Vitiligo: Compendium of clinico-epidemiological features

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ABSTRACT

Vitiligo, an autoimmune disorder characterized by localized and/or generalized depigmentation of the skin and/or mucous membranes, is a well-recognized entity. The imperatives of its epidemiology both in rural India and in global reckoning have been highlighted frequently. Its morphology is striking and is characterized by asymptomatic ivory/chalky white macule(s) that may be frequently surrounded by a prominent pigmented border, the 'trichrome vitiligo'. However vitiligo may have morphological variations in the form of: trichrome, quadri-chrome, penta-chrome, blue and inflammatory vitiligo. Its current topographical classification into segmental, zosteriform and nonsegmental, areata, vulgaris, acrofacialis and mucosal represent its well acclaimed presentations. Its adult and childhood onset is well appreciated as also its presentation in males and females. Occasionally, it may be possible to identify triggering factors. Vitiligo may be associated with cutaneous, ocular and systemic disorders, the details of which are discussed in this article.

Key Words: Clinical connotation, Definition, Epidemiology, Segmental and Nonsegmental vitiligo, Vitiligo

REMINISCENCES

Vitiligo is an ancient malady and a historical background will facilitate continuity with current research. The earliest authentic reference of the condition can be traced back to the period of Aushooryan (2200 BC), in the classic Tarikh-e-Tib-e-Iran.[1] Pharonic medicine in the Ebers Papyrus (1550 BC) described two types of diseases affecting the color of the skin - (a) with tumors; probably leprosy and (b) with only color change, probably vitiligo. The latter was believed to be treatable.[2] Vitiligo occurs worldwide and since time immemorial, world literature is replete with references to the condition and different aspects of its causes and therapy.[3-10] Prior to its current nomenclature, it used to be pronounced by several other names, a short resume of which is formed in the following Table 1. 'Vitiligo' appears to have been derived from the Latin word 'vitium', meaning a "defect".[13,14] Documentation of the word "vitiligo" is present in the book, De-Medicina, by the Roman physician Celsus.[15]

Table 1: Vitiligo: Historical reminiscence

<table>
<thead>
<tr>
<th>Epic (classic) / language</th>
<th>Era (period)</th>
<th>Nomenclature</th>
</tr>
</thead>
</table>
| Amarkosh[3,4] | 600 AD | Suitra - A) Padasphota
| Arabic medicine[12] | 1200 AD | Bohak, bahak, baras Zoraat |
| Bible[6] | | Shirabito |

DEFINITION

Vitiligo is a common, acquired, discoloration of the skin, characterized by well circumscribed, ivory or chalky white macules which are flush to the skin surface. In contrast to this, leukoderma refers to such macules wherein the cause of such a change is known. The hair over the lesion may be either normal or white (poliosis).[16-23]
EPIDEMIOLOGY

Vitiligo occurs worldwide with an overall prevalence of 1%. However, its incidence ranges from 0.1 to > 8.8% across the country and in different countries of the globe. The highest incidence of the condition has been reported in India from the Indian subcontinent, followed by Mexico and Japan [Table 2]. The difference in its incidence may be due to a higher reporting of vitiligo in a population, where an apparent color contrast and stigma attached to the condition may force them to seek early consultation. Behl et al. [11,17] had organized camps in rural areas and industrial pockets in India to evaluate the status of vitiligo. Its incidence was found to be higher in villagers living near dyeing, printing, and carpet industries. A higher incidence of vitiligo in such areas may be due to inclusion of cases with chemically induced depigmentation by industrial phenols and quinones, which might have a completely different pathomechanism. Its incidence, however, was relatively low amongst those residing adjoining copper-mines [Table 3].

Adults and children of both sexes are equally affected although the greater number of reports among females is probably due to the greater social consequences to women and girls affected by this condition. [11,24,46-53] However, majority of the vitiligo cases reported begin during the period of active

