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Pediatric Vitiligo

Authors
Aditi Sharma[1], Dhaarna Wadhwa[2], Himang Jharaik[3]*, Rajni Sharma[4], Shailja Chauhan[5]

[1]Medical Officer, Department of Dermatology, Civil Hospital Theog, District Shimla,
Himachal Pradesh, India. 171201
[2]Senior Resident, Department of Dermatology, Vardhaman Mahavir Medical College and Sarfdarjung
Hospital, New Delhi, Indi
[3]*Medical Officer, Department of Obstetrics and Gynaecology, Civil Hospital Theog, District Shimla,
Himachal Pradesh, India 171201
[4]Senior Resident, Department of Dermatology, Indira Gandhi Medical College Shimla,
Himachal Pradesh, India 171001
[5]Medical Officer, Department of Dermatology, Civil Hospital Rampur, District Shimla,
Himachal Pradesh, India
*Corresponding Author
Himang Jharaik
Obstetrics & Gynaecology Deptt, Civil Hospital Theog, District Shimla 171201. Himachal Pradesh, India

Introduction

Vitiligo is an acquired disorder characterised by progressive loss of functional melanocytes resulting in depigmented skin and hair.

Epidemiology

Its prevalence in the general population varies between 0- 2.16% worldwide with one third to one half having their onset in childhood.[1,2] Childhood vitiligo (CV), defined as disease onset before the age of 12 years, is common. In India 2% of children attending a pediatric clinic were diagnosed with vitiligo.[3] The childhood cases of vitiligo, with an age of onset less than or equal to 12 years are typically associated with more halo nevi, Koebner phenomenon, positive family history, segmental disease and personal history of atopy. Those with late onset of more than 12 years are associated with more acrofacial lesions and thyroid disease.[4] Even though disease onset in less than two years is unlikely as opposed to congenital disorders of pigmentation, the disease onset increases through the first two decades.[5] Onset before age 2 years represents 11% of pediatric-onset cases, 28% of cases start between 2 and 5 years, 40% of cases begin between 5 and 10 years, and 21% between 10 and 18 years, demonstrating that median age of onset is between 5 and 10 years of age.[6] The prevalence of vitiligo by gender is usually close to if not equal, with some studies supporting female predilection in the youngest age groups.[4] In a cohort of 268 Indian children 12 years and younger, 56.7% were girls ($n = 152$) and 43.3% were boys ($n = 116$). The breakdown of vitiligo types in a pediatric population varies by population reviewed. In a case series of 119 pediatric patients with vitiligo,

34% had generalized disease, 13% acrofacial, 3% mucosal, 29% segmental, and 21% undetermined. Lower estimates of segmental disease include 17.6% of cases in children who were 12 years or younger in an Indian cohort.[7]

Clinical Features

Vitiligo patches typically appear as well circumscribed amelanotic well defined macules which may be round-oval or irregular ranging from few millimetres to several centimetres in diameter which may appear anywhere on body with a predilection for trauma prone sites like face, hands, feet, fingers, elbows, knees and anogenital region.[8] Koebner phenomenon, characterized by the development of vitiligo lesions in sites of trauma, has been observed in 11% to 24% of children with vitiligo in India.[7,9] The head and neck area (particularly eyelids) is commonly the site of initial disease presentation in childhood vitiligo in 31-59% patients.[7,9,10,11] In contrast the upper limbs especially the hands and fingers are the common sites in adults, perhaps due to koebnerisation[10]. Leukotrichia may be associated with childhood vitiligo due to the involvement of the melanocytic reservoir that exists in the hair follicles and has been reported in 3.7%-32.5% of children with vitiligo.[7,9,11] (Figure 1)

Figure 1: Leukotrichia in a focal patch of Vitiligo in a 12 year old girl.

