Ann Natl Acad Med Sci (India), **52(1):** 29-38, 2016

Vitiligo – An Indian Perspective

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SUMMARY

The prevalence of vitiligo in India is high. It affects DLQI. Exact aetiology is not clear. Melanocytorrhagy hypothesis is important. Classification into segmental and non segmental vitiligo is satisfactory from prognosis and treatment point of view. Onset of vitiligo after the age of 30 years is defined as late onset vitiligo: separate subset with strong genetic background and presence of precipitating environmental factors. Mucosal vitiligo is a distinct subset. Koebner type 2 A phenomenon needs redefining.

Oral minipulse and minocycline are effective in progressive unstable vitiligo. Narrowband UVB phototherapy is effective in both children and adults: it has an edge over PUVA. NCECS is the most common surgical technique used in treatment. Suspension in patient's serum gives better results. NCECS is better than SEBG. Camouflaging and depigmentation are required in some cases.

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DR. R.V. RAJAM ORATION delivered during NAMSCON 2014 at the All-India Institute of Medical Sciences, Rishikesh.

INTRODUCTION :

Vitiligo is a common acquired chronic pigmentation disorder characterized by white patches. It affects 0.5 to 1 % of the world's population. India is amongst the countries with highest prevalence rates varying from 0.46 % in Calcutta to 2.16 % in Chandigarh. It is a disorder of great cosmetic significance and a source of considerable psychological distress and social isolation especially in dark races. It is associated with significant impairment in the quality of life. Patients suffer low self esteem and depression and they have difficulties in finding a job or getting married. Pandit Jawahar Lal Nehru, the first Prime Minister of India ranked vitiligo as one of the three major medical problems of India, the other two being leprosy and malaria.

Historical Background :

The word vitiligo is derived from Latin 'vitium' meaning blemish. In Atharveda from India, it is described as 'kilas' or white disease. In 'Charaka Samhita' it has been designated as 'svitra'.

Aetiopathogenesis :

The exact aetiopathogenesis of vitiligo is not clear. There are a number of theories and each has some contribution to its pathogenesis.

Genetic theory: Most cases of vitiligo occur sporadically; about 15-20% of patients have a positive family history. Familial aggregation takes a non-Mendelian pattern that is suggestive of polygenic, multifactorial inheritance. Increased prevalence of HLA-DR4, HLA-B13, HLA-DRW6, HLA-DRW52, HLA-DQW1, HLA-DQW3, HLA-CW6 and decreased prevalence of HLA-CL4AQO has been found to be associated with vitiligo.

Autoimmune hypothesis:

A number of clinical conditions alleged to be of autoimmune origin like thyroid dysfunction, Addison's disease and pernicious anemia have been shown to be associated with vitiligo. Auto-antibodies have been found against certain surface antigens of melanocytes and the titers of these antibodies correlate well with the extent of depigmentation and response to therapy. Antityrosinase antibodies have also been detected.

Neurogenic hypothesis:

This is based on the observations of autonomic dysfunction in the vitiliginous patches. Lesions may also exhibit increased levels of nor epinephrine and neuripeptide-Y (cytotoxic to the cells or indirectly by causing vasoconstriction).

Melanocyte self destructive hypothesis:

Melanocytes may be destroyed by the very factors that are responsible for melanogenesis (accumulation of some toxic metabolites like indoles, breakdown products of pterin homeostasis (such as 6-BH- 4 and 7-BH-4).

Oxidative stress hypothesis:

Lesional and nonlesional skin of vitiligo patients exhibits low levels of catalase levels which correlate with high levels of hydrogen peroxide.

Viral infections:

Cytomegalic virus infection has been implicated.

Growth factor defect hypothesis:

Basic fibroblast growth factor deficiency can be associated with vitiligo.

Melanocytorrhagy hypothesis:

This theory is getting important. Melanocytes are weakly anchored in skin. A minor friction can cause their detachment and produce depigmentation-Koebner's phenomenon. We carried out a study in which Perilesional skin melanocytes from patients with stable and unstable vitiligo were cultured and studied for morphological changes, adhesion to collagen type IV and caspase 3 expression.