<p>| Table 2: Vitiligo: Global incidence patterns |</p>
<table>
<thead>
<tr>
<th>Authors</th>
<th>Year</th>
<th>City / country</th>
<th>Incidence in percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>El Mofty[19]</td>
<td>1968</td>
<td>Egypt / Africa</td>
<td>1</td>
</tr>
<tr>
<td>Levaj[21]</td>
<td>1958</td>
<td>Vellore / India</td>
<td>4</td>
</tr>
<tr>
<td>Punshi and Thakre[22]</td>
<td>1969</td>
<td>Amravati / India</td>
<td>8</td>
</tr>
<tr>
<td>Behl and Bhatia[17]</td>
<td>1972</td>
<td>Delhi / India</td>
<td>8.8</td>
</tr>
<tr>
<td>Sehgal[23]</td>
<td>1974</td>
<td>Goa / India</td>
<td>2.9</td>
</tr>
<tr>
<td>Koranne and Sachdeva[34]</td>
<td>1988</td>
<td>Delhi / India</td>
<td>1.25</td>
</tr>
<tr>
<td>Howitz[35]</td>
<td>1977</td>
<td>Denmark / Europe</td>
<td>0.38</td>
</tr>
<tr>
<td>Grunnet[36]</td>
<td>1970</td>
<td>Denmark / Europe</td>
<td>1.44</td>
</tr>
<tr>
<td>Dawber[37]</td>
<td>1968</td>
<td>England / Europe</td>
<td>0.15</td>
</tr>
<tr>
<td>Desmons[38]</td>
<td>1974</td>
<td>France / Europe</td>
<td>0.15</td>
</tr>
<tr>
<td>Fomara[40]</td>
<td>1941</td>
<td>Italy / Europe</td>
<td>0.3</td>
</tr>
<tr>
<td>Robert[41]</td>
<td>1941</td>
<td>Switzerland / Europe</td>
<td>0.39</td>
</tr>
<tr>
<td>Canizares[42]</td>
<td>1960</td>
<td>Mexico / United States</td>
<td>4</td>
</tr>
<tr>
<td>Ruiz Maldonado[42]</td>
<td>1977</td>
<td>Mexico / United States</td>
<td>2.6</td>
</tr>
<tr>
<td>Fitzpatrick[43]</td>
<td>1974</td>
<td>Massachusetts</td>
<td>8</td>
</tr>
<tr>
<td>Arakawa[44]</td>
<td>1941</td>
<td>Japan / Other</td>
<td>1.64</td>
</tr>
<tr>
<td>Ito[45]</td>
<td>1952</td>
<td>Sendai / Other</td>
<td>1.3</td>
</tr>
<tr>
<td>Kooh Qoon Teik[46]</td>
<td>1962</td>
<td>Malaysia / Other</td>
<td>0.7</td>
</tr>
</tbody>
</table>

<p>| Table 3: Vitiligo in rural India: Association with industries[11,17] |</p>
<table>
<thead>
<tr>
<th>City</th>
<th>Number in out-patients</th>
<th>Vitiligo number (%)</th>
<th>Industry</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rajkot</td>
<td>452</td>
<td>136 (30)</td>
<td>Dyeing industries</td>
</tr>
<tr>
<td>Dadna</td>
<td>300</td>
<td>20 (7)</td>
<td>Jungle area</td>
</tr>
<tr>
<td>Alwar</td>
<td>300</td>
<td>15 (5)</td>
<td>Township</td>
</tr>
<tr>
<td>Chandelao</td>
<td>529</td>
<td>146 (28)</td>
<td>Copper industry</td>
</tr>
<tr>
<td>Narnaul</td>
<td>400</td>
<td>1 (0.25)</td>
<td>Bio-farming</td>
</tr>
<tr>
<td>Rewari</td>
<td>800</td>
<td>8 (1)</td>
<td>Township</td>
</tr>
<tr>
<td>Khetri</td>
<td>320</td>
<td>1 (0.3)</td>
<td>Copper mines</td>
</tr>
<tr>
<td>Philakwa</td>
<td>300</td>
<td>30 (10)</td>
<td>Printing industry</td>
</tr>
</tbody>
</table>

Sex and age distribution
growth. Almost half the patients present before the age of 20 years and nearly 70-80% before the age of 30 years.[53-58]

**Family history**

The proportion of patients with positive family history vary from one part of the world to another. In India, in particular, it ranges from 6.25-18%. In some studies it is as high as 40%. The mode of transmission of vitiligo is quite complex. It is probably polygenic with a variable penetrance.[53,59-62]

**Triggering / precipitating factor(s)**

It is difficult to precisely define the triggering factors for vitiligo. Nevertheless, it is essential to elicit the details of history of emotional stress, drug intake, infections, trauma / injury (Koebner’s phenomenon)[63] existent prior to the development of vitiligo lesions.[24,53,64] Figure 1 attempts to bring into focus the various probable triggering factors in the natural history /development of vitiligo. It is believed that major oxidative stress occurs in vitiligo skin, which is evidenced by low catalase levels and cellular vacuolization in the epidermis.[65,66] Several factors may contribute to the oxidative stress, thus leading to the accumulation of epidermal hydrogen peroxide. The presence of the hydrogen peroxide can be demonstrated in vivo by using noninvasive Fourier transform Raman spectroscopy.[65-68] A better understanding of these factors may prove to be helpful in the management of vitiligo.

