

# Vitiligo in children: a review of classification, hypotheses of pathogenesis and treatment\*

## *Vitiligo em crianças: uma revisão de classificação, hipóteses sobre patogênese e tratamento\**

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**Abstract:** Vitiligo is a relatively common dermatologic finding and one that has been observed since ancient times. Depigmentation of the skin, with loss of melanocytes on histology characterizes this disorder. A range of clinical phenotypes lead to varying degrees of morbidity. The cause of vitiligo remains unknown, although an autoimmune pathogenesis seems most likely. Treatment also remains difficult. A number of new therapies show significant potential. In this review, we will focus on the classification of childhood vitiligo, hypotheses of pathogenesis and treatment.

**Keywords:** Epidermis/ transplantation; PUVA therapy; Vitiligo

**Resumo:** Vitiligo é um achado dermatológico relativamente comum, observado desde a Antiguidade. A doença caracteriza-se por despigmentação da pele, com perda de melanócitos ao exame histológico. Diversos fenótipos clínicos resultam em diferentes graus de morbidade. A causa do vitiligo ainda é desconhecida e a etiologia mais provável parece ser auto-imune. O tratamento é difícil e várias alternativas mostram um potencial terapêutico significativo. Nesta revisão, abordaremos a classificação do vitiligo na infância, as hipóteses sobre a patogênese e o tratamento.

**Palavras-chave:** Epiderme/transplante; Terapia PUVA; Vitiligo

### INTRODUCTION

Vitiligo was first noted in 1500 BC.<sup>1</sup> The term vitiligo is thought to come from the Greek vitelius (calf), and thereby to connote the resemblance of the white spots of vitiligo to white patches on a calf. Its initial use is attributed to the Roman physician Celsus in the second century AD.<sup>2</sup>

Vitiligo presents as sharply demarcated depigmented macules, that can appear anywhere on the

skin. There is a predilection for orifices - eyes, nostrils, mouth, nipples, umbilicus, and genitalia.<sup>2</sup> The natural history of the disorder is either that it spreads quite quickly (over months) and then is stable, or it relentlessly spreads over the body with time (over years). Sites of trauma (koebnerization), such as the elbows, may develop vitiligo.<sup>2</sup> One percent of the population is affected by vitiligo. Twenty-three to

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twenty-six percent of these are children under the age of twelve.<sup>3,5</sup> It is the most commonly acquired hypomelanosis.<sup>6</sup>

Vitiligo can be extremely disfiguring, leading to significant patient morbidity. A number of different studies have measured the quality of life for patients with vitiligo. Low self-esteem, poor body image and poor quality of life has been found in patients with vitiligo, including significant psychiatric morbidity (up to 25% in one study).<sup>7</sup> This is of particular concern for children and adolescents, as they are in their formative years and are developing their sense of self.

### CLASSIFICATION

Recognizing that not all vitiligo behaves in the same way or has the same characteristics, classification systems have been proposed for the last 50 years. We suggest that vitiligo can be divided into essentially two categories - generalized and segmental, with perihalo nevi as an adjunct. Segmental vitiligo is characterized by early onset, rapid progression and then persistence without change. There are no specific precipitating factors. The disease spreads in a linear fashion and may also lead to poliosis. An area roughly related to the trigeminal dermatome is the most commonly affected.<sup>8</sup> A novel classification of facial segmental vitiligo was put forth by Hann et al in 2000. Five subtypes were proposed. Importantly, they noted that segmental vitiligo of the face does not always follow Blaschko's lines, dermatomes or acupuncture lines.<sup>3</sup>

### DIFFERENTIAL DIAGNOSIS

The differential diagnosis of vitiligo includes other hypopigmented disorders such as pityriasis alba, postinflammatory hypopigmentation, piebaldism, morphea, leprosy, tuberous sclerosis, and lichen sclerosis et atrophicus, in addition to chemically-induced vitiligo with catechols, alkylated phenols and cinnamic aldehyde.<sup>2</sup> Differentiating vitiligo from these disorders is crucial to the diagnosis and often quite simple, but sometimes can prove more difficult. A Wood's lamp is very useful in characterizing the extent of depigmentation (partial versus complete). The borders of the lesion(s) should also be noted (irregular versus sharply demarcated).<sup>2</sup> Vitiligo will have complete depigmentation with sharply demarcated borders. Pityriasis alba can resemble early vitiligo, with more subtle borders. Piebaldism can progress during early infancy, and this may lead to an erroneous diagnosis of vitiligo. A biopsy is rarely necessary for the diagnosis. If histopathology is obtained, an absence of epidermal melanocytes and melanin will be seen.

