Symposium - Vitiligo

Childhood vitiligo

Aparna Palit, Arun C. Inamadar

Department of Dermatology, Venereology and Leprosy, Sri B.M. Patil Medical College, Hospital and Research Center, BLDE University, Bijapur, Karnataka, India

Address for correspondence:
Dr. Arun C. Inamadar, Department of Dermatology, Venereology and Leprosy, Sri B.M. Patil Medical College, Hospital and Research Center, BLDE University, Bijapur - 586 103, Karnataka, India.
E-mail: aruninamadar@gmail.com

ABSTRACT

Childhood vitiligo is often encountered in dermatological practice. When present in infancy or early childhood, various nevoid and hereditary disorders are to be differentiated. In many cases, familial aggregation of the disease is seen and other autoimmune disorders may be associated. Segmental presentation is more common, and limited body surface area involvement is usual in this age group. Children with vitiligo often suffer from anxiety and depression because of their unusual appearance. Management of vitiligo in children is difficult as therapeutic options are restricted when compared to that in adult patients. Selection of treatment should be careful in these patients with the aim to achieve best results with minimal side effects as well as relieving patients' and parents' anxiety.

Key words: Children, non-segmental vitiligo, segmental vitiligo

INTRODUCTION

Vitiligo is an acquired pigmentary disorder occurring irrespective of age, sex and race. The most important aspect of vitiligo is the cosmetic concern it arouses in the psyche of patients and their family members because of the stigma associated with it. This is more so among dark races for the obviousness of the disease.

Vitiligo may present anytime in life, including the neonatal period and childhood. Childhood vitiligo deserves special attention as frequently (50%), the disease onset is before 20 years of age and, in 25% of the cases, it starts before the age of 10 years.[1] In general, childhood vitiligo differs from the adult disease in the following aspects: a female preponderance is observed, segmental presentation is more common and associated other autoimmune or endocrine disorders are rarer.[2]

Access this article online	
Quick Response Code:	Website: www.ijdvl.com
	DOI: 10.4103/0378-6323.90944

CLASSIFICATION

In most of the epidemiological studies, childhood vitiligo has been categorized as "segmental" and "non-segmental" types. Segmental vitiligo (SV) implies occurrence of depigmented macules and patches along dermatomal or quasi-dermatomal pattern, without crossing the midline [Figure 1].[3] In non-segmental vitiligo (NSV), the skin lesions may be generalized (vitiligo vulgaris, universal vitiligo) or localized (focal, mucosal, acrofacial, acral). Vitiligo vulgaris implies widely scattered depigmented lesions, whereas almost-total depigmentation of skin is termed as universal vitiligo.[2] Focal vitiligo is the occurrence of one or few depigmented lesions localized to one body area not corroborating to a dermatome [Figure 2].[2] Acral vitiligo is confined to the distal extremities [Figure 3]; in combination with facial lesion it is of the acrofacial type, and mucosal vitiligo involves one or multiple mucosae.[2]

PATHOGENESIS

Detailed discussion on the pathogenesis of vitiligo is beyond the scope of this article. Recent advances in this aspect of vitiligo have been discussed in brief.

How to cite this article: Palit A, Inamadar AC. Childhood vitiligo. Indian J Dermatol Venereol Leprol 2012;78:30-41.
Received: June, 2011. **Accepted:** August, 2011. **Source of Support:** Nil. **Conflict of Interest:** None declared.

Genetic susceptibility in vitiligo is evidenced by frequent clustering in families and occurrence in monozygotic twins. Various susceptibility loci (autoimmunity susceptibility gene) for vitiligo are AIS1 (chromosome 1), AIS2 (chromosome 7), AIS3 (chromosome 8) and SLEV1 (chromosome 17).[4] Association of vitiligo with "transporter associated with antigen processing protein-1 (TAP-1)" gene is suggestive of the possible role of MHC class I antigen in antimelanocyte autoimmune response.[5] Studies on HLA class I and class II genes in vitiligo have revealed strong association and negative association with certain HLA types.

Various hypotheses prevail regarding the pathogenesis of NSV. These include autoimmune mechanism, autocytotoxic hypothesis, aberration of cellular immunity with melanocyte destruction, inhibition of melanogenesis and aberration of vitamin D3 metabolism.[4] Autoimmune mechanism for NSV and neural hypothesis for SV are most explanatory.[4]

NACHT-leucine-rich-repeat protein-1 (NALP1) gene (chromosome 17p13) confers to the occurrence of a group of multiorgan autoimmune and autoinflammatory disorders, including vitiligo.[6] Mutation in the autoimmune regulator (AIRE) gene (chromosome 21q22.3) results in a rare recessive disorder, "autoimmune polyendocrinopathy candidiasis ectodermal dystrophy syndrome (APECED)."[5] Vitiligo is more than 10-times common in patients with APECED compared with the general population.[5] Link to NALP1 and AIRE gene may explain the association of vitiligo to other autoimmune disorders and presence of circulating autoantibodies in these patients.[5]

There is wide expression of NALP1 in all tissues, especially at a high level in T cells and Langerhans' cells. NALP1 forms a complex termed "NALP1 inflammasome" by the recruitment of adapter protein ASC, caspase 1 and caspase 5.[6] NALP1 inflammasome activates proinflammatory cytokine interleukin-1β, which has been found to be raised in generalized vitiligo.[6] Hence, this pathway might be involved in the pathogenesis of vitiligo.

