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Review Article

VITILIGO - An Overview

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A B S T R A C T

Vitiligo is a common, disfiguring autoimmune disease that negatively affects patients' self-esteem and quality of life. Vitiligo is a common acquired disorder of skin depigmentation in varying patterns, varying from small macules with scalloping borders to near-total depigmentation of body. The presence of autoimmune diseases like autoimmune thyroiditis, Grave's disease, Addison's disease, diabetes mellitus, alopecia areata, and pernicious anemia in patients and their first degree relatives favours its autoimmune etiology. Clinically, the usual age of onset is before 20 years of age in nearly half of the cases. It affects both genders equally at any age but most studies report a peak incidence between 18 and 21 years (mean 24 years).

Keywords: Autoimmune disorder, Vitiligo, Depigmentation.

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INTRODUCTION:

Vitiligo is a common, disfiguring autoimmune disease that negatively affects patients' self-esteem and quality of life.[1.]vitiligo is an asymptomatic but cosmetically disfiguring disorder that results in the formation of depigmente dpatcheson skin and/ormucosae.[2] white macules on the skin and can cause significant psychological stress and stigmatization.[3.] Which is phenotypically characterized by white macules on the skin caused as a result of the systematic destruction of functional melanocytes[4] depigmented macules or patches thought to occur secondary to melanocyte dysfunction and loss.[5]

History of vitiligo:

The earliest known reference to Kilăsa was in 2200 B.C. in the period of Aushooryan. In 1550 B.C. information regarding Vitiligo was noted in the Ebers Papyrus.[6.] Vitiligo has been mentioned in the tomes of every major religion, with its first description dating back more than 3000 years, to the earliest Vedic and Egyptian texts. Despite this ancient recognition, confusion with disorders such as leprosy has been a problem throughout the ages. This has lead to the stigmatization of vitiligo sufferers. This is a social problem that is still widespread in some, but not all, parts of the world. The ancients also practiced phototherapy for vitiligo. This practice only became common in the Western world with development of psoralen plus ultraviolet and later ultraviolet B photo therapy in the latter half of the 20thcentury. In this article, the history of vitiligo up until the end of the 20th century is outlined, covering medical, scientific, and socialaspects[7.] The mean age of onset is before 20 years of age in case of childhood vitiligo but varies between 18 and 32 years inadults[.11]

Epidemiology:

Vitiligo is a common acquired disorder of skin depigmentation in varying patterns, varying from small macules with scalloping borders to near-total depigmentation of body. The disorder affects nearly 1%–2% of the world population irrespective of race and

ethnicity with highest incidence recorded in Indian subcontinent followed by Mexico and Japan.[8.] The prevalence of vitiligo in India has been invariably reported between 0.25% and 4% of dermatology outpatients across studies from India and up to 8.8% in Gujarat and Rajasthan.[9] Vitiligo affects both genders almost with equal frequency in most reports or with a predilection for women being affected two times more of ten than men as an exception[10.]

The presence of Koebner's phenomenon, a frequent occurrence in 20%–60% vitiligo patients and in our 27.5% patients also corroborates this observation.[12.]Similarly, scalp, face, and/or neck in 26.3% patients in this study too have been frequent site of onset of vitiligo in many reports and attributed to sunlight/UV light-induced Koebnerization.[11, 13, 20.]

The vitiligo vulgaris in our 59.5% followed by focal vitiligo in 18.7% patients, facial involvement in nearly 8%, and lip-tip variety in 0.4% patients, respectively, in that order conforms to their reported frequencies.[14]

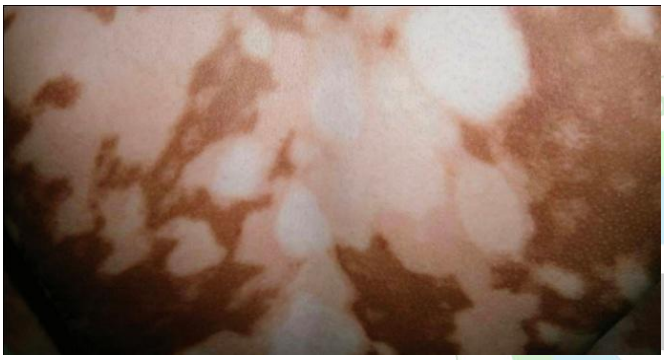

Figure 1: Representing the appearance of skin of patient with vitiligo [69.]

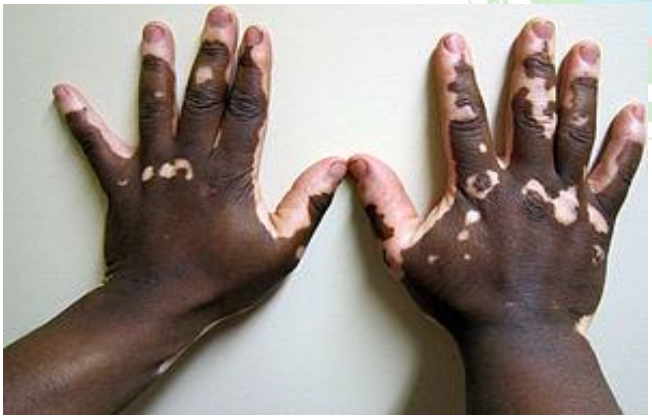

Figure 2: Representing the appearance of hands of patient with vitiligo [22.]