Melanocytes from unstable vitiligo showed significantly low adhesion to collagen type IV compared with controls and stable vitiligo melanocytes. Caspase 3 and annexin staining was significantly greater in melanocytes cultured from unstable vitiligo as compared with the controls (1).These morphological and adhesion findings support the theory of melanocytorrhagy as the primary defect underlying melanocyte loss in unstable vitiligo.

Liver X receptor alpha has been implicated in proliferation, carcinogenesis, differentiation and permeability barrier function of skin. We observed that LXR-alpha mRNA expression was significantly higher in Perilesional skin as compared to uninvolved skin of non segmental vitiligo patients. This leads to decreased cell adhesion molecule and proliferation resulting in detachment of melanocytes from basement membrane (2).

Convergence Theory :

There are now probably too many hypotheses of vitiligo; all are not mutually exclusive. Combination of these mechanisms can contribute to vitiligo.

Classification of Vitiligo :

The vitiligo global issue conference classification divides vitiligo into two main types: Segmental and Non segmental. Among segmental vitiligo, it may be uni-, bi-, or pluri-segmental. The non segmental vitiligo includes Acrofacial, mucosal, generalized, universal and mixed.

Clinical Presentation :

Clinically the disease starts as focal patch and thereafter it may either stabilize leading to localized disease or spread explosively or more gradually into

generalized vitiligo. The most common sites involved are fingers, hands, face and other trauma prone areas of the body.

There is no sex predilection for vitiligo as such. Peak incidence of vitiligo is found in 10-30 years of age. Incidence of vitiligo decreases with increasing age.

Segmental vitiligo:

It affects young patients mainly before the age of 20 years with a relatively rapid course of a few months and then gets stabilized. Involvement of one side of body is usually observed. There is poor response to medical/phototherapy. High rates of repigmentation are achieved with surgical techniques.

Non segmental vitiligo:

It is a slowly developing condition with a tendency to progress throughout the years. In a small percentage of these individuals, arrest of the condition may occur.

We studied the effect of age at onset on disease characteristics in vitiligo (3). Of 1416 patients, 1211(85.5%) had an early onset of disease whereas 205 (14.5%) patients had late onset vitiligo. Patients with disease onset after 30 years (late onset) had a significantly higher association with precipitating factors such as trauma and stress; higher incidence of positive family history and a higher association with leucotrichia. Early onset non segmental vitiligo was associated with a higher incidence of photosensitivity and pruritus compared to early onset segmental vitiligo. Late onset vitiligo is defined as vitiligo occurring after the age of 30 years. It is a separate subset that manifests in patients with a strong genetic background and the presence of precipitating environmental factors. Hands are the most common initial sites to be involved and the disease onset may be preceded by a precipitating factor in a significant proportion of patients.

Few studies have suggested that mucosal involvement is associated with progression of the disease. We carried out a comprehensive review of 241 cases to find out if it is true (4). Of 241 cases, 70 had pure mucosal involvement, 35 had onset in mucosae and then spread to skin and 136 had onset in skin and then spread to mucosae. The mean age of patients with pure mucosal involvement was 31 years. Fifty five had involvement of lips. History of smoking was commoner as compared to other groups. Smoking probably acts as low grade thermal trauma to the lips thus precipitating vitiligo in genetically predisposed individuals. There was no difference in groups related to history of associated autoimmune disease, family history and sites of mucosal involvement. In our opinion no relation is there between involvement of mucosae and extent of skin involvement. We think that pure mucosal vitiligo is a distinct subset.

Koebner phenomenon in Vitiligo :

Koebner phenomenon (KP) has been reported as occurring in 21-62% of

patients with vitiligo. Patients showing KP have a significantly older age at onset of vitiligo. Presence of KP in a patient with segmental vitiligo may be an indicator of subsequent development of non segmental vitiligo. In a retrospective study of 1416 patients, we observed that 6.6% had KP. Patients with KP had significantly older age of onset and shorter duration of illness as shown in earlier studies (5). Recently the vitiligo European task force group has divided KP into three types:

Type 1: for which diagnosis of KP is based on history
Type 2A: for which depigmentation is present on areas of chronic friction
Type 2B: for which depigmentation is clearly induced by trauma
Type 3: which refers to experimentally induced KP.