EPIDEMIOLOGY

In various studies, the prevalence of vitiligo in childhood (age <12 years) has been quoted to be around one quarter of vitiligo patients of all ages. In a Chinese study, 24.1% of the vitiligo patients were in the pediatric age group.[7] Among Korean patients with vitiligo, 16% were children.[8] In two Indian studies, the prevalence has been reported to be 26% (south India)[9] and 23.3% (north India),[10] respectively. The prevalence of SV is higher in children (17–29%) as compared to that in adults (5%).[8] Among the various ethnic groups, SV is more common in the Korean population.[8] Cho *et al*[8] have reported 32.5% of SV in their series of Korean children.

Onset of the disease is usually below 10 years of age. The Mean age at onset of childhood vitiligo in an Indian study was 6.2 years;[10] the same was 5.6 years and 7.28 years in Korean and Chinese studies, respectively.[7,8] SV presents earlier, may be soon after birth.[3] Hann *et al*[3] have reported disease onset below 10 years of age among 41.3% of their series of patients with SV. In a Chinese study on childhood vitiligo ($n = 541$), eight children had skin lesions present at birth (focal 7, acrofacial 1).[7]

An Indian study[10] has quoted a statistically significant difference in the occurrence of vitiligo among boys and girls, but few other studies have not recorded such a difference.

Family members of the affected children have a higher incidence of vitiligo and other autoimmune disorders compared to controls.[2] Positive family history in childhood vitiligo varies between 11%[7] and 46%[11] in various studies.[7,8,11] Pajvani *et al*[2] have reported an earlier onset of vitiligo in children in whom family history of the disease, leukotrichia or other autoimmune disorders were present. In children with focal and segmental disease, family history of vitiligo or other autoimmune disorders is usually negative.[2,12]

CLINICAL FEATURES

Vitiligo is characterized by asymptomatic, well-demarcated, ivory-white macules and patches that may be localized or generalized.

Any of the clinical variants of vitiligo may occur in childhood. Vitiligo vulgaris is the most common clinical type observed in various clinical studies, followed by focal vitiligo and SV.[7,8,10,11] Acrofacial and mucosal vitiligo have a lower incidence in childhood. Different studies have quoted variable incidence of mucosal vitiligo in children; Halder *et al*[13] 0%, Handa *et al*[10] 0.6% and Jaisankar *et al*[9] 13.8%. Of the mucosal sites, oral mucosal vitiligo is rarer in children

as compared to adults.[4] The rarest type seen during childhood is the universal vitiligo.

Common initial site of onset of both NSV and SV in children is the face and neck.[3] In NSV, initial lesions are periocular, perinasal or perioral, and gradually spread to other body parts, in a more or less symmetrical manner. Perineum, perianal area and, in infancy, the diaper area may be the initial site of occurrence of skin lesions [Figure 4].[4] Individual vitiligo macules may enlarge attaining a geographic pattern or there may be appearance of new lesions at other sites. Although extensive areas of depigmentation may be present, majority of the children have <20% body surface area (BSA) involvement.[4,10] Focal vitiligo may subsequently evolve into generalized disease.

In the series of patients with SV studied by Hann *et al*,[3] trigeminal segment was the most common dermatome involved, followed by thoracic, cervical, lumbar and sacral. Majority of the children in this series (87%) had a single lesion.[3]

In white-skinned children, vitiligo lesions may remain unapparent initially and may become evident for the first time following suntan during a holiday.[4] In dark-skinned children, typical multishaded trichrome patches may be present. Mazereeuw-Hautier *et al*[14] have recorded the occurrence of a hyperpigmented rim around the depigmented lesions only among the children with NSV (8.99%).

Koebner phenomenon may be noted in both SV and NSV in children, more commonly in the latter type. In SV, Koebnerization is confined to the involved segment only. Koebnerization may be more frequent