Statistics:

The medical records of all patients with vitiligo attending out patient clinic during Jan 2013 to Dec 2017 were analyzed retrospectively for this descriptive observational study. The study was approved by the Institutional Protocol Review Board and Institutional Ethics Committee. The diagnosis of vitiligo was essentially clinical, confirmed by at least three senior dermatologists. Clinically ambiguous cases and lesions not accentuating under Woods'light was excluded. They were also evaluated for presence of other cutaneous and systemic disorders. The extent of body surface area involvement was measured by Wallace rule of nine and various clinical patterns were classified according to Vitiligo Global Issues Consensus Conference 2011–12report.[14]

The study comprised 945 patients with vitiligo accounting for 0.43% of 2, 17, 518 patients attending dermatology outpatient clinic during the study period. Their clinico-epidemiological profile, frequency of vitiligo patterns, and associated disorders are shown in one study[15]

Etiology:

The exact etiology of vitiligo is poorly understood and is often considered as a multifactorial disease with a complex pathogenesis encompassing several postulations implicating autoimmune, cytotoxic, biochemical, oxidant– antioxidant, viral, and neural mechanisms for destruction of the melanocyte function in genetically predisposed. The presence of autoimmune diseases like autoimmune thyroiditis, Grave's disease, Addison's disease, diabetes mellitus, alopecia areata, and pernicious anemia in patients and their first degree relatives favors its autoimmune etiology.[16]

A proportion of up to 30% patients with positive family history vary across regions and ranges from 6% to 18% in general and was as high as 40% in an Indian study.[4,5] .Since its occurrence does not conform to a set pattern of inheritance in studies of whole families and both twins, it is perhaps polygenic or may be determined by an autosomal dominant gene of variable penetrance.[15]

Factors such as poor nutrition, emotional stress, autoimmunity, trauma, drugs, infections, sepsis, and exposure to the sun, chemicals, and toxins are often considered to trigger it.[12.] Clinically, the usual age of onset is before 20 years of age in nearly half of the cases[7] It affects both genders equally at any age but most studies report a peak incidence between 18 and 21 years (mean 24 years).[13,17.] Few studies reporting women being affected almost two times more often. than men is attributed to their health seeking behavior for cosmetic concerns as vitiligo can be comparatively more stigmatizing and psychosocially devastating for them [18,19.]however, in children, vitiligo shows a female preponderance, a higher proportion of segmental presentation than acrofacial and mucosal vitiligo, and association with other autoimmune or endocrine disorders being uncommon.[20,21.]

SIGN AND SYMPTOMS

*There is a loss of skin color and they appear in a patchy form mostly on the areas exposed to the sun.

*This may appear in various parts of the body like hands, feet, arms, scalp, genitalia, face, lips etc.

*Premature graying or whitening of the hairs is also one of the major indications.

*Change in color of the eye or reduction in the vision is also one of the major indication[22]

Pathogenesis:

The ëxact pathophysiology of vitiligo is not fully understood. There are a few major hypotheses for the pathogenesis of vitiligo: (i) Autoimmune pathogenesisis a long-standing and popular hypothesis; (ii)the neural hypothesis suggests that nerve endings release neurochemical substances that can decrease melanin production or damage melanocytes [23] (iii) the biochemical hypothesis implicates the accumulation of toxic intermediate metabolites of melanin synthesis [24] and defective free radical defense [25,] and the build-up of excessive quantities of hydrogen peroxide (H2O2) as a cause for destruction of melanocytes [26.] Other hypotheses include genetic factors, defects in the structure and function of melanocytes, and deficiency in melanocyte growth factors are playing a role in the depigmentation process.

Genetics:

Familial clustering is seen in vitiligo. Various studies have found that the frequency of vitiligo among first-degree relatives varies from 0.14% to as high as 20%. Such figures suggest a definite genetic component. Nevertheless, only 23% concordance has been observed amongst monozygotic twins, which suggests that a significant non-genetic component exists in the pathogenesis of vitiligo. As vitiligo is a polygenic disease, several candidate genes including major histocompatibility complex (MHC), angiotensin-converting enzyme (ACE), catalase (CAT), cytotoxic T lymphocyte antigen-4 (CTLA-4), catechol-O-methyltransferase (COMT), estrogen receptor (ESR), mannan-binding lectin (MBL2), protein tyrosine phosphatase, non-receptor type 22 (PTPN22), human leukocyte antigen (HLA), NACHT leucine-rich repeat protein 1 (NALP1), X-box binding protein 1 (XBP1), forkhead box P1 (FOXP1) and interleukin-2 receptor A (IL-2RA), that are involved in the regulation of immunity have been tested for genetic association with generalized vitiligo.In patients with various vitiligo-associated autoimmune/auto-inflammatory syndromes, HLA haplotypes, especially HLA-A2, −DR4, −DR7 and −DQB1*0303, have been frequently found to play an important role At the same time, in patients with vitiligo alone, PTPN22, NALP1 and XBP1 have been found to play a causal role.

Genome-wide linkage analysis has revealed autoimmune susceptibility (AIS) loci associated with vitiligo. AIS1 was discovered to be located on chromosome 1p31.3–p32.2,AIS2 on chromosome 7 and AIS3 on chromosome 8.AIS1 and AIS2 linkages were found to occur in families with vitiligo along with other autoimmune diseases, while AIS3 was found in the non-autoimmune family subgroup. Another gene, that is, systemic lupus erythematosus vitiligo-related gene (SLEV1) located on chromosome 17, was found to be associated with generalized vitiligo present in association with other concomitant autoimmune diseases.