Overall, vitiligo can be divided into segmental vitiligo (SV) and vitiligo/ nonsegmental vitiligo (NSV), which encompasses rare forms of vitiligo. When first seeing a patient, it is of prime importance to differentiate between them, as they differ in prognosis, evolution, and response to treatment.[12] The terms vitiligo and NSV both represent multifocal lesions varying in size with a tendency for symmetrical distribution evolving as the disease progresses often with poliosis. It is usually more common than SV and accounts for 67-95% of patients in CV.[7,10,11,13] NSV is further divided into generalized, acrofacial, universal, mucosal and mixed vitiligo, and also includes the rare types of vitiligo punctata and hypochromic vitiligo/vitiligo minor.[12] Generalized vitiligo is the most common form of the disease with multiple body site involvement often symmetrically. (Figure 2, 3)

Figure 2: Non segmental vitiligo in a 9 year old girl

Figure 3: Symmetrical arm involvement in generalised vitiligo in 7 year old boy.

Acrofacial vitiligo is limited to the face (especially lips) and acral sites namely hands (especially finger tips) and feet (toes). (Figure 4)

Figure 4: Eyelid involvement in acrofacial vitiligo in 6 year old boy.

Acrofacial vitiligo may evolve into generalised vitiligo later. Universal vitiligo in which majority (80-90%) body surface area is involved may show only few pigmented sites in sun exposed areas, is often an end point of generalized progressive vitiligo and is not a common presentation in children. Mucosal vitiligo has involvement of the oral and/or genital mucosae with skin involvement. If skin lesions are not present it is classified as undetermined. Mixed vitiligo refers to the presence of SV and NSV together, with the former often evolving into the latter, with halo naevi and leukotrichia being poor prognostic markers.[14,15,16] Vitiligo punctata is a rare type of vitiligo characterized by confetti like, multiple and small depigmented macules which may exist with typical vitiligo. Hypochromic vitiligo/vitiligo minor is a newly described rare form characterised by hypopigmented macules alone or with depigmented areas in dark skinned individuals on the trunk and scalp with hypopigmented seborrhoeic areas on face and neck and needs to be distinguished histologically to rule out hypopigmented mycosis fungoides. SV is a distinct clinical form of vitiligo confined to a unilateral segment which usually do not cross the midline. Mono-SV is the commonest with only one segment involved (Figure 5).

Figure 5: Mono segmental vitiligo in 6 years boy.
SV is characterised by leukotrichia (early involvement of melanocytes of hair follicles), early age of onset and being more common in childhood vitiligo (5-33% of cases). [4,7,9, 10,11, 13]

The group of undetermined/unclassified vitiligo includes pure mucosal vitiligo and focal vitiligo. Pure mucosal vitiligo is characterized by oral and/or genital mucosal lesions without skin involvement. Focal vitiligo refers to one or more localized depigmented macules that do not fit a segmental distribution. (Figure 6)

Figure 6: Focal vitiligo on chin in 5 year old boy showing specks of repigmentation

This form may evolve either into SV or NSV.[12] Overall, NSV has an unpredictable course with disease exacerbations, stabilisation or remissions.[18] Disease progression is characterised by either centrifugal expansion of pre existing lesions, or appearance of new lesions. If they do not progress in last 12 months, they are termed as stable.[12] SV typically has a rapid course since depigmentation progresses within the involved segment over a period of 6–24 months and then usually stabilizes without further extension. Segmental vitiligo may progress to mixed vitiligo with appearance of NSV lesions.

Another common clinical entity seen in childhood vitiligo is a halo nevus also called the Sutton's nevus. It represents a melanocytic nevus surrounded by a depigmented halo. It represents ongoing cellular immune responses against melanocytes.[15] The prevelance of halo nevi in children varies between 2.5%-26% with the nevus appearing before, simultaneously or after the onset of vitiligo.[11,13,19] However not all children with halo nevi tend to develop vitiligo, although it has been suggested that in such children the risk of vitiligo and other autoimmune diseases seems to be higher, suggesting that a close follow up should be done for early detection and further management.[20]