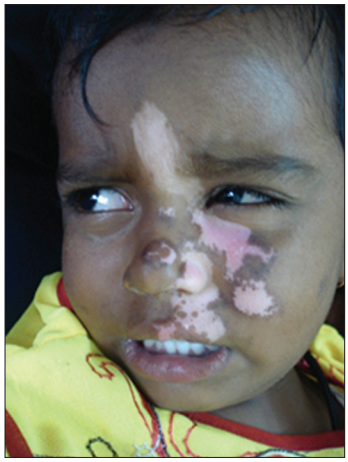

Figure 1: Segmental vitiligo over the face

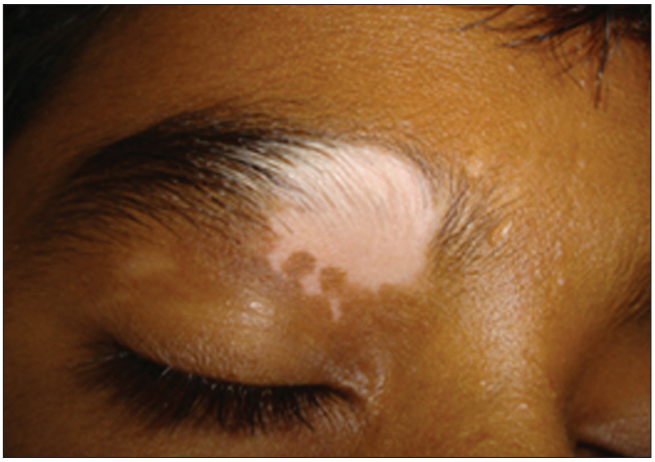

Figure 2: Focal vitiligo with leukotrichia

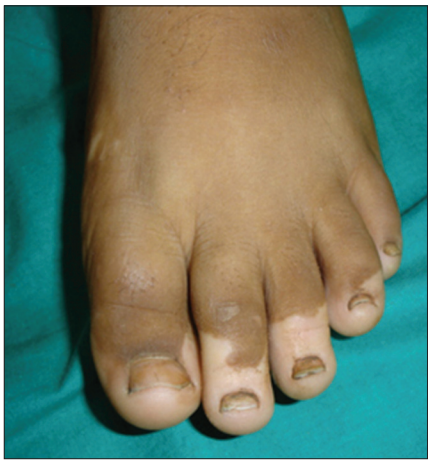

Figure 3: Acral vitiligo in a child

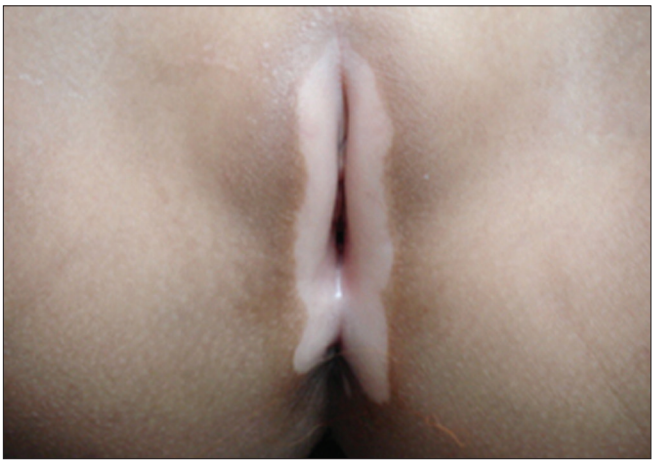

Figure 4: Genitalia as the site of onset in childhood vitiligo

in childhood vitiligo because of higher mobility and playfulness in this age group. Presence of Koebnerization is indicative of the disease activity.

Cho *et al*[8] have reported scalp involvement in 25% of the children with vitiligo. Scalp leukotrichia, defined as "significant extent of graying of scalp hair without underlying vitiliginous area before 30 years of age,"[3] is a frequent finding in children with vitiligo and their family members. Poliosis, defined as a localized patch of white hair,[15] is commonly seen in patients with vitiligo, more so in SV.[11] Prcic *et al*[11] observed poliosis among 55.55% of children and Hann *et al*[3] among 48.6% of the patients with SV. Eyebrows were the most commonly involved sites.[3]

ASSOCIATIONS

Vitiligo may be associated with other autoimmune disorders like alopecia areata, diabetes mellitus, pernicious anemia, Addison's disease and thyroid disorder. An Indian study has quoted associated autoimmune disorders in 1.3% of the children with vitiligo.[10] Several authors have reported vitiligo-associated autoimmune disorders occurring exclusively in children suffering from NSV.[1,14] Mazereeuw-Hautier *et al*[14] have reported associated thyroid function abnormalities without clinical disease in 11.23% of the children with NSV but in none with SV. In the study by Hann *et al,*[3] associated autoimmune disorders were found in 3.4% of the children with SV.

Among adult patients with vitiligo, autoimmune thyroiditis (Hashimoto's) resulting in hypothyroidism is more common (30%)[16] as compared to the general population (10%).[12]

Lacovelli *et al*[1] have studied the relevance of thyroiditis and other autoimmune diseases in 121 pediatric patients with vitiligo. The significant findings of this study were as follows:[1]

- Sixteen percent of the children with NSV showed altered thyroid function parameters, but none among the children with SV.
- Altered thyroid parameters were more common in girls than in boys.
- Hypothyroidism was the more common association of childhood vitiligo as compared to hyperthyroidism, in the ratio of 6:1.

Authors of this study have stressed upon routine thyroid screening in pediatric patients with vitiligo as diagnosis of autoimmune thyroiditis is particularly important in this age group to avoid the negative impact of hypothyroidism on growth and health status.[1] Kakourou *et al*[17] have reported an occurrence of autoimmune thyroiditis among 24.1% of children and adolescents with vitiligo. In this study, female preponderance was observed among adolescents (>12 years) with vitiligo and autoimmune thyroiditis (F:M = 6:1) when compared to children (F:M = 1:2).[17] The authors have suggested that this gender predilection for adolescent females may be estrogen mediated.[17] In majority of the cases, skin lesions of vitiligo precede the clinical features of thyroid dysfunction.[17] Rarely, occurrence of thyroid autoantibodies may precede the appearance of vitiligo lesions.[4,17]