In a recent study, gene expression profiling was performed in patients with SV and NSV to analyze the changes in gene expression in patients with vitiligo and compare the two groups with each other as well as healthy individuals (HI). High-throughput whole genome expression microarrays were used to assay the gene expression profiles among HI, SV and NSV. In this study, they found that in patients with SV with HI as a control, the differently expressed genes included the ones involved in the adaptive immune response, cytokine–cytokine receptor interaction, chemokine signalling, focal adhesion and sphingolipid metabolism. On the other hand, the differently expressed genes in patients with NSV mainly controlled the innate immune system, autophagy, apoptosis, melanocyte biology, ubiquitin-mediated proteolysis and tyrosine metabolism. Thus, they concluded that different genetic patho-mechanisms were involved in the two distinct subtypes of vitiligo. In another study from China, the C allele of rs35652124 located on the promoter region of nuclear factor E2-related factor 2 (Nrf2) gene was found to have a protective effect against vitiligo. Lately, the role of microRNAs (miRNAs) and toll-like receptors (TLRs) in the pathogenesis of vitiligo has been explored. In a study by Šahmatova et al., miR-99b, miR-125b, miR-155 and miR-199a-3p levels were found to be increased while that of miR-145 was found to be decreased in the skin of patients with vitiligo. MiRNAs (miR-155) when over-expressed lead to the inhibition of melanogenesis-associated genes and altered interferon-regulated genes in the melanocytes and keratinocytes. Traks et al. recently established the role of TLRs and vilitgo in their study, wherein they found that single nucleotide polymorpisms (SNPs) in TLR7 were associated with vitiligo making them a future target for targeted therapies.Recently, Shen et al. also reviewed the various key loci that have been implicated in the pathogenesis of vitiligo, and interested readers can refer them.[24] Thereupon, the data available so far suggest that vitiligo has a polygenic inheritance with no single gene dictating its pathogenesis.[27]

Cellular Immunity

As far as cellular immunity is concerned, the main culprits are the CD8+ cytotoxic T-cells. Perilesional skin biopsies have shown epidermotropic cutaneous lymphocyte antigen positive lymphocytes with an increased CD8+/CD4+ ratio, substantiating the role of cytotoxic T-cells in the pathogenesis of vitiligo.These T-cells have been shown to bring about degenerative changes in melanocytes and vacuolization of basal cells in the normal-appearing perilesional skin in patients with actively spreading lesions.An increased expression of CD25 and MHC II (specifically HLA-DR) and ability to secrete interferon gamma (IFN γ) has been noted in these T- cells which lead to increased expression of intercellular adhesion molecule-1 and, consequently, increased T-cell migration to the skin leading to a viciouscycle.

Also, high frequencies of Melan-A-specific CD8+ T-cells have been found in patients with vitiligo, and their number may correlate with disease extent. Another subset of T-cells, called the follicular T helper (Tfh) cells, has been described lately in the pathogenesis of vitiligo. The Tfh cells secrete interleukin (IL) 21 IL-21 which brings about B-cell activation, thereby, playing a pivotal role in autoimmune diseases such as vitiligo. They are also key players in cytotoxic responses as they promote

an increase in CD8+ T-cells and prolong their cytotoxic responses.

Interferon γ (IFN γ) has been recently identified as a part of the 'signature cytokine profile' implicated in the pathogenesis of vitiligo. In an engineered mouse model of vitiligo, Harris and co- workers found IFNs to play a central role in the spread of vitiligo lesions by bringing about an increased expression of CXCL10, which subsequently regulates the invasion of epidermal and follicular tissues by CD8+ T-cells. Similar results were seen in an avian model, in which an increased expression of IFN γ correlated well with the progression of vitiligo.

IL-17 and T helper type 17 (Th17) cells, which elaborate this cytokine, have been increasingly recognized to play an important role in autoimmunity. Singh et al. recently reviewed their role in vitiligo and found increased levels of IL-17 in the blood as well as the tissue samples of patients with vitiligo. These findings were further sub stantiated by Zhou et al. and Bharadwaj et al., who found that the levels of Th17 cells correlated well with disease activity in generalized vitiligo. The laterals of ound significant increase in the expression of IL-1βandtransforming growth factor-beta (TGF-β) in patients with active NSV.

In a recent study, serum levels of IL-33 were found to be significantly increased in patients with vitiligo and showed positive correlation with disease activity. This study suggested a possible etiologic role of IL-33 in the pathogenesis of vitiligo and concluded it to be a target for future therapies.

In recent times, various studies have highlighted the pivotal role of regulatory T-cells (Tregs) in the pathogenesis of vitiligo. Tregs are known to fight against autoimmunity and their levels have been reported to be lower in patients with vitiligo, especially, in the lesional and perilesional skin. Not only are they decreased in number but they also have impaired functioning. Both TGF-β and IL 10, which are physiological inducers of Tregs, have been found to be decreased in active vitiligo iuulesions.

Humoral Immunity:

Various subsets of antibodies are seen in patients with vitiligo and are categorized as those against cell surface pigment cell antigens, intracellular pigment cell antigens and non-pigment cell antigens. Certain antigens namely VIT 40/75/90, named after their respective weights, have been identified in around 83% patients with vitiligo. Although VIT 90 is found exclusively on pigment cells, VIT 40 and VIT 75 are considered common to both pigment and non-pigment cells. Non-specific antibodies against these antigens have been found in patients with vitiligo. As melanocytes are much more sensitive to immune-mediated injury, it is probable that minimal injury from non-specific antibodies may induce lethal harm to melanocytes, but not to the surrounding cells.(104) Antibodies against tyrosinase and tyrosinase-related proteins 1 and 2 (TRP-1 and TRP-2), SOX9 and SOX 10 (transcription factors involved in the differentiation of cells derived from the neural crest) have also been detected in patients with autoimmune polyendocrine syndrome type 1 (APS1) and in patients with vitiligo without any concomitant disease.