**CLINICAL FEATURES**

Vitiligo is characterized by the appearance of patchy discoloration evident in the form of typical chalky-white or milky macule(s) [Figure 2]. The macules are round and / or oval in shape, often with scalloped margins.[24,53] The size of the macules may vary from a few millimeters to several centimeters with the lesions affecting the skin and / or mucous membranes. By and large, the lesions are asymptomatic although itching / burning may precede or accompany the onset of the lesions in a few patients.[53,69-73] Vitiligo is a slow and progressive disease and may have remissions and exacerbations correlating with triggering events.[53,70-74] Occasionally, the lesions of vitiligo may begin to form around a pigmented nevus[75] (Sutton’s nevus, leukoderma aquitum centrifugum) and then go on to affect distant regions.[52,73]

Although any part of the skin and / or mucous membranes is amenable to develop vitiligo, the disease has a predilection for normal hyperpigmented regions such as the face, groin, axillae, aerolae and genitalia. Furthermore, lesions may develop in other areas like the ankles, elbows, knees, which are subjected to repeated trauma / friction, an outcome of Koebner’s phenomenon.[63] In the event of extensive disease, the lesions are symmetrically distributed with an exclusive dermatomal distribution or mucous membrane involvement.[53,79-81] Lip-tip syndrome, another variant of vitiligo is characterized by depigmentation of the terminal phalanges and the lips.

Vitiligo may show morphological variations in the form of:

**Trichrome vitiligo:** It is recognized by the presence of a narrow to broad intermediate color zone between a vitiligo macule and normal pigmented surrounding skin [Figure 3]. Hann et al.[82] had highlighted its clinical and histopathological characteristics and concluded that it is a variant of unstable vitiligo. Cockade-like vitiligo is a variant of trichrome vitiligo.[83]

**Quadri-chrome vitiligo:** It is a well-documented fourth color in vitiligo lesions, usually seen in darker skin phenotypes. A macular perifollicular or marginal hyperpigmentation is its salient feature and denotes a repigmenting disease.[53]

**Penta-chrome vitiligo:** It is an infrequently encountered variant in which there is a sequential display of white, tan, brown, blue-gray hyperpigmentation and the normal skin. Black-skinned individuals are predisposed to have this disorder.[84]

**Blue vitiligo:** It usually corresponds to vitiligo macules occurring at the site of postinflammatory hypermelanos. Ivkar et al.[85] reported the development of extensive blue vitiligo following the simultaneous progression of vitiligo and postinflammatory hyperpigmentation in an acquired immunodeficiency syndrome (AIDS) patient.

**Inflammatory vitiligo:** It is an entity which may reveal an erythematous, raised border in a vitiligo macule with frequent itching and / or burning. These changes could be induced by aggressive therapy.[60,86,87]

**Classification**

Vitiligo is classified into focal, segmental, generalized and universal types, a conventional self-explanatory arrangement.[24,53,59] However, Lerner[59] classified vitiligo into 3 groups namely: a) segmental [Figure 4], localized, partial or focal vitiligo corresponding to a dermatome / adjacent dermatomes b) vitiligo vulgaris generalized, involving the hands, face, axillae and limbs and c) complete, total or universal vitiligo involving the entire or nearly entire body surface. Behl[53] et al. had introduced another classification which took cognizance of clinical stage(s) of vitiligo purported to assist or support its management [Table 4].
Based on sweat stimulation studies, Koga and Tango divided vitiligo into types A and B. Type A was nondermatomal and was considered to be an autoimmune disease that responded to steroids. On the other hand, type B (dermatomal) had shown sympathetic dysfunctions and responded to nialamide. Jerret and Szabo had classified vitiligo into absolute and partial (subtypes I and II) depending upon complete or partial absence of melanocytes. After studying the pattern of vitiligo in the Indian context, we suggest a topographical classification that is helpful in deciding the treatment and prognosis [Table 5].

ASSOCIATIONS OF VITILIGO

Cutaneous associations

It is important to recapitulate associations of vitiligo as they commonly provide circumstantial evidence to its possible etiopathogenesis. Premature graying of the hair, leukotrichia, halo nevus, lichen planus and alopecia areata are frequently reported associations. Of these, leukotrichia (poliosis) is found in up to 45%, premature graying of the hair (canities) in 37%, followed by halo nevus in 35% and alopecia areata in up to 10% of cases. Occasionally, other skin disorders like dermatitis herpetiformis, giant congenital melanocytic nevus with neurotization, chronic urticaria, nevus depigmentosus, polymorphic light eruption and malignant melanoma have also been recorded in association with vitiligo. Furthermore, psoriasis vulgaris confined to vitiligo patches and occurring...
Interestingly, there has been a steady increase in the incidence of childhood vitiligo\textsuperscript{[126]} during the past 2 decades.