Other autoimmune disorders are also more common in NSV. The reported disorders in association with childhood vitiligo are alopecia areata, celiac disease,[17,18] diabetes mellitus,[1,10] polyglandular autoimmune syndrome,[10] Addison's disease[10] and pemphigus vulgaris.[10] Rodríguez-García *et al*[18] have reported a 9-year-old girl with vitiligo vulgaris unresponsive to conventional therapy. Subsequently, she was diagnosed to have celiac disease and institution of gluten-free diet resulted in progressive repigmentation of her skin lesions by 1 year, which continued even after 7 years without any active treatment for vitiligo.[18] Atopic disorders, urticaria, Down syndrome and uveitis may be associated.[1,3]

Although associated endocrinopathies and autoimmune disorders are lower in childhood vitiligo as compared to adults, asymptomatic occurrence of autoantibodies are more common in this age group.[19] Often, anomalous laboratory parameters may be the only finding. Some authors have reported altered thyroid function tests (10.74%),[1] positive anti-gastric parietal cell antibodies (0.8%)[1] and positive antinuclear antibody (4.8%) in children with vitiligo.[13] Incidence of antinuclear antibody positivity is lower in children with vitiligo as compared to that in adults.[11]

Vitiligo-associated dermatosis, like halo nevi, occurs commonly in children, the incidence in various studies varying from 2.5% to 34%.[7,8,10,11] These occur more commonly in children with NSV.

COURSE OF THE DISEASE

The course of childhood vitiligo is mostly stable or regressive; only few patients experience progressive or recurrent disease.[2] Complete spontaneous repigmentation of NSV is unusual. However, as compared to adults, the rate of spontaneous repigmentation is more in children, especially in tropical countries and during summer months.[20] Repigmentation may be diffuse, marginal or perifollicular. Following the initial onset, SV spreads fast only along the affected dermatome. Thereafter, it remains stationary for the rest of the patient's life.[3] In a large series of patients of all ages suffering from SV, progression was seen among 55.3% of patients, lesions were stable in 40.9% patients and minimal regression without treatment was seen in 3.8% of patients.[3]

DIFFERENTIAL DIAGNOSIS

Various nevoid and hereditary disorders with depigmentation may simulate vitiligo in children. It is important to differentiate hereditary disorders from early-onset childhood vitiligo as these are usually multisystemic. Moreover, therapeutic intervention is possible in vitiligo but not feasible in nevoid and hereditary conditions. Table 1 presents the list of various congenital and acquired conditions simulating

Table 1: Differential diagnosis of childhood vitiligo[20]

Disorder	Clinical differentiating point from vitiligo
Congenital	
1. Nevoid pigmentary disorders	
• Nevus depigmentosus	Margins of the lesions are usually serrated or fuzzy, as shown in Figure 5.
• Nevus anemicus	Pale white lesions with very indistinct border. Becomes unnoticeable on diascopy of the surrounding skin
2. Ash-leaf spots (tuberous sclerosis)	Hypopigmented macules with a typical lanceolate shape present over the trunk
3. Piebaldism	Stable, patterned, depigmented patches, with small areas of normal-colored skin, distributed mainly over the ventral aspects of the body, present since birth. White forelock present in 85% of the cases
4. Waardenburg syndrome	Depigmented patches present since birth, with white forelock. Associated features are heterochromia of irides, dystopia canthorum and congenital sensorineural deafness
5. Linear lesions	
• Hypomelanosis of Ito	Hypopigmented, linear streaks and whorls along Blaschko's lines
• Fourth stage of incontinentia pigmenti	Linear, atrophic, hypopigmented streaks with lack of hair and sweat pores. Easily seen by Wood's lamp. History suggestive of occurrence of previous stages
6. Oculo-cutaneous albinism	Universal depigmentation involving skin, hair and eyes. Total leukotrichia in depigmented areas that may not be so over a vitiligo patch
Acquired	
1. Inflammatory	
• Pityriasis alba	Hypopigmented lesions with fine scaling, mostly over the face and upper arm
• Lichen striatus	Linear hypopigmented lesions; initial lesions are composed of shiny lichenoid papules
• Post-inflammatory hypopigmentation	History of active skin lesions in the past. May retain the shape and size of the original skin lesion. Self-resolution is common
2. Infection	
• Pityriasis versicolor	Hypopigmented macules covered with furfuraceous scale involving widespread areas of the trunk
• Leprosy	Hypopigmented macules/patch with decreased or loss of sensation. Involvement of peripheral nerves
• Post-Kalaazar dermal leishmaniasis	Hypopigmented macules with widespread, symmetrical distribution, mostly over the trunk. Associated papules and nodules may be present
• Pinta	Late dyschromic stage appears during adolescence. Widespread slate-blue hyperpigmentation replaced by depigmented macules, located over the face, waist and bony prominences. Found in endemic areas. Many family members are affected
3. Miscellaneous	
• Polymorphous light eruption	Pruritic, scaly, hypopigmented, papule/macule/patch over the photoexposed area. History of photoexacerbation and recurrence
• Contact depigmentation	Patterned area of depigmentation (footwear, diaper, etc.). Involvement of only the contact area
• Lichen sclerosus et atrophicus (LSEA)	Porcelain-white atrophic macules with mild atrophy and follicular plugging. In case of genital lesions, phimosis is the feature in boys, and atrophy, hemorrhagic areas and resorption of genital structure are the features in girls
• Topical steroid abuse	Atrophic macule/patch with surface telangiectasia with or without excess hair. History of long-term topical steroid application over a pre-existing dermatosis

vitiligo and the important differentiating features [Figure 5].[20]