In a recent study, 15 out of 19 patients with unstable vitiligo were found to be positive for antibodies against melanocytes. Anti-melanocyte antibodies have been found to localize in the cytoplasm of melanocytes. In another study, antibodies against membrane and cytoplasmic antigens were discovered in patients with vitiligo and, using protein mass spectrometry, these membrane antigens were identified to be Lamin A/C and Vimentin X. Thus, the role of anti-melanocite antibodies in the pathogenesis of vitiligo cannot be refuted.[27]

Oxydativstress

The oxidative stress theory of vitiligo suggests that the main culprit in the pathogenesis of vitiligo is the intra-epidermal accumulation of reactive oxygen species (ROS), the most notorious of which is H_2O_2 whose concentration may reach upto one milimole. At this concentration, H_2O_2 leads to changes in the mitochondria and, consequently, apoptosis/death of the melanocytes.

Alterations in the markers of redox status are commonly seen in patients with vitiligo. Important markers of interest are malondialdehyde (MDA), selenium, vitamins, glutathione peroxidase (GPx), superoxide dismutase (SOD) and CAT.MDA is a product of lipid peroxidation and an indicator of oxidative stress' Selenium is required for GPx activity and is a major antioxidant present in the erythrocytes. SOD scavenges superoxide radicals and reduces their toxicity (converts O_2^- to O_2 and H_2O_2), and CAT converts H_2O_2 to O_2 and H_2O. Significantly higher levels of SOD, decreased erythrocyte GPx activity, low levels of enzyme CAT and vitamins C and E have been detected both in the epidermis and in the serum of patients with vitiligo Ines et al. found that SOD activity was increased in both stable and active disease, while MDA and selenium levels were increased most notably in active disease only. The erythrocyte CAT activity and serum vitamin A and E levels were not significantly different from controls. The researchers insisted that enhanced SOD activity could result in the accumulation of H_2O_2. Additionally, CAT and GPx are downstream enzymes that detoxify H_2O_2, and GPx levels were found to be lower in patients with vitiligo, thereby, compounding H_2O_2 accumulation. In a later study, it was found that SOD, GPx and MDA levels were increased in active and stable disease jointly, with higher increases consistently present in the active group. On the contrary, CAT activity was notably more decreased in the active group than in stable disease. The authors suggested that increase in SOD activity ultimately resulted in H_2O_2 accumulation (as it catalyses a reversible reaction) that is not broken down by CAT, because its levels are lower than normal.

SNPs interfering with the CAT enzyme's subunit assembly and function have been found more frequently in patients with vitiligo. In addition, H_2O_2 accumulation brings about degradation of the active site of CAT enzyme, thereby making it unsuitable to function. Furthermore, deranged melanin synthesis pathways involving 6-biopterin lead to

increased synthesis of ROS and subsequent oxidative injury to melanocytes.

A new theory, called the haptenation theory, has been proposed to establish the pathogenic role of oxidative stress in vitiligo.According to this hypothesis, high levels of H_2O_2 lead to increased levels of tyrosinase enzyme and its activity which, because of a genetic polymorphism specific to 'vitiligo' melanocytes, is capable of binding to a variety of substrates such as noradrenalin (during severe mental stress and bereavement), tri-iodothyronine and estrogen, thereby, generating orthoquinone metabolites. These metabolites act as putative haptogenic substrates for tyrosinase and convert the tyrosinase enzyme into a neoantigen, which eventually acts as an autoantigen for the immune system. Thus, an autoimmune reaction is triggered which brings about depigmentation by selective destruction of melanocytes containing the autoantigen in the form of altered tyrosinase enzyme.[27]

Melanocytorrhagy:

Theory of melanocytorrhagy proposes that NSV is a primary melanocytorrhagic disorder with altered melanocyte responses to friction which induces their detachment, apoptosis and subsequent transepidermal loss. This theory adequately explains the Koebner's phenomenon because it proposes that weakly anchored melanocytes upon facing minor friction and/or other stress undergo separation from the basement membrane, migrate upward across the epidermis and are eventually lost to the environment resulting in vitiligo at the sites of trauma.

Kumar et al. found that the melanocytes were poorly attached to Type IV collagen in patients with unstable vitiligo, whereas the attachment was fairly firm in patients with a stable disease.More importantly, they demonstrated that in patients with unstable vitiligo, the dendrites of perilesional melanocytes were small, clubbed and retracted which were unable to adhere melanocytes to the basement membrane and the surrounding keratinocytes, thereby, rendering them more prone to transepidermal loss.

Tenascin, an extracellular matrix molecule that inhibits the adhesion of melanocytes to fibronectin, has been found to be elevated in vitiliginous skin contributing to the loss of melanocytes or ineffective repopulation. This results in focal gaps and impaired formation of basement membrane resulting in weakening of the basal attachment of melanocytes and subsequent chronic melanocyte loss known as melanocytorrhagy It has been proposed that during their transepidermal migration, damaged melanocytes could induce an immune response, thereby, perpetuating vitiligo.