Trauma to the dermis rather than superficial epidermis is required to induce KP.

We carried out a prospective study of Type 2A Koebner phenomenon in 202 patients. KP was present in 130 (64.4%) of patients. Type 2 A was the commonest type present in 116 (57.4%) patients (6). Since the predilection sites of vitiligo are located at areas of friction and pressure, we question the value of assessing Type 2A KP. We propose that the definition of Type 2A KP needs more clarification since it is different from other subtypes. Patients exhibiting KP have higher mean age and age at onset, more body surface area is involved and hence systemic therapies are required to control disease activity.

Treatment :

Multiple treatment options are available. A positive approach is recommended involving explaining the nature of disease process, the likely prognosis and the treatment options with their expected results to the patients.

Various therapies used for treatment of vitiligo are divided into TWO major groups-Medical and surgical. Choice of treatment also depends on the morphologic subtype and extent of vitiligo.

Corticosteroids :

Corticosteroids can be used both topically and systemically. Topical corticosteroids are first line therapy for localized vitiligo and are recommended for facial and/or small lesions and in children. Topical potent and ultrapotent corticosteroids though found to be most effective should be limited to 2-4 months. Systemic corticosteroids are indicated in vitiligo when it is progressive and unstable. A study was carried out to assess the efficacy of low dose dexamethasone oral mini pulse therapy 2.5 mg per day for two consecutive days in progressive unstable vitiligo. A total of 444 patients were analyzed (7). In 408(91.8%) patients, arrest of disease activity was achieved at a mean of 16.1 plus minus 5.9 weeks. In addition, some repigmentation of the lesions was seen in all patients after a mean of 16.1 plus minus 5.9 weeks. Fifty of 408 (12.25%) patients experienced one or two episodes of relapse in disease

activity and were treated with reinstitution of oral mini pulse therapy. The mean disease free survival until the first relapse was 55.7 plus minus 26.7 weeks. Adverse reactions such as weight gain, lethargy and acneiform eruptions were observed in 41 (9.2%) patients. Low dose OMP therapy with dexamethasone is a good therapeutic option to arrest the activity of progressive unstable vitiligo. Its effectiveness in controlling disease activity is comparable to that of other schedules in which systemic steroids are administered at a much higher dose, albeit with less adverse effects. However, it is not suitable alone for repigmentation of vitiligo lesions.

Minocycline has wide range of anti inflammatory, immunomodulatory and free radical scavenging actions. In 32 patients with gradually progressive vitiligo, 100 mg oral minocycline once a day was administered for 3 months. In 29 patients, the progression of the disease was arrested. In a comparative study of OMP and oral minocycline, a total of 50 patients with rapidly spreading vitiligo were randomized to revive either minocycline 100 mg a day or OMP 2.5 mg dexamethasone on two consecutive days in a week for 6 months (8). Both OMP and minocycline were observed to be effective drugs for managing the arrest of disease activity in vitiligo.

Tacrolimus:

Topical tacrolimus was first used for treatment of vitiligo by Grimes *et al* (9). It acts by suppression of autoantibody recognization of melanocyte antigen and inhibition of cytotoxic T cell proliferation.We carried out a study of topical treatment with tacrolimus 0.03% ointment in 25 children (10). Tacrolimus was applied twice daily for 12 weeks. 19 (86.4%) children showed some repigmentation at the end of three months and other 3 had no response. Of these 19 children, repigmentation was marked to complete in 11 (57.9%), moderate in five (26.3%) and mild in three (15.7%) children.

Phototherapy :

Ultraviolet B can induce T-regulatory (suppressor) cell activity. Releases IL 10 is important for differentiation and activation of T-regulatory cells which may suppress autoimmune conditions. UVB exposure increases the number of residual melanocytes most probably by enhancing melanocyte growth factors such as bFGF and endothelin-1(ET-1).