Co-morbidities

Vitiligo (mainly NSV) may be associated with several other autoimmune disorders, including autoimmune thyroid disease, rheumatoid arthritis, alopecia areata, psoriasis, pernicious anemia, Addison's disease, and adult-onset type 1 diabetes in the patient or in the family suggesting an

autoimmune basis of pathogenesis[21,22]. Thyroid disorders are the most common co-morbidity in patients with NSV, hypothyroidism being more common and the incidence being as high as 13%- 22% in children with vitiligo.[23,24] Since vitiligo usually precedes the development of thyroid dysfunction, and since thyroid dysfunction can be subclinical, annual thyroid screening with the thyroid autoantibodies TSH, T3, and T4 is suggested for children with vitiligo, especially for those with non-segmental disease.[25] However, some studies suggest that the incidence of allergic diseases and atopic diathesis is even more common in children with vitiligo than thyroid abnormalities.[10,26] Vitiligo causing a change in skin colour is associated with significant psychological and emotional morbidity in both children and their families, especially when visible areas are affected. This might lead to impairment of quality of life, social stigmatization leading to avoidant behaviour, emotional distress, anxiety, depression, embarrassment, low self-esteem, deterioration of self-confidence, and social isolation.[18] It has been seen that lesions on head and neck of boys and on genitals and legs in girls are the sites most commonly associated with negative impact on quality of life.[27] This impairment of life seems to increase with age and is maximally seen in adolescents who experience the most self consciousness.[28,29] This necessitates a requirement for active assessment of quality of life effects on both children and their family members and providing early psychological support. Support groups often help with the quality of life, one of which is the Vitiligo Support International (https ://vitiligosupport .org). [18,30,31]

Differential Diagnosis

Thorough clinical examination, Wood's light evaluation, detailed medical history, and histological examination of the lesions can contribute to the precise diagnosis of vitiligo in children with hypopigmented lesions. The differential diagnosis of non-segmental CV includes a wide range of congenital and acquired disorders. For congenital lesions (appearing before 2 years), congenital hypomelanosis like piebaldism, tuberous sclerosis, albinism, and Waardenburg syndrome should be ruled out. (Figure 7)

Figure 7: Ash leaf macule in a 10 year old boy needs to be differentiated from vitiligo.

For acquired lesions appearing at a later age, acquired inflammatory, infectious or neoplastic hypomelanoses must be excluded, including pityriasis versicolor, progressive macular hypomelanosis, idiopathic guttate hypomelanosis, post-inflammatory hypopigmentation, chemical leukoderma, atopic dermatitis, pityriasis alba, morphea, lichen sclerosus et atrophicus, and hypopigmented mycosis fungoides. Nevus depigmentosus and nevus anemicus are the most important differential diagnosis of segmental vitiligo in children. Nevus depigmentosus is usually a congenital, stable-in-shape lesion, which grows in proportion to the child's growth in which the production of melanin is reduced with normal melanocyte number. Nevus anemicus is a congenital, solitary, hypopigmented lesion most frequently located on the trunk, which is based on vascular disturbances in which melanin and melanocyte number is normal.[32]

Treatment

Childhood vitiligo even though a cutaneous disease has a high potential to cause major psychological impact and the patients and their families must be offered the armamentarium of therapeutic options available. Simultaneously the chronic and unpredictable nature of vitiligo, lack of universally effective treatment should be explained with stress on adherence to treatment and frequent follow ups when required. Adequate

sun protection and consistent use of sunscreens are recommended for children with vitiligo in order to prevent potential burning of vitiliginous skin, as well as tanning of healthy skin, which will increase the contrast with lesional skin. Cosmetic camouflage may be used to conceal visible affected areas and reduce the clinical appearance of disease in children who are concerned about their vitiligo lesions. Self-tanning agents, pigmented cover creams and foundations can also be color-matched to the skin and used for corrective make-up in children with vitiligo[33,34].