In a recent study by Kumar et al., alterations in the nuclear receptor protein 'liver X receptor alpha (LXR α)' was found to play a crucial role in bringing about melanocytorrhagy in patients with NSV. They reported an increased expression of LXR-α, a promoter of apoptosis, in the perilesional skin of patients with NSV. In the same study, treatment with LXR-α agonist, 22(R)-hydroxycholesterol, was found to significantly decrease melanocyte adhesion and proliferation. Thus, they concluded that a higher expression of LXR-α in the melanocytes of the perilesional skin significantly decreased the adhesion and proliferation and increased the apoptosis of melanocytes.[27.]

Vitamin D deficiency

1,25-dihydroxyvitamin D3 or vitamin D is a fat-soluble vitamin, which is obtained by humans through diet and is synthesized in the skin from 7-dehydrocholesterol under the influence of UV light. It regulates calcium and bone metabolism, controls cell proliferation and differentiation and exerts immunoregulatory activities.

Vitamin D has a nuclear receptor called vitamin D receptor (VDR).VDRs are present in the cells involved in calcium and bone metabolism, and also in the keratinocytes, melanocytes, fibroblasts and immune system cells of the skin.Vitamin D exerts a significant effect on the melanocytes and keratinocytes via various mechanisms. Invitro studies have shown that vitamin D3 increases melanogenesis and tyrosinase content of cultured human melanocytes and protects the melanocytes from UVB-induced apoptosis, thus, contributing to repigmentation in vitiligo macules..Evidence supporting the role of vitamin D in inducing repigmentation in vitiligo skin comes from various studies in which vitamin D analogues, including calcipotriol and tacalcitol, have been shown to enhance repigmentation in patients with vitiligo.In addition, vitamin D has been shown to exert immunomodulatory effects by suppressing the levels of proinflammatory cytokines such as IL-6,IL-8,tumour necrosis factor (TNF)-α and TNF-γ.

In a recent investigation by Ustun et al., insufficient (<30 ng/ml) or very low (<15 ng/ml) levels of vitamin D were observed in majority of patients, although the difference was not significant when 41 control patients were compared to 25 patients with vitiligo.. Another study investigated 40 patients with vitiligo and 40 age- and gender-matched controls wherein significantly lower serum vitamin D levels were seen in the patients in relation to the controls. In a recent systematic review and meta-analyses by Upala et al., it was concluded that a significantly lower concentration of serum 25-hydroxyvitamin D was seen in patients with vitiligo compared with healthycontrols.

The following reasons have been theorized behind decreased vitamin D levels in vitiligo patients:

(i) consumption of vitamin D in the autoimmune process and (ii) decreased sun exposure by patients in an attempt to prevent sunburn. The former was supported by a study by Saleh et al., who found that patients with vitiligo and autoimmune diseases have lower serum (OH)D levels than patients with vitiligo without autoimmune diseases, though, the difference was not statistically significant.

On the contrary, recent studies by Karagün et al.,Karagüzel et al. and Khurrum et al. could not find any statistically significant difference in vitamin D levels between patients and healthy controls. Nonetheless, Karagüzel et al. concluded that after six months of treatment, lesion size decreased in patients who received combination treatment with topical tacrolimus 0.1% and vitamin D daily ($P < 0.001$); while the lesion size

increased in patients who received only topical therapy (P < 0.01), thereby, substantiating the role of vitamin D supplementation in patients with vitiligo.[27]

Risk factors:

You may be at increased risk of developing non-segmental vitiligo if: other members of your family have it there's a family history of other autoimmune conditions – for example, if one of your parents has pernicious anaemia (an autoimmune condition that affects the stomach) having another autoimmune condition having melanoma (a type of skin cancer) or cutaneous T-cell lymphoma(cancer of the lymphatic system) having particular changes in your genes that are known to be linked to non-segmental vitiligo.

Complications of vitiligo:

Vitiligo can sometimes cause other problems.

Because of a lack of melanin, your skin will be more vulnerable to the effects of the sun. Make sure you use a strong sunscreen to avoid sunburn.

Vitiligo may also be associated with problems with your eyes, such as inflammation of the iris (iritis), and a partial loss of hearing (hypoacusis).

Problems with confidence and self-esteem are common in people with vitiligo, particularly if it affects areas of skin that are frequently exposed.

DIAGNOSIS:

It can be diagnosed by physical examination, a questionnaire test and several other tests which include

Tissue culture test: A sample of tissue is taken from the skin is taken and is diagnosed for the changes in the cells and tissues.

Blood test: by doing this blood test the sample of blood is extracted from the patient and then it is tested to see the level of melanin in the blood.

Eye test: in about 5% of people affected with vitiligo it may also affect the eyes in various ways like reducing the vision. Redness of eye and inflammation is eye etc.[22]

MANAGEMENT:

Management of vitiligo includes both pharmacological and non-pharmacological procedures. Non-pharmacological treatment: There are many home remedies which can reduce this discoloration of skin and also has been very effective. Some of them are mentioned below.

Homemade preparation of formulation:

Tamarind and Psoralea seeds: The most effective herb (psoralen) is used for the treatment of vitiligo. Turmeric has anti-inflammatory and antiseptic properties In it also plays an important role in Ayurvedic medicine because of its health benefits. When both of them are combined with turmeric as an effective cure for vitiligo. The psoralen should be handled very carefully and with complete information about it, as otherwise, it could be harmful.

Direction for Use: Soak seeds of Psoralea and turmeric in water for about four days. Dry the soaked seeds and grind to a paste. The paste should be applied on the white Spots for at least one month. Within a month, you will be noticing changes in the skin, for best results, it is recommended to continue treatment beyond one month.