Vitiligo as a component of hereditary syndromes

Vitiligo in older children and adolescents may be one of the components of certain syndromes.[20]

Vogt-Koyanagi-Harada syndrome: It is a rare syndrome affecting children, especially of south-east Asian origin. Characteristic features are uveitis, aseptic meningitis, dysacusia, alopecia, poliosis and vitiligo. Uveitis is the presenting feature and vitiligo may appear later, during the chronic stage (fourth stage) of the disease (adolescence or adulthood). Vitiligo lesions tend to be symmetrical, involving the head, neck and trunk. The sacral region is a common site of involvement with vitiligo. Poliosis may involve the scalp, eyebrows and eyelashes.

Alezzandrini syndrome: This syndrome is characterized by SV (cheek), poliosis, ipsilateral uveitis resulting in decreased visual acuity and same-sided partial hearing loss. Manifestation starts during adolescence.

In both these disorders, uveitis and related ocular manifestations are the main clinical features. Vitiligo appears later and is usually persistent, despite therapy.

MANAGEMENT

Diagnosis

Diagnosis of vitiligo is mostly clinical. Invasive and sophisticated investigations are not required to confirm the diagnosis. In children with fair skin, it may be difficult to differentiate a lesion of vitiligo from the surrounding normal skin. In these cases, examination under Wood's lamp is helpful.[20] Complete blood count and fasting blood sugar should be performed as a routine work-up for all patients. In case of diagnostic difficulty, skin biopsy may be taken; histopathological examination shows total absence of melanocytes in established lesions of vitiligo. In early lesions, melanocytes are still retained but with multiple abnormalities like vacuolization, dilated endoplasmic reticulum and granular deposits.[4] Presence of mild inflammatory infiltrate is sometimes seen, and is indicative of disease activity.[4]

Associated autoimmune disorders should be ruled out in the pediatric age group. Screening for autoantibodies may be performed if facilities are available. Antinuclear antibody may be positive even in normal children. Thyroid function status of the child is assessed by estimating T3, T4 and TSH levels. Coexistence of autoimmune thyroiditis may be ruled out by the estimation of antithyroglobulin antibody (anti-Tg) and antithyroperoxidase antibody (anti-TPO). Kakourou *et al*[17] have proposed a management protocol for children with vitiligo and positive antithyroid antibodies [Figure 6].

Therapy

Various therapeutic modalities are available for the treatment of vitiligo; however, all of these cannot be used in children. Medical therapy is considered as the first line of management in this age group. All children with widespread vitiligo should undertake photoprotection preferably with opaque sunscreens during daytime outdoor activities. In general, localized vitiligo is treated with topical therapy. Widespread or generalized disease is managed with phototherapy or systemic therapy. Surgical methods may be chosen for stable (size of the lesion is stationary for > 2 years and no new lesion has developed recently)[21] localized vitiligo and SV. Different therapeutic options available for the treatment of childhood vitiligo are presented in Table 2.[22] Certain clinical features are poor prognostic markers for treatment. These include acral vitiligo, presence of leukotrichia over vitiliginous area and lesions over bony prominences like elbow, knee and ankle. An algorithm for treatment options in childhood vitiligo has been presented in Figure 7.

Medical treatment

Topical therapy

Mid-potent topical corticosteroids are the first-line therapy for children with localized vitiligo. Although high-potency steroids are more effective in vitiligo, these are not recommended for use in children. Available studies report a 45–60% response rate to topical steroid in childhood vitiligo.[8,19] It requires long-term therapy for several months, increasing the chances of developing tachyphylaxis and local side effects like atrophy, telangiectasia, hypertrichosis and striae. There are risks of serious side effects like glaucoma (prolonged application on periorbital vitiligo), suppression of hypothalamic-pituitary-adrenal axis and growth retardation (long-term use over large BSA). Hence, parents should be cautioned about the inadvertent use of topical steroids.

Topical calcineurin inhibitors (TCI), tacrolimus and pimecrolimus are effective alternatives to topical

corticosteroids in terms of avoidance of side effects of the latter. Several authors have demonstrated the effectiveness of tacrolimus in children with vitiligo.[23-25] In a double-blind randomized placebo-controlled trial of topical tacrolimus (0.1%) versus topical clobetasol propionate (0.05%) in childhood vitiligo (age 2–16 years), the efficacy of both the

Table 2: Various treatment modalities for childhood vitiligo[22]

Therapy
1. Medical
a. Topical
• Corticosteroids
• Tacrolimus/pimecrolimus
• Calcipotriol
• Pseudocatalase
• Combination
b. Systemic
• Corticosteroids (OMP with betamethasone/ methylprednisolone)
2. Phototherapy
• Topical PUVA
• NB-UVB
• Systemic PUVA (>12 years)
• Phenylalanine + PUVA
• Excimer laser (308 nm)/targeted NB-UVB phototherapy
3. Surgical therapy
Conventional
• Mini-punch graft
• Suction blister epidermal graft
• Thin Thiersch graft
Newer cellular transplantation techniques
• Epidermal cell suspension
• Cultured melanocyte suspension
• Cultured epidermis
4. Cosmetic camouflage
5. Total depigmentation using MBEH