Topical Treatment: Corticosteroids and Calcineurin Inhibitors

Sun-exposed areas (face and neck), patients with dark skin, and recent lesions respond better to topical treatments, while acral lesions respond poorly[33]. Topical corticosteroids (TCS) have been the most commonly used treatment modality for vitiligo in children, and have been found to offer benefit in both facial and non-facial pediatric vitiligo.[18] Despite the efficacy of TCS, their long-term use is a concern due to local and systemic adverse effects. Topical calcineurin inhibitors (TCI), e.g. tacrolimus and pimecrolimus, have emerged as alternatives showing good therapeutic efficacy without the adverse effects related to long-term use of TCS. These agents are not atrophogenic and therefore can be applied long-term on the face, intertriginous regions, and genitalia. To date the use of tacrolimus and pimecrolimus is off label in many countries for vitiligo, even though they have been approved for atopic dermatitis. Results are often very good for limited or focal disease and in facial and non facial vitiligo with repigmentation rates comparable to moderate-high potency corticosteroids with facial lesions showing higher rates of repigmentation.[35,36] Adverse effects of topical tacrolimus and pimecrolimus include transient pruritus, burning sensation, and erythema.

The European Dermatology Forum consensus group has recommended the use of TCS as first-line treatment for limited forms of childhood vitiligo. Potent TCS (such as mometasone furoate) should be preferred since they appear to be as effective as high-potency TCS (such as clobetasol propionate) and have fewer adverse effects.[33] Once-daily application of potent TCS for a period no longer than 3 months, or once-daily application for 15 days per month for 6 months, are well-tolerated and effective treatment choices for children with limited and extrafacial vitiligo. For new, actively spreading lesions on thin skin, in particular on the head and neck areas, TCI can be used twice daily. The treatment should be prescribed initially for 6 months, but, if effective, may be prolonged.[18]

Phototherapy

Narrow-band (311 nm) ultraviolet B (NB-UVB) phototherapy has become the phototherapy modality of choice for vitiligo, resulting in not just repigmentation but also stabilization of lesions in widespread and progressive disease.[37] Response to treatment is variable. Dark skin phototypes (IV–V) respond better in both adults and children with repigmentation rates being >75% in darker phototypes.[38,39] Lesions on the face and neck respond better, compared with lesions elsewhere.[37] Acute adverse effects of NB-UVB are mild and transient and include erythema, pruritus and xerosis and long-term therapy carries a potential risk for photoaging and photocarcinogenesis. Vitiligo earlier was itself thought to increase risk for skin cancers, but studies report a lower risk, perhaps due to inverse relation between vitiligo related genes and skin cancer risk.[40,41] Current evidence does not support an association between NB-UVB treatment in vitiligo patients and increased risk of cutaneous malignancies[40] However, large, prospective studies with enough follow- up time on the risk of carcinogenicity after NB-UVB are lacking. Thus, we should continue to recommend sun protection at all other times and should perform a full skin examination regularly for patients who have received this treatment.[18] NB-

UVB and TCI seem to act synergistically, but the combination might cause increased risk of carcinogenicity.[42] Even though data to document causality of cancer with their combined use is lacking, they should be used together with caution.[33,43]

Targeted Ultraviolet B Phototherapy with the 308- nm Excimer Laser

The Excimer laser emits a wavelength of 308 nm and induces photobiological effects similar to NB-UVB. The main advantage of the Excimer laser is the selective targeted treatment of vitiligo lesions only, sparing the adjacent healthy skin from unnecessary exposure to radiation with the added advantage that children do not experience isolation or fear in the enclosed and claustrophobic NBUVB cabinets. The disadvantage is that excimer laser does not stabilize vitiligo as no exposure occurs on clinically normal skin and it may cause mild to severe erythema, pruritus and blistering on exposed skin. The 308-nm Excimer laser is indicated for localized vitiligo when <10% of BSA is affected. Response rates are comparable to NB-UVB. A synergistic effect between the Excimer laser and pimecrolimus has been described. In case of non-response after 20–30 sessions (3–5 months of a twice-weekly treatment schedule), different therapeutic options should be considered.[44-46]