Marginal skin has both melanin and enlarged epidermal melanocytes with elongated dendritic processes. Basal layer vacuolization with a sparse lymphohistiocytic infiltrate may or may not be present. The appearance of T cells and macrophages in marginal skin coincides with the disappearance of melanocytes.<sup>2,9</sup> The loss of melanocytes occurs first in the epidermis and then in the follicular reservoir.<sup>6</sup>

### ETIOLOGY

The pathogenesis of vitiligo has long been debated. An autoimmune etiology appears to be the most plausible, with melanocytes destroyed secondary to auto-antibodies. Recent work has shown high numbers of cytotoxic T lymphocytes specific for melanocytic antigens in vitiligo, which supports a direct melanocyte specific attack.<sup>10</sup> As vitiligo is often seen in the setting of coexisting autoimmune disorders, organ-specific antibodies and aberrations in T and NK cell profiles are seen, a role for cell-mediated immunity is also supported.<sup>10</sup> In addition, Smyth line chickens (the animal model for vitiligo) also develop blindness, autoimmune thyroiditis, and an alopecia-like feathering defect. A melanocyte specific T-cell mediated autoimmune response is seen in the pathogenesis of Smyth line vitiligo.<sup>11</sup>

This observation is recapitulated in human vitiligo, as a strong association with autoimmune diseases is seen. Autoimmune thyroiditis is the most common association in children with vitiligo. A recent study showed that 16% of patients with non-segmental vitiligo had thyroid alterations, whereas all patients with segmental subtype had normal thyroid studies.<sup>12</sup> This led the authors to suggest checking thyroid studies in all children with non-segmental vitiligo, so as to find thyroid dysfunction early. This appears to be a rational course of action. Another recent report found four children with Hashimoto's thyroiditis,<sup>13</sup> a type of autoimmune thyroiditis.

Pernicious anemia, Addison's disease, and lupus<sup>14</sup> have all been documented in adults with vitiligo. MELAS syndrome (in which there is decreased melanogenesis, but no evidence of melanocyte loss), and ataxia telangiectasia (in which vitiligo improved with IVIG monthly) have also been associated with vitiligo.<sup>6</sup> Recently, a report of two children with unilateral poliosis of the eyelashes was described, in association with vitiligo. In one child, the findings occurred simultaneously. In the other, poliosis occurred first.<sup>15</sup>

A significant association between familial non-segmental vitiligo and HLA-B46 has been discovered. By contrast, HLA-A31 and CW4 are seen in non-famil-

ial patients, who also develop lesions at an older age than those with the segmental subtype.<sup>16</sup>

### CHILDHOOD VITILIGO

The first study of childhood vitiligo was conducted by Halder et al. Previously, the observation had been made that vitiligo was an "acquired, sometimes familial depigmentary disorder of skin and hair" and that 50% of patients develop vitiligo before age 20. 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 PUVA.<sup>4</sup>

### TREATMENT

Treatment of vitiligo is often difficult and frustrating, both for the patient as well as the physician. Many modalities have been and continue to be used. The following therapies and their efficacy will be discussed: topical corticosteroids; topical immunomodulators; phototherapy including PUVA, topical PUVA, UVB and monochromatic excimer laser or light, as well as microphototherapy; surgical options including autologous mini-punch grafting; blister roof grafting, and epidermal cell transplantation. The issue of bleaching accomplished by hydroquinone, monobenzone, or Q switched ruby laser will also be addressed. In determining efficacy of treatment, greater than 75% repigmentation is considered a cosmetically acceptable level of repigmentation.<sup>17</sup>

### MEDICAL

#### Topical Corticosteroids

Topical corticosteroids are often used as therapy for vitiligo. A meta-analysis in 1998 found that class 3 and 4 corticosteroids resulted in more than 75% repigmentation of 56% of segmental vitiligo patients and 55% of generalized vitiligo patients.<sup>18</sup> In 1999, the same group made an attempt to establish evidence based guidelines for treatment of vitiligo in children and adults. Another meta-analysis of the literature was performed, which again showed that class 3 corticosteroids are the most effective and safest therapy for segmental vitiligo.<sup>17</sup>

#### Topical Immunomodulators

With the introduction of topical immunomodulators (tacrolimus and pimecrolimus), many had hoped they would be a panacea for a number of cutaneous disorders, including vitiligo. A number of studies have shown their efficacy or near-efficacy to topical corticosteroids, without the attendant adverse effects, such as atrophy.<sup>19-21</sup> With new concerns regar-

ding their long-term safety, the topical immunomodulators may best be 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 recently described.<sup>22</sup>

#### Systemic PUVA

Photochemotherapy (PUVA) was originally developed in the 1940's by an Egyptian physician for the treatment of vitiligo. It has subsequently been used for many different cutaneous disorders. Repigmentation with PUVA is widely variable and rarely is 100% achieved. In general, dark skin types have better repigmentation than paler skin types. Usually, one to three years of treatment are needed for optimal results, which is one of the drawbacks.<sup>23</sup> PUVA has the highest rates of adverse effects among nonsurgical treatments, such as nausea, vomiting, phototoxic reactions and a theoretical increased long-term cutaneous malignancy risk. For these reasons, this method is not being used as often for vitiligo, particularly in the United States.