14 patients aged 12-56 years with generalized vitiligo were treated thrice weekly with NBUVB radiation therapy for a maximum period of 1 year. 10 patients (71.4%) had marked to complete repigmentation and 2 each (14.3%) had moderate or mild repigmentation. It was concluded that NBUVB therapy is effective and safe in Indian patients with vitiligo (11).

Twenty six children with generalized vitiligo manifesting a minimal extent of depigmentation of 5 %

of the body surface were recruited. Patients were treated with starting dose of 280 MJ/cm2 and treated for one year. Dose of NBUVB was increased by 20% on subsequent visits. Marked to complete repigmentation was observed in 15 (75%). Average of 34 plus minus 2 visits were required for 50 % repigmentation. It was concluded that NBUVB is effective and well tolerated modality for childhood vitiligo (12).

PUVA versus NBUVB:

Studies to evaluate PUVA versus NBUVB seem to depict some advantages in favour of NBUVB with higher repigmentation rates and better color matching. However, comparing with NBUVB with monochromatic excimer laser, 308-nm MEL was found to be more effective and faster than NBUVB. In an open prospective study comparing systemic PUVA and NBUVB in treatment of vitiligo, we observed that mean degree of repigmentation attained in the NBUVB group was 52.24% over a mean treatment period of 6.3 months whereas in the PUVA group it was 44.7% in a mean time of 5.6 months. Although repigmentation was better in the NBUVB group, the difference was not statistically significant (p=0.144).Color match was better and side effects minimal (13).

Surgical Treatment :

The aim of surgical induction of repigmentation is to replenish melanocytes in the depigmented lesions of vitiligo which either have no reservoir or fail to activate melanocytes in outer root sheath with known treatment modalities. Although surgical trauma induces proinflammatory cytokines which have an effect on melanogenesis and pigment cell migration, the presence of melanocytes in grafts is crucial for repigmentation.

Before carrying out the surgical treatment it is important that the vitiligo should be stable. The concept of stability in vitiligo is multifaceted and no consensus has yet been reached on defining the criteria for this so far. There are clinical, ultra-structural, serological and biochemical parameters to distinguish between stable and active disease. However these studies are cross sectional and hence do not shed light on the correlation of these parameters with the course and prognosis of the disease. The Indian Association of Dermatologists and Venereologists (IADVL) taskforce defines stability as: no reporting of new lesions; no progression of existing lesions and absence of Koebner phenomenon during the past one year.

Autologous non cultured epidermal cell suspension (NCECS) is the most common used method. This technique pioneered by Gauthier and Surleve-Bazeille (14) in 1992 has revolutionized the scenario of surgical therapy of vitiligo. Cold trypsinization was further modified by Olsson and Juhlin (15) thereby significantly reducing the duration of the procedure. NCECS yields cosmetically acceptable results in a short period of time.

The NCECS technique involves 3 steps: harvesting of donor skin; preparation of melanocyte rich basal layer cell suspension and dermabrasion followed by application of the cells over recipient area.

Acral vitiligo and lesions over the joints were treated with NCECS (16).

In total, 36 patients with 80 lesions over acral areas and joints were reviewed. Of 80 treated lesions, 51 had regained more than 75 percent repigmentation and 23 had regained 50-75% repigmentation. In another study (17) it was observed that suspending the melanocytes in the patient's own serum gives better repigmentation. Even repigmentation of leucotrichia was observed (18). In a comparative study between NCECS and suction blister epidermal grafting in stable vitiligo, it was observed that NCECS has an edge over SBEG in terms of extent of repigmentation, patient satisfaction and DLQI (19). Recently non cultured extracted hair follicle outer root sheath cell suspension has been shown to be effective in surgical treatment of vitiligo. Both these techniques were compared and their efficacy was similar (20).

Some patients would require camouflaging and in those patients with extensive vitiligo, mono benzyl ether of hydroquinone (MBEH) at a concentration of 20% is used to remove the residual melanocytes.

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