Surgical Treatment

Surgical procedures are based on the transplantation of functional melanocytes from a normally pigmented autologous donor site to vitiligo lesions. Surgical grafting is indicated for stable segmental or focal vitiligo non-responsive to other treatment modalities. Disease stability is defined by the absence of new or expanding lesions and a negative history of Koebner phenomenon for at least 1 year. No consensus exists regarding the appropriate minimal age for surgery, and surgical treatment is not usually recommended for children with vitiligo; however,

several tissue and cellular grafting techniques have been used in children with satisfactory results.[37] Excellent results have been revealed by suction blister grafting and non cultured cellular grafting with repigmentation rates as high as 88.5% to >90% in children and adolescents with stable vitiligo.[47,48,49] Studies have also shown excellent results using cultured melanocyte transplantation which were comparable to the results seen in adults.[50,51] However the adverse effects of surgical intervention like pain and potential scarring, mottled pigmentation, irregular texture, koebnerization, or infection should be kept in mind.[37] Therefore, surgical techniques may be considered as an alternative to conventional therapy. Repigmentation can be improved when grafting is combined with Excimer laser or NBUVB.[33]

Since halo nevi may be linked with vitiligo, it has been suggested that their excision may result in the regression of vitiligo.[52] However, some studies also show recurrence of vitiligo after some time duration.[53,54] Hence the utility of halo nevus removal remains controversial and more data is required to establish guidelines for removal.

Minipulse Oral Steroids

Oral minipulse (OMP) steroid therapy has been widely used in adults with fast spreading vitiligo to arrest disease activity using low doses of dexamethasone or betamethasone on two consecutive days weekly for 3-6 months.[33] Although this therapy has been seen to be effective for children and adolescents, studies have shown that after discontinuation upto one third children may relapse after 1 year.[55] Taking into consideration the potential adverse effects of steroids on children like stunted growth, precocious puberty and development of diabetes and hypertension, OMP steroid therapy should be used very cautiously in children with vitiligo.

Antioxidants

Although systemic and topical antioxidants alone or in combination with phototherapy have been

suggested to promote repigmentation in patients with vitiligo, more evidence of efficacy is needed before their recommended administration in vitiligo.[33] Pseudocatalase is a NB-UVB-activated synthetic catalase that reduces H_2O_2 which has been reported to play a role in pathogenesis of vitiligo. A retrospective, uncontrolled study evaluating the combination therapy of topical pseudocatalase with low-dose NB-UVB in 71 children with vitiligo, demonstrated > 75% repigmentation in most lesions on the face, neck, trunk, and extremities treated with the combined therapy, while 70% of children treated with NB-UVB monotherapy showed disease progression.[56] Until more data are available, the role of antioxidants in the management of childhood vitiligo is unclear.

Depigmentation

Depigmentation of the remaining normally pigmented skin through destruction of melanocytes may be an option in adults with extensive and refractory vitiligo usually achieved by monobenzyl ether of hydroquinone, cryotherapy, or laser, and is permanent but is usually not required or recommended in children.[57]

Targeted Immunotherapy

The interferon (IFN)-γ–CXCL10 chemokine axis may be used for the development of targeted immunotherapies for vitiligo. The Janus kinase (JAK) inhibitors tofacitinib and ruxolitinib inhibit IFN-γ signaling and have produced repigmentation in a few adult vitiligo patients.[58,59] The efficacy and safety of these agents has not yet been assessed in children and further studies are required for assessing efficacy and safety.

Conclusions

Vitiligo onset during childhood is common and may have a significant impact on the quality of life of the whole family. Site of initial presentation, prevalence of segmental vitiligo and co-morbidities may differ between children and adults. Treatment options include topical corticosteroids and calcineurin inhibitors, phototherapy, and, in selected stable cases, surgical procedures. Treatment is usually long, may be unpredictable and repigmentation may not be achieved, especially on acral lesions.

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