#### Topical PUVA

Topical PUVA is an attempt to limit the area that becomes photosensitized and avoid some of the effects of systemic psoralen. This method also has side effects, including erythema, blistering and hyperpigmentation of normal, adjacent skin. When topical PUVA was compared to narrowband UVB in the treatment of generalized vitiligo, the therapies were found to be comparable, but narrowband UVB had fewer adverse effects and less cumulative UVB dose.<sup>24</sup>

#### Narrowband UVB

Narrowband UVB for the treatment of generalized vitiligo in children has recently emerged as a promising therapy. A meta-analysis in 1999 found that narrowband UVB was the most effective and safest therapy for generalized vitiligo.<sup>17</sup> Subsequently a number of open trials in children with generalized vitiligo have been conducted, with the best results on the face and neck and in vitiligo present for a shorter duration. Hands and feet show little response. Treatment three times per week seems to have a somewhat better response than twice per week.<sup>25-28</sup>

#### Microphototherapy - UVB

A variation of narrowband UVB, microphototherapy has been used to treat both segmental and non-segmental vitiligo. The beam is focused only on areas affected by vitiligo. An open trial of adults and children with both segmental and generalized vitiligo were treated with this modality. Seventy percent

achieved normal pigmentation in greater than 75% of treated areas. This may be the treatment of choice in patients with <30% BSA (body surface area) involvement and the best treatment for children, as the cumulative dose of radiation is very low and non-affected skin does not become hyperpigmented.<sup>29</sup>

#### **Monochromatic excimer light (MEL)**

Monochromatic excimer light (MEL) has been used to treat adults with either segmental or generalized vitiligo. Good results were found, with 95% of patients showing some repigmentation and approximately 50% greater than 75% repigmentation. Significantly, three patients responded to MEL who had not responded to narrowband UVB in the past. The results are similar to those with excimer laser; however, MEL has the advantage of lower power density leading to reduced risk of overexposure, the possibility to treat larger areas at a time, and shorter treatment duration. These advantages may allow this method to be useful in children, however it has unknown efficacy, as no children under 15 years were treated in this study.<sup>30</sup>

#### **SURGICAL**

##### **Epidermal grafting (autologous mini-punch grafting, blister roof grafting)**

Surgical methods offer other options in the treatment of vitiligo. Segmental vitiligo is the best indication for surgical repigmentation and these patients are good candidates for epidermal grafting.<sup>2,3,8</sup> A retrospective case series of 143 patients treated with suction blister epidermal grafting showed the best results in segmental subtypes, and in patients less than 20 years old. However, no children less than 10 years were included in the study. Significantly, localization of the vitiliginous area did not affect treatment outcome, as it often does in medical therapies such as narrowband UVB phototherapy.<sup>31</sup>

A comparison of mini-punch grafting and split-skin grafting in chronic, stable, segmental vitiligo showed better results with split-skin grafting, particularly over the face and extremities. In this study, which included children as young as 10 years, the surgical technique was followed by three months of PUVA.<sup>32</sup>

##### **Epidermal cell transplantation**

There are limitations to autologous mini-punch grafting and blister roof grafting, primarily a cobblestone appearance and limited treatment area per session. Therefore, epidermal cell transplantation has been investigated as a treatment option.<sup>33</sup> A recent study of epidermal cell transplantation found that the best results are seen in segmental vitiligo, with some improvement for those with generalized 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 to this technique is that only one time treatment is necessary, if successful.<sup>33</sup>

##### **Cosmetic coverups**

If all treatments have failed; the patient does not wish to undergo treatment; or while treatment is ongoing, cosmetic coverups can be very useful. A recent study investigated quality of life in vitiligo patients and the effect of using camouflage. Using camouflage, particularly for the face, head and neck improved the patients' quality of life, especially for "feelings of embarrassment and self consciousness" and "choice of clothing".<sup>34</sup> A number of brands are available including Dermablend, Covermark, Derma Color, Dermage, and Elizabeth Arden Concealing Cream.

##### **BLEACHING**

Finally, in adults, bleaching of remaining pigmented skin may be considered. Emphasis must be made that this is NOT recommended for children. The child may not fully comprehend the permanent depigmentation of monobenzyl ether of hydroquinone (monobenzone), or the Q switched ruby laser, or even the fading effect of hydroquinone.

##### **CONCLUSION**

In conclusion, childhood vitiligo is unique and different than adult vitiligo. We suggest that an autoimmune pathogenesis seems most likely and that thyroid studies should be obtained regularly in children with generalized vitiligo. Treatment of vitiligo depends on subtype and age, with a number of promising treatments for children on the horizon, including narrow-band UVB phototherapy and surgical techniques. □

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