-tanning creams containing dihydroxyacetone are useful for light-skinned and olive complexioned patients with acral lesions [5].

The goal of treatment

The goal of treatment is to suppress depigmentation and stimulate repigmentation. This is achieved by suppression of inflammation or oxidation in early active lesions and/or stimulation of melanocyte division and migration. The melanocytes that migrate into the basal layer of the depigmented skin come from contiguous pigmented skin (melanocytes migrate approximately 2–3 mm into the depigmented skin) and from the hair follicle of the lesion [21].

Therefore, early small lesions have a better response to treatment than the long-standing larger ones. Lesions on the face and neck respond better to treatment than those on the trunk, distal extremities, and bony prominences with a low density of hair follicles or without hair follicles [22].

Management of vitiligo in children

The choice of medical treatment depends on the type, location, and duration of lesions as well as the eagerness of the child and his/her parents to pursue therapy [23].

Topical corticosteroids

The most widely prescribed treatment in children is topical corticosteroids, classes 3 and 4 corticosteroids. Class 3 corticosteroids are the most effective and safest therapy for segmental vitiligo [24].

Moreover, topical corticosteroids of high potency have been recommended for short courses in children with vitiligo [25].

Topical immunomodulators and calcineurin inhibitors

These are used to treat small and/or difficult areas, such as the eyelids. An interesting report of focal hypertrichosis in a child while using topical tacrolimus for vitiligo was described [26].

Vitamin D_3 analogs

They are used as monotherapy or combined with exposure to narrow-band ultraviolet B (NB-UVB) phototherapy, sunlight [27], or topical corticosteroids [28]. For the children who had previously failed trials of topical corticosteroids alone, the combination of the two agents might be more efficacious [23].

Phototherapy

NB-UVB phototherapy is considered as a safe and effective therapeutic option in the treatment of vitiligo in children (this is discussed later in details) [23].

Systemic psoralen plus ultraviolet A

Repigmentation with PUVA is widely variable, and rarely 100% is achieved. In general, dark skin types have better repigmentation than paler skin types. Usually, 1–3 years of treatment are needed for optimal results, which is one of the drawbacks. PUVA is not recommended for the treatment of children younger than 12 years as it is considered less effective and less tolerated than NB-UVB [29].

PUVA has the highest rates of adverse effects such as nausea, vomiting, phototoxic reactions, and a theoretical increased long-term cutaneous malignancy risk [30].

Topical psoralen plus ultraviolet A

Topical PUVA is an attempt to limit the area that becomes photosensitized and avoid some of the adverse effects of systemic psoralen. This method also has adverse effects, including erythema, blistering, and hyperpigmentation of normal, adjacent skin [30].

Excimer laser (308 nm excimer laser)

It is described for pediatric vitiligo with or without concurrent topical calcineurin inhibitors [31]. Efficacy is good in all skin types, but darkly pigmented men with facial lesions seem to repigment best with this therapy [32].

Excimer laser is better at inducing repigmentation and faster than NB-UVB but does not stabilize disease and is impractical for widespread lesions. Treatment results are achieved more slowly with once weekly treatment than twice or thrice weekly. Addition of hydrocortisone butyrate [33] to therapy can speed response, as can tacalcitol, a vitamin D topical preparation. These compounds do not have a black box warning [34].

Pseudocatalase

Topically applied pseudocatalase –Karin U Schallreuter (PC-KUS) activated by a low-dose NB-UVB phototherapy has been used in the treatment of vitiligo in children. The total dose of NB-UVB per annum for each child was in the range of 42–60 mJ/cm^2, which is equivalent to ~5.6 h of sun exposure per annum. The therapy had no adverse effects [35].

Surgical

Epidermal grafting (autologous mini-punch grafting and blister roof grafting)

Segmental vitiligo is the best indication for surgical repigmentation, and these patients are good candidates for epidermal grafting. This surgical technique was followed by 3 months of PUVA [36].

Epidermal cell transplantation

The best results are seen in segmental vitiligo. In this technique, a melanocyte-rich suspension is applied to the affected area and then allowed to graft. The best results are seen when only one site is involved. The main advantage is that only one time treatment is necessary, if successful [30].

Noncultured melanocytes and keratinocytes transplantation

It is an easy economic technique, which may be used in resistant area of stable vitiligo. The smaller the size of the lesion and the longer the stability duration, the higher the percentage of repigmentation response obtained [37].

In this technique, noncultured cell suspensions can be immediately transplanted, unlike culturing of the melanocytes, which takes ~3 weeks to accomplish [38].

Narrow-band ultraviolet B phototherapy

NB-UVB offers a potential for the management of childhood vitiligo.

Mechanism of action of narrow-band ultraviolet B pertaining to vitiligo

A two-step effect of NB-UVB has been proposed – both of them may occur simultaneously [39].

First, there is immunomodulation (local as well as systemic), leading to down-regulation of immune attack against the melanocytes. Subsequently, the melanocytes are stimulated to migrate to the epidermis and synthesize melanin. NB-UVB has been shown to induce immunosuppressive effects including induction of interleukin-10, reduced natural killer cell activity, and lymphoproliferation [39].

NB-UVB phototherapy increases synthesis of interleukin-1, tumor necrosis factor alpha, and leukotriene C4, and these cytokines induce melanocyte mitogenesis, melanogenesis, and melanocyte migration. However, the roles of interleukin-1 and tumor necrosis factor alpha in melanogenesis are controversial and contradictory, as has been observed in some studies [40].

Second, release of prostaglandins (PGE2 and PGF2) is another mechanism of action of phototherapy. PGE2 is synthesized in the skin and regulates melanocyte and Langerhans cell function and promotes melanocyte mitogenesis [41].

NB-UVB stimulates the dopa-negative, amelanotic melanocytes in the outer hair root sheaths, which are activated to proliferate and migrate outward to adjacent depigmented skin, resulting in perifollicular repigmentation, and subsequently, these melanocytes migrate downward to the hair matrices to produce melanin. This was substantiated by Awad [42], who reported that melanocyte precursors can be demonstrated histopathologically and immunologically on tissue samples after ultraviolet therapy, which are capable of proliferation and migration into depigmented epidermis to repopulate it with new generations of melanocytes.

Interestingly, patients receiving NB-UVB have shown an increase in the serum levels of 25(OH) vitamin D, indicating the role of vitamin D in NB-UVB-induced repigmentation [43].

Adverse effects of narrow-band ultraviolet B in patients with vitiligo: short and long term

Erythema is the most significant short-term adverse effect of NB-UVB, and the incidence varies between 10 and 94% according to the treatment regimen and definition of erythema [44].

The long-term risk remains unclear. UVB is a complete carcinogen, and TL-01 has been shown to induce DNA damage in human skin cells and animal models.

In a knockout mice model, development of malignant skin tumors was significantly higher for NB-UVB than broadband ultraviolet B following equivalent dose exposure [45].

No significant increase in squamous cell carcinoma or melanoma was observed, and there was only a small increase in basal cell carcinoma (unlikely to be related to treatment, as it appeared during the first 3 months of therapy) [46].

In children, the maximum period recommended is 12 months. If there is no response at 6 months of treatment, further therapy is discouraged, in view of the greater susceptibility of vitiliginous skin to sunburn and photodamage owing to lack of melanin [18].

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

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