Mustard oil and turmeric: Turmeric hasanti-inflammatory and antiseptic it has higher health benefits. It increases the body's natural immunity when used on wounds that can prevent bacterial infection. Home remedies which are made from mustard oil and turmeric is very beneficial for patients with vitiligo. The oil is antibacterial and can help detoxify the body.

Direction for Use: Mix5 table spoons of turmeric powder with 250ml of mustard oil. Ensure that turmeric is mixed thoroughly with the oil. Apply this mixture twice a day On the white patches on the skin. Treatment ought to be strictly followed for a year to get good results. The spots will disappear and Your skin will be healthier. The remedy is natural and safe.

Lemon juice and Basil leaves: Basil leaves are one of the common useful kitchen ingredients. It has an anti-aging and antiviral effect and has proved effective in curing Vitiligo and stress. Lemon juice has much positive effect as it also acts as an anti-inflammatory effect and a good source of vitamin C. When lemon juice and basil Leaves extracts are combined They stimulate the stimulation of melanin the body.

Direction to Use: In a bowl, mix the lemon juice and basil leaf extract. Apply the mixture on the white spots and leave it for a while. Use this treatment 3or 4times daily. Within 5-6months you can see visible results. The treatment has no side effects and is absolutely safe for patients with vitiligo.

The water stored in copper utensil: As vitiligo is also caused due to the deficiency of vitamins and some other deficiencies. Water reserves in copper bottles, glasses are very useful.

Directions for use: The water used in copper utensil is kept overnight. The water should be taken every morning and within six months we can notice a difference in the skin. The treatment promotes the production of melanin by melanocytes stimulation in the body. It is a safe home remedy and with no side effects.[22]

Pharmacological therapy

Medical therapies:

The most recent advances on the medical front have been Narrowband Ultraviolet B (NB-UVB) therapy, Targeted Ultraviolet B (UVB), Excimer laser therapies, topical immunomodulator treatment in the form of topical calcineurin inhibitors, topical pseudocatalase, and topical Vitamin D analogues in combination with Ultraviolet (UV) light.

NB-UVB:

NB-UVB, using UV-lamps with a peak emission of around 311nm has now emerged as the treatment of first

choice in generalized vitiligo as well as vitiligo vulgaris (patchy vitiligo).[28, 29, 30.]The efficacy of NB-UVB in vitiligo was first demonstrated by Westerh of and Nieuwboer-Krobotova in 1997[31.]Since then there have been a large number of clinical studies that have demonstrated the therapeutic benefit of NB-UVB in vitiligo patients. The mechanism of action of NB-UVB in vitiligo is through induction of local immunosuppression and stimulation of the proliferation of melanocytes in the skin and the outer root sheath of hair follicles. There is a stimulatory effect on melanogenesis and on the production of Melanocyte Stimulating Hormone (MSH)[28.]Comparison studies have shown a significantly enhanced rate of repigmentation with NB-UVB compared with topical Psoralen and Ultraviolet A (PUVA) therapy.[(32)].Furthermore, the incidence of adverse effects seen commonly with topical PUVA, such as phototoxicity, is significantly reduced with the use of NB-UVB.

NB-UVB has shown a number of advantages over PUVA in vitiligo patients in addition to its excellent efficacy. These advantages include its extremely low side-effect profile particularly on the systemic front, its established safety in children, and safety in pregnant females. NB-UVB also has considerably better patient compliance as there is no need to time the exposure with any drug intake or any need for eye protection beyond treatment exposure time. A recent double-blind randomized study comparing NB-UVB with PUVA demonstrated a much better efficacy with NB- UVB. The study found that repigmentation achieved with NB-UVB was much better with respect to colour matching with uninvolved skin, and this was also more persistent than that achieved with PUVA[33.]

In addition NB-UVB has been used in childhood vitiligo with excellent results.[34.]No additional adverse effects were seen in children with NB-UVB as compared with those in adults. Furthermore, given the long-term safety profile of NB-UVB in comparison with PUVA as far as skin malignanciesare concerned, NB- UVB is now preferred over all other treatment options in the management of generalized vitiligo in both adults and children.[35]

NB-UVB has been used in combination with different topical agents to increase its efficacy and thus shorten the total duration of treatment. Treatment options that have been used with NB-UVB in vitiligo till date include topical tacrolimus,[36,37] pimecrolimus,[38] Vitamin D analogues[39,40] and even topical pseudocatalase.[(41)]While some studies have shown a synergistic effect with these combinations, others have found the efficacy of the combinations to be similar to NB-UVB alone. In one half-body comparison study, topical placental extract was used in combination with NB-UVB but the combination was shown to offer no added benefit than NB-UVB alone.[42].Therefore, the ideal topical agent to be combined with NB-UVB remains unknown.

Laser Therapy:

Excimer laser, which uses Xenon-Chlorine (Xe-Cl) gas and produces a monochromatic laser light of 308nm wavelength, is another innovative treatment option for vitiligo. The laser system has been used with increasing frequency over the last few years for targeted treatment of individual vitiligo lesions.[43] The laser is used either alone or in combination with topical immunomodulator or PUVA-sol therapy.[(44,45)].Treatment with this laser is claimed to give extremely good and early results in both localized and segmental vitiligo. In a pilot study21 on 18 patients with 29 affected areas 57% of lesions showed varying degrees of repigmentation after just six exposures over two weeks. The figure was increased to 87% after 12 treatments over four weeks.[(46)]. Another recent study has reported are pigmentation of >75% in 61% of lesions after.