**DIFFERENTIAL DIAGNOSIS**

Numerous dermatoses enter into the differential diagnosis of vitiligo.\textsuperscript{[91]} Pityriasis versicolor, nevus depigmentosus, tuberous sclerosis, idiopathic guttate hypomelanosis, Waardenberg’s syndrome, systemic sclerosis, pityriasis alba, postinflammatory hypopigmentation, leprosy [tuberculoid tuberculoid (TT)\textsuperscript{[126]}/borderline tuberculoid (BT), borderline borderline (BB)], melanoma-associated leukoderma, chemical leukoderma, piebaldism and Vogt-Koyanagi-Harada syndrome\textsuperscript{[90,127-131]} are some of these dermatoses.

**NATURAL COURSE**

The natural course of vitiligo is highly unpredictable. However, after an abrupt onset, the disease may slowly progress for some time followed by a period of stability, which may last for several months to decades. A few of the cases may once again start progressing at a rapid pace after a period of dormancy. Such an occurrence is not uncommon in nonsegmental vitiligo types namely vitiligo vulgaris, acrofacialis and areata. Vitiligo zosteriformis / segmental, however, is the most stable form and may show a better prognosis.\textsuperscript{[86-90]} In addition, several other factors may assist in evaluating its prognosis a) the younger the patient, the shorter the duration, the better is the prognosis, b) the lesions located on the fleshy regions of the body may show better chance of recovery in contrast to that on bony / friction points and c) the presence of leukotrichia or lesions on mucous membranes or mucocutaneous junctions may account for a poor prognosis.\textsuperscript{[86]}

**REFERENCES**


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**Table 5: Vitiligo: Suggested classification\textsuperscript{[16,32,90]}**

<table>
<thead>
<tr>
<th>Non-segmental</th>
<th>Segmental</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Vitiligo areata [Figure 5] (localized, partial or focal)\textsuperscript{[99]}</td>
<td>Macules distributed along a dermatome or a near dermatome or lines of body cleavage</td>
</tr>
<tr>
<td>2. Vitiligo acrofacialis</td>
<td>Macules affecting the face and tips of the hands and feet</td>
</tr>
<tr>
<td>3. Vitiligo vulgaris (generalized, universal)\textsuperscript{[99]}</td>
<td>Generalize macules involving extensive body areas</td>
</tr>
<tr>
<td>4. Vitiligo mucosal</td>
<td>An exclusive involvement of mucous membranes</td>
</tr>
</tbody>
</table>

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contemporaneously in the same patient has recently been described\textsuperscript{[103]} Other interesting autoimmune associations include morphea and Hashimoto’s thyroiditis.\textsuperscript{[104]} While presenting strong direct and indirect evidence of the autoimmune etiology of alopecia areata, Hordinsky and Ericson,\textsuperscript{[103]} stressed its association with vitiligo in many patients.

**Ocular associations**

Vogt-Koyanagi-Harada syndrome\textsuperscript{[106-111]} refers to the full constellation of vitiligo, poliosis and alopecia with panuveitis and auditory and neurological manifestations. However, iris and retinal pigmentary abnormalities may be present as isolated findings in a few vitiligo patients. Although visual acuity is unaffected in such patients, choroidal abnormalities may be detected in up to 30% and iritis in 5% of vitiligo patients.\textsuperscript{[90]} Infrequently, choroidal halo nevus may be associated.\textsuperscript{[112-114]}

**Systemic associations**

Systemic disorders like hyp / hyperthyroidism, diabetes mellitus, Addisons’ disease, pernicious anemia, lymphoma, leukemia and human immunodeficiency virus (HIV) infection, autoimmune polyendocrinopathy candidiasis-ectodermal dystrophy (APECED) are a few of the diseases associated with vitiligo.\textsuperscript{[86,90,107-109,115-117]} Egli and Walter\textsuperscript{[118]} recently highlighted the association of vitiligo with pernicious anemia while Federman et al.\textsuperscript{[119]} recorded the occurrence of ulcerative colitis in Vogt Koyanagi-Harada syndrome. Other significant associations include Sjogren syndrome,\textsuperscript{[120]} giant cell myocarditis,\textsuperscript{[121]} plexopathy\textsuperscript{[122]} and amelanotic melanoma.\textsuperscript{[123]} Autoimmunity in children and adolescents with vitiligo was studied by Kurtev and Dourmishev to discover its possible role in the etiopathogenesis of vitiligo.\textsuperscript{[124]} Autoimmunity and immune responses are of paramount significance in vitiligo, a detailed discussion of which can be found elsewhere.\textsuperscript{[125]}

**Childhood (juvenile) vitiligo**

Morphological characteristics in childhood (juvenile) vitiligo are more or less identical to those of adult onset vitiligo.
44. Arakawa A. Quoted by Robert P. Über die Vitiligo, Dermatologica 1941;84:257-319.

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