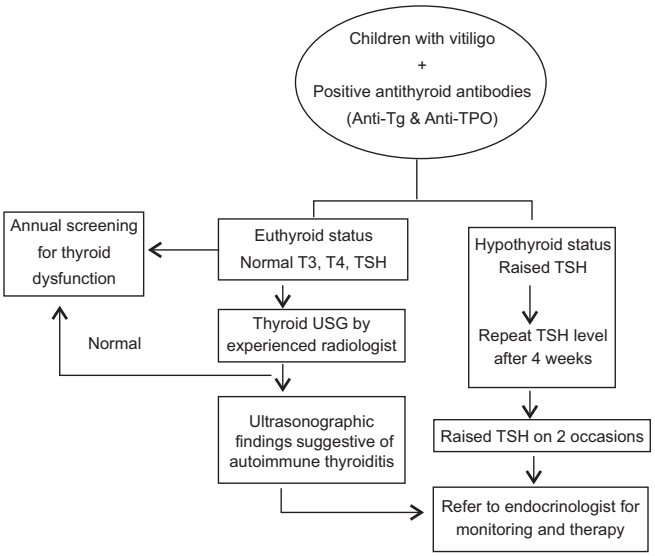

Figure 6: Proposed protocol for the investigation and management of children with vitiligo and positive antithyroid antibodies[17]

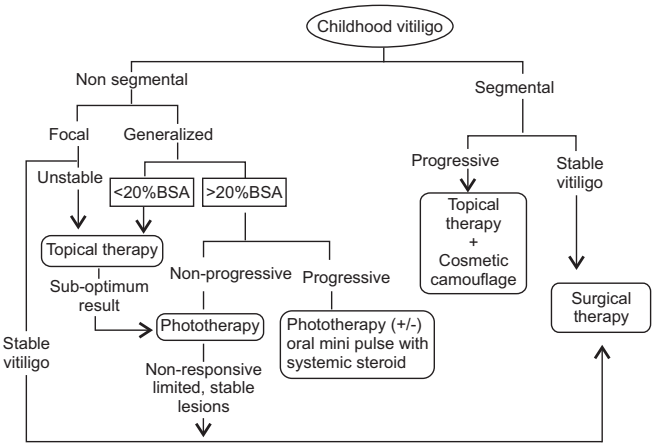

Figure 7: Algorithm presenting the treatment options for childhood vitiligo

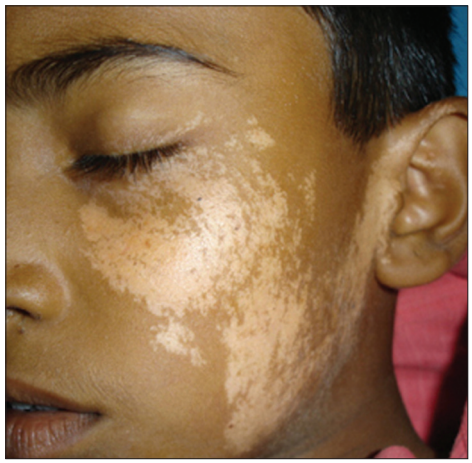

Figure 5: Serrated margin of nevus depigmentosus

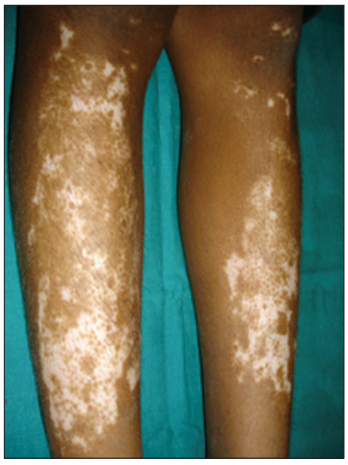

Figure 8: Perifollicular repigmentation following narrow-band ultraviolet B phototherapy

therapeutic agents was comparable and no significant adverse effect was recorded in either group.[26]

In an open comparative trial of mometasone cream (0.1%, once-daily application) and pimecrolimus cream (1%, twice-daily application) in the treatment of localized childhood vitiligo, the repigmentation rates were 65% and 42%, respectively, at the end of 3 months.[27] Mometasone cream was found to be equally effective in all body parts whereas pimecrolimus was effective only over the face.[27]

TCIs are slower to exert beneficial effect compared to topical corticosteroid.[28] Best response is observed on the thinnest areas of the skin (eyelids).[28] As the skin barrier function is not compromised in children with vitiligo (unlike atopic dermatitis), highest strength (0.1%) of tacrolimus may be used safely.[28] Calcineurin inhibitors are not yet approved for the treatment of vitiligo and are not recommended for use in children <2 years.[22]

Topical calcipotriol has been found to be effective in the treatment of vitiligo in children and adolescents. In a trial of topical calcipotriol in childhood vitiligo, repigmentation was recorded as early as 4 weeks of treatment.[29] Some interesting observations made in this study were: repigmentation of untreated lesions, continuation of repigmentation in both treated and untreated lesions even after stoppage of calcipotriol and response in previously treatment-resistant lesions (range 21.18–93.46%). These findings led the author to hypothesize that a systemic effect of topically applied calcipotriol might have been operative.[29] Combination therapy of topical corticosteroids and calcipotriol[30] may be used to reduce the side effects of corticosteroids as well as to enhance the efficacy of calcipotriol as the latter may not be as effective when used as monotherapy.[22]

Side effects of calcineurin inhibitors and calcipotriol are mild and transient and hence, easily tolerated by children. However, both these agents are more expensive compared to topical corticosteroid, and may not be easily affordable by the families from the low socioeconomic strata.