Topical therapies, particularly topical tacrolimus, have been used in combination with Excimer laser. This combination has been claimed to be more effective than Excimer laser alone.In a randomized right-left comparison study22 with 14 patients, Excimer light monotherapy was compared with a combination of Excimer laser with topical tacrolimus. While 20% of lesions treated with Excimer laser alone achieved >75% repigmentation, the same degree of repigmentation was obtained in 70% lesions with the combination treatment[47.] Topical methoxsalen has also been used in combination with Excimer laser phototherapy and this has been claimed to have worked better than laser therapyalone.[48]

The advantage of Excimer laser therapy over conventional UVB therapy is the targeted mode of treatment with no exposure of the uninvolved skin. Moreover, the onset of repigmentation is earlier with Excimer laser therapy than with UVB therapy.[49]

Targeted UVB therapy

This is another recent innovation in vitiligo management that has arrived over the last few years. The beauty with this therapy is that it delivers high intensity UVB light only to the affected vitiliginous areas, avoiding any exposure to the uninvolved skin. This not only decreases the cumulative UVB dose received by an individual patient, but is also claimed to improve the efficacy of treatment quitesignificantly.[50.]

Targeted UVB therapy, as expected, finds its use more in the treatment of focal and segmental types of vitiligo. In fact, the first study with targeted UVB therapy was done on eight patients with segmental vitiligo. Five of these patients achieved >75% repigmentation of their lesions with this therapy.[51]

Targeted UVB therapy offers certain advantages over Excimer laser phototherapy. The treatment is safer and more efficacious compared with conventional UVB therapy, and almost as efficacious but much less costly than Excimer lasertherapy.[52]

Systemic immunomodulator therapy

Vitiligo is thought to be an immune-mediated disease and thus immune-suppressive and immunomodulator agents have been used on a regular basis in this disease. Among the immunosuppressant, systemic steroids have been the most commonly used. However,

systemic steroid therapy has always been associated with a high incidence of adverse effects especially in children which is the age-group most commonly affected. To overcome this limitation, steroids have been given in pulse or even in mini-pulse form. A prospective study involving[14]patients with progressive or static vitiligo showed cessation of disease ctivityanda repigmentation rate of % after high-dose methyl prednisolone pulse therapy administered on three consecutive days.[53].Systemic steroids have also been administered in a mini-pulse form on two consecutive days every week, known as Oral Minipulse (OMP) therapy. The first study demonstrating the efficacy of OMP with oral betamethasone (0.1mg/kg with a maximum of 5mg) was described in 1991.[54.] In a later study on childhood vitiligo, betamethasone was replaced by oral methylprednisolone and combined with topical fluticasone ointment on the vitiligo lesions. The disease was arrested in >90% of patients, and >65% of children achieved good to excellent (>50%) repigmentation of their vitiligolesions.[55]

Topical Vitamin D analogues:

Vitamin D analogues, particularly Calcipotriol, have been used topically either alone or in combination with topical steroids in the management of vitiligo. The basis for the use of these agents is that Vitamin D3 affects the growth and differentiation of both melanocytes and keratinocytes. This has been further proved by the demonstration of receptors for 1 alpha- dihydroxyvitamin D3 on the melanocytes. These receptors are believed to have a role in stimulating melanogenesis.[55].Vitamin D analogues have given variable results in the treatment of vitiligo in different studies. These agents have also been used in combination with UV-light (including NB-UVB) and topical steroids with variable results.[56, 57, 58]

Topical immunomodulators:

Topical immunomodulators, such as tacrolimus and pimecrolimus, have been the most promising recent additions to topical vitiligo therapy. In fact because of their efficacy and a remarkable safety profile the use of these agents in vitiligo has shown a consistently increasing trend over the last few years. These agents can be safely administered in young children, as they don't cause any atrophy or telangiectasia of the skin even after prolonged use. There is also no risk of hypothalamic-pituitary-adrenal (HPA) axis suppression as seen with the widespread use of potent topical steroids.[60.]The first study that demonstrated the efficacy of tacrolimus in vitiligo was published in 2002.In this study tacrolimus was used in six patients with generalized vitiligo and five of them achieved >50% repigmentation of their lesions by the end of study period.[61.]Since then many additional studies have been published on this subject and have clearly demonstrated the role of topical tacrolimus in vitiligo. The best results with topical immunomodulator therapy have been seen on exposed parts of the body such as the face and neck and, as with any other therapy, the acral parts of the body respond the least.[62].Similar results were obtained with the use of topical pimecrolimus in vitiligopatients.[63]

Pseudocatalase:

Pseudocatalase has been used in combination with Dead Sea climatotherapy or UVB exposure for the treatment of vitiligo. The basis for the use of this agent in vitiligo is the evidence of oxidative stress and high H2O2 levels in the lesional skin. While some earlier studies demonstrated[64] excellent results with this agent in inducing repigmentation in vitiligo, later studies have cast doubts on its efficacy[65.] Pseudocatalase is used topically on the lesional skin,and this is followed by UV B exposure to the whole body or to the lesional skin.The combination is claimed to correct the oxidative stress on melanocytes in vitiligo patients and thus lead to correction of the depigmentation.