Recalcitrant cases of widespread vitiligo or universal vitiligo with only few islands of normal skin may be considered for total depigmentation therapy with 20% monobenzyl ether of hydroquinone (MBEH), with an advice of life-long stringent photoprotection.[20,22]

Systemic therapy

Rapidly progressive generalized vitiligo in older children and adolescents may be treated with a short course of systemic steroid. A better way to avert the side effects is administering oral betamethasone as a single morning dose (0.1 mg/kg body weight) on two consecutive days in a week (oral mini-pulse therapy) for 12 weeks, and thereafter reducing the dosage by 1 mg/month for the next 3 months.[31] Pasricha *et al*[32] have studied the effect of oral mini-pulse therapy (OMP) in children and adults with extensive or fast-spreading vitiligo, and have observed a 26–50% response in 25%, 51–75% response in 7.5% and >75% response in 15% of patients. Phototherapy may be added to such regimen.[31] Majid *et al*[33] have used methylprednisolone OMP in combination with topical fluticasone for 6 months in 400 children with progressive vitiligo. Complete halt of progression was noted in >90% of the children after initiation of therapy, and >65% of children had well to excellent repigmentation at the end of the study period.[33]

Phototherapy and photochemotherapy

Systemic photochemotherapy with psoralen-ultraviolet A (PUVA) is contraindicated in small children and can be used only beyond 12 years of age. It is used when >20–25% of the BSA is involved or in patients in whom other treatment modalities are not giving optimum result.[22] Topical PUVA can be used even in younger children with limited BSA involvement. Various authors have reported an overall response rate of approximately 75% in 50–60% of the children with vitiligo treated with topical or oral PUVA therapy.[22]

Oral supplementation of L-phenylalanine (a precursor of tyrosine in melanin synthesis) and UVA phototherapy have been found to be effective in children with extensive vitiligo (50–100% repigmentation in 69% of children).[34]

Narrow-band ultraviolet B (NB-UVB) phototherapy is an effective modality for the treatment of generalized childhood vitiligo with >20% BSA involvement.[22] There are several studies on the effectiveness of NB-UVB phototherapy in children.[34-36] Brazzelli *et al*[37] have reported this therapeutic modality as effective and safe in children. Of the 10 children with vitiligo

included in this trial, better therapeutic response was noted in those with recent-onset disease (duration <1 year).[37] Best repigmentation occurred on skin lesions over the face and neck, and moderate response was seen in lesions on the trunk and proximal extremities. Lesions over the acral region (fingers and toes), bony prominences and less-hairy areas (wrist, ankle and joints) were poorly repigmented.[37] The side effects recorded were minimal erythema, amenable to emollients and topical steroid.[37] Other topical therapeutic agents like pimecrolimus and pseudocatalase may be used in combination with NB-UVB phototherapy.[22] In a large series of children and adolescents with vitiligo, Schallreuter *et al*[38] have recorded a significantly better repigmentation rate (>75%) with the use of combined treatment of pseudocatalase and NB-UVB as compared to NB-UVB alone. Rath *et al*[31] have compared the efficacy of combined phototherapy (PUVA, NB-UVB and broad band UVB) and OMP with OMP alone in 86 patients (aged 10–50 years) with progressive vitiligo. Combination therapy was found to be superior to OMP alone, the most effective being with NB-UVB, followed by PUVA and broad band UVB.

Excimer laser (308 nm)/targeted UVB phototherapy has been used in the treatment of localized childhood vitiligo with the advantage of more focused therapy at the site of lesion, avoiding the risk of photoageing of the surrounding skin.[22] Cho *et al*[39] have treated 30 children with localized vitiligo (40 patches) with 308 nm excimer laser. A repigmentation rate of >50–75% was recorded in this trial, especially over the face, neck and trunk. Side effects related to this mode of therapy are usually minimal and transient. Hui-Lan *et al*[40] have studied the effect of 308 nm excimer laser and topical pimecrolimus cream (1%) compared to excimer laser alone in 49 Chinese children with NSV. The effect of this combination therapy was statistically superior to the laser therapy alone, and this effect was most evident on facial lesions.[40]

Repigmentation following phototherapy is either marginal or perifollicular [Figure 8]. During phototherapy, genitalia of the children should always be protected.[41] It is preferable to follow the "skin-saving principle," i.e. shielding of uninvolved body sites during phototherapy.[41] Already repigmented body parts should also be covered with clothing during further therapy.[41] Carcinogenic potential of NB-UVB phototherapy in children is not yet determined.[42] However, theoretically, there may be an increased chance of developing long-term skin cancers because of the higher number of expected years of life in children.[42] Such risk may be lower in children with darker skin types. In resource-poor countries, the facility of phototherapy is available mostly in tertiary health care centers. Hence, it may not be easily accessible to families from remote localities. Moreover, multiple hospital visits confer loss of school days of children and working days of parents, reducing compliance to treatment.[42]

Surgical therapy

Only stable localized vitiligo lesions (segmental or non-segmental), unresponsive to other treatment modalities, are chosen for surgical treatment. Surgical procedures are not performed in very young children. This is because segmental or stable focal lesions in younger children extends proportionate to their body growth. Moreover, success of many surgical procedures depends upon the post-operative immobility of the operated part, which becomes difficult to maintain in young children. Older children and adolescents may be counseled about the procedure and the possible outcome of the surgery to achieve their cooperation. The restrictive factors for surgical procedures are inability to treat larger area and the risk of Koebnerization of the donor site.

Among the various surgical techniques, suction blister epidermal grafting (SBEG) has been found to be most convenient and effective for children and adolescents.[22] Gupta *et al*[43] have reported >75% repigmentation in 86.7% patches in 80% children and adolescents with vitiligo following the SBEG technique. The success rate of this technique is better in children as compared to adults.[43] However, this procedure requires prolonged immobility to facilitate smooth generation of the blisters, more so in children because of their strong dermoepidermal adherence; hence, it may be a difficult task to keep children in restricted posture till the required duration.[43]

Surgical procedures in combination with medical therapy have been tried in childhood vitiligo. In a randomized, placebo-controlled trial using microdermabrasion and pimecrolimus cream (1%) in childhood NSV, >50% repigmentation was observed after 3 months in 60.4% of patches treated with this combination as compared to pimecrolimus alone (32.1%) and placebo (1.7%).[44]

Non-cultured autologous epidermal transplantation has been used successfully in children and adolescents with stable vitiligo. Mulekar *et al*[45] have used this technique in 25 children with focal vitiligo and SV with follow-up till 4 and 4.5 years, respectively. Seven children with focal vitiligo ($n = 12$) and eight children with SV ($n = 13$) had near-complete to complete repigmentation with this technique.[45] Sahni *et al*[46] have used this technique to treat stable vitiligo lesions in 13 children and adolescents. Repigmentation rate at the end of 1 year in these patients varied from 75% to >90%.

Cultured melanocyte transplantation is a relatively tedious technique requiring specialized set up, trained staff and a preparation time of 6–8 weeks.[47] Cost may be a restrictive factor for poor families in availing this treatment modality.[47]

Cosmetic camouflage

Good-quality cover-up cosmetics (available in commercial names; Dermablend, Covermark, Dermacolor) may be used to cover localized vitiligo lesions over exposed body parts in children.[20,22] Well-counseled older children may use this as an effective adjunctive while on treatment or when failed to respond to other treatment modalities. White-skinned children in whom conventional treatment is contraindicated or ineffective may be managed with stringent photoprotection and cosmetic camouflage.

Treatment of vitiligo in hereditary disorders

Vitiligo lesions in hereditary disorders like Vogt-Koyanagi-Harada syndrome and Alezzandrini syndrome are usually resistant to treatment. These patients would be on long-term systemic corticosteroid and various immunosuppressive agents for the treatment of uveitis. Topical steroid may be used for localized lesions of vitiligo. Sunscreens should be used regularly and cosmetic camouflage may be used. Phototherapy should be used with great caution in these patients as this may enhance ocular inflammatory disease.[48]

All children with vitiligo, especially among dark races, require thorough counseling as they may be the victims of peer-teasing and avoidance at schools. This may lead to anxiety, introvert personality and childhood depression. In a qualitative psychosocial development survey of children with vitiligo, Schwartz *et al*[49] have recorded a higher frequency of fear to strangers and predominant fear and shyness to a change in close relative in them as compared to their healthy siblings. The child's perception about the illness and difficulties in interaction with other children should be discussed in detail during routine follow-up.[4] Parents of affected children should also be counseled regarding tackling such issues. A well-counseled child with vitiligo may render full cooperation to the treating physician, making his job easier. Mulekar *et al*[45] have observed that all the children with localized vitiligo in their series, treated by non-cultured cellular grafting technique, accepted the treatment procedure willingly, even if it was a repeat session.

Childhood vitiligo requires special consideration. Many of the adults with vitiligo had disease onset during the first or early second decades of life and had grown up with the psychological trauma associated with this stigmatizing disease. Early institution of medical care (therapy and/or counseling) in all cases of childhood vitiligo ensures better cope up with the associated stress as well as understanding the nature and course of the disease during adolescence and adulthood.

Treatment of vitiligo at any age remains a challenge for clinicians, more so during childhood. None of the available therapies is absolutely effective, and the disease runs a relapsing course. With any of the treatment modalities, >75% repigmentation (achieved by approximately 60% of treated children) is considered as the best therapeutic response.[22,41] Long-term treatment requirement is the rule with chance of cumulative side effects of the drugs. Some patients (15–30%) remain unresponsive to all treatment[22] and even in responsive cases, there are treatment-resistant body sites. Often, multiple therapeutic modalities may have to be used to obtain optimum result in a given patient. The art of treatment of childhood vitiligo is a fine balance between addressing all these issues and achieving the best result out of the available modalities.

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