Topical 5-Fluorouracil:

Topical 5-fluorouracil is supposed to induce repigmentation of vitiligo lesions by over stimulation of follicular melanocytes which migrate to the epidermis during epithelialization. This form of topical therapy can be combined with spot derm abrasion of the vitiligo lesions to improve the repigmentation response. In a study by Sethi et al, a response rate of 73.3% was observed with a combination of spot derm abrasion and topical 5-fluorouracil after a treatment period of six months[50]

Surgical therapies:

Surgical therapies for vitiligo have further increased the percentage cure of the disease by an appreciable degree, with the consequent increase of their use in the management of unresponsive vitiligo both in India and abroad. These surgical therapies, as a rule, are indicated in those patients who have a stable (non-progressive) disease of at least one year and not responding to medical treatment. In general the most important advantage with these procedures is that the chances of repigmentation of lesions are in the range of 90-100%. Moreover, these interventions are becoming better and easier to perform with every passing day.[50]

Different surgical therapies that have been attempted in the management of vitiligo include autologous suction blister grafting, split-thickness grafting, punch grafting, smash grafting, single follicular unit grafting, cultured epidermal suspensions and autologous melanocyte culture grafting. All these grafting procedures, except the melanocyte culture grafting, are easy to perform and do not require any sophisticated instruments. These grafting techniques have now been divided into two types, tissue grafts and cellular grafts, depending on whether whole epidermal/dermal tissue is transplanted or the individual cellular compartment.[50]

Tissue grafting technique:

Suction blister grafting:

Here, thin epidermal grafts are taken from suction blisters on the donor site, usually on the buttocks or thighs. These suction blisters are produced by applying sufficient negative pressure on the skin at the donor site by using a suction apparatus or syringes with three-way cannulae.

The epidermal grafts are then transplanted on to dermabraded vitiligo lesions. This leads to repigmentation of the recipient areas with an excellent cosmetic matching. The ease of the procedure, the high success rate and the excellent cosmetic results have all made suction blister grafting the procedure of choice in vitiligografting.[50]

Split thickness grafting:

In this grafting technique a thin split thickness graft is taken from a donor site with the help of a dermatome, Humby's knife, Silver's knife or a simple shaving blade. This graft is then transplanted on to dermabraded recipient areas. This technique also gives excellent cosmetic matching after repigmentation and the incidence of repigmentation in this technique is also quite high. In fact, most comparison studies on grafting techniques in vitiligo have shown that maximum repigmentation is achieved with either suction blister grafting or split thickness grafting.[50].The advantage of partial thickness grafting over the suction blister method is that a relatively larger area of vitiligo can be tackled in a single sitting. Both partial thickness skin grafting as well as suction blister grafting can be followed up by NB-UVB to achieve faster and better results.

Miniature punch grafting

Here full-thickness punch grafts of 1.0 to 2.0 mm diameter are taken from a suitable donor site and then transplanted on to similar punch shaped beds on the recipient vitiligo lesions. The recipient area is then treated with either PUVA/PUVA-sol or topical steroids leading to spread of pigment from the transplanted punches to the surrounding skin. With time the whole of the recipient area gets repigmented. The advantages of this procedure are that it is easy to perform and can take care of a relatively larger vitiligo area compared with the above two procedures. Also vitiligo lesions with irregular or geographical shapes can be treated with this procedure. However there are certain limitations. There is the risk of 'cobblestone appearance', 'polka-dot appearance', and hypertrophic changes at the recipient site. All these side effects can be minimized by proper patient selection and by use of smaller sized punches of 1.0 to 1.5 mm diameter. Miniature punch grafting is presently the commonest surgical procedure performed in India on vitiligopatients.[50]

Follicular unit grafting:

In this technique, single-hair follicular units are harvested/prepared from a suitable donor area as in the case of hair transplantation. These follicular units are then cut above the level of the follicular bulb and then transplanted into vitiligo lesions. The idea behind this technique is that the melanocytes in the follicular unit are 'donated' to the vitiliginous skin and serve as a source of pigment at the recipient site. The repigmentation process here simulates the normal process of repigmentation of vitiliginous skin quite closely and thus gives an excellent cosmetic result. This procedure combines the advantages of punch grafting with the excellent cosmetic results of split thickness or blister grafting techniques. The procedure is however tedious and need good surgeons [(50).]

Smash grafting:

In this technique, a partial thickness graft is taken and is 'smashed', or cut into very small pieces, by means of a surgical blade on a suitable surface such as a glass slide. This 'smashed' tissue is then transplanted on to the derm abraded recipient skin and covered with a special powder or corrugated tube dressing so as to keep the smash-graft undisturbed on the recipient area. The advantage of this technique, over a simple partial thickness grafting, is that thicker grafts can be used with a good cosmetic result. The procedure has been indicated for those who are relatively inexperienced and cannot take an ideal, thin and transparent partial thickness graft from the donorarea.[50]

Cellular grafting techniques:

Non-cultured epidermal suspensions:

Here a split-thickness graft is taken from a donor area and then incubated overnight. On the next day the cells are mechanically separated using trypsin-EDTA solution and then centrifuged to prepare a suspension. This cell suspension is then applied to the derm abraded vitiligo lesions, and a collagen dressing is applied to keep it in place. A relatively large area of vitiligo, about ten times the size of the donor graft can be taken care of with this procedure.[66] the recipient area however has to be treated with either NB-UVB or PUVA for two to three months to achieve the desired pigmentation.[50]

Melanocyte culture transplantation:

This is a relatively more advanced grafting procedure where, once again, a split-thickness graft is taken from a donor area and incubated in an appropriate culture medium to grow the melanocytes or the keratinocytes-melanocyte combination in vitro. The cultured cells are then applied onto laser dermabraded, or even mechanically abraded, lesional skin.[67,68.] The procedure is obviously more difficult to perform, as it needs the advanced laboratory facilities for melanocyte culture. However the results with this procedure are excellent and a relatively large area of involved skin can be tackled by a single donorgraft.[50]

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