VITILIGO

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INTRODUCTION

Vitiligo is disease that has affected people of all nationalities and all communities since time immemorial. It is however, necessary to stress that Vitiligo is a completely harmless disease and a patient having Vitiligo can lead almost normal and useful life. Still if a patient wants to get rid of it, a large variety of therapeutic procedures are now available to treat this disease.[1]

AETIOPATHOGENISIS

Aetiopathogenisis of vitiligo is still not completely understood; possibly different mechanisms are involved in different clinical manifestations. The following hypotheses has been proposed from time to time for the aetiopathogenesis of vitiligo.

1. Autoimmune Hypothesis

It is at present most commonly accepted. It proposes that an aberration in the immune system leads to destruction of the melanocytes in vitiligo patients. This defect may result from a primary autoimmune reaction against an antigen of the melanogenic system, or an antigenic substance may be getting released during an injury to the melanocytes and cause autoimmune reaction.[2]

2. Neurogenic Hypothesis

According to the hypothesis a neurochemical mediator released from nerve endings may inhibit melanogenesis and cause destruction of melanocytes.[3]

3. Self Destruction Hypothesis

Catechols and phenols are known to inhibit melanogenesis. Certain tyrosine analogues, intermediate substances and metabolites such as dopa and 4,5 dihydroxyindole produced during melanogenesis are also toxic to the melanocytes. A defect in the melanocytes inherent protective mechanism to eliminate these toxic melanin precursors is believed to lead to an accoumulation of indoles, which can destroy melanocytes.[4]

4. Cytokines Hypothesis

According to this hypothesis normal growth and density of melanocytes is regulated by growth factors derived from skin and other tissue. depigmentation in vitiligo may be due to a reduction in this growth factor level.[5]

5. Catalase Hypothesis

The epidermis of vitiligo patients have been found to have low catalase activity and the production of hydrogen peroxide due to low catalase levels may result in depigmentation.[6]

HISTOPATHOLOGY OF VITILIGO

On H and E staining the vitiligo lesion shows absence of melanocytes and melanin granules in the epidermis-. There may be

lymphocytic infiltrate involving the papillary and reticular dermis, perivascular and the periappendigeal region especially when lesions are inflammatory.[3,4] The stable lesions may show vacuolization of the basal cells and extra cellular granular material. Melanin may be present in the dermal melanophages.

On electron microscopy the melanocytes are less dendritic and appear necrotic. They have few melanosomes, show fatty degeneration and abnormal mitochondria and cytoplasmic filaments, but all these features are not consistently present.

PREDISPOSING FACTORS

1. Genetic predisposing

Vitiligo may occur in more than one member of a family. This explains genetic predisposition. Further more there is frequent occurrence of vitiligo in monozygotic twins.[7]

2. Trigger Factors

Factors, which trigger the onset of dipigmentation, are not clear. However in some patients the role of chemical (Phenols and catechols), pressure (Plastic footwear), trauma (sites of injury with subsequent spread to other areas).

Physiology of pigmentation

Melanin and carotenoid in the epidermis determine the colour of human skin.

There are two types of melanin pigment.

1. Genetically determined
2. Inducible skin colour due to sun exposure and other causes.

Melanogenesis

It is an enzymatic process, which involves the copper containing enzyme tyrosinase, which converts tyrosine into dihydroxy phenylalanine (DOPA).

DOPA is oxidized to dopaquine, which further converts into eumelanin or phaeomelanin.

Eumelanin is a more prominent component than phaemelanin in human skin.

Melanin synthesis takes places in melanosomes present in melanocytes. During the processes of melanization melanosomes develop from stage 1 to stage 6 and gradually move from the central part of melanocytes into the dendritic processes. The tips of these dendrites are phagocytozed by the keratinocytes. In the keratinocytes, the melanosomes are phagocytozed by the lysosomes to form the melanosome complex. As the keratinocytes move towards the outer surface of the epidermis the melanin is gradually degraded and finally thrown out with the loss of stratum corneum.[8]

The melanogenisis is stimulated in culture by:-

1. Beta fibroblast growth factor (beta-FGF).
2. UV radiations
3. Melanocyte stimulating hormone (MSH) ACTH and beta lipotropin.

Melanogenesis is inhibited by:-

1. Cytokines
   i. Interleukin 1- alpha (1L-1 alpha)
   ii. Interleukin 6- alpha (1L- 6 alpha)
2. Tumor necrosis factor.

Social Aspects

Social stigma has always been attached to vitiligo in all classes of society. Treatment by friends at school, job involving handling of food, may have to be changed and most important of all difficulty in getting married of the affected person and even of their children or sibling. As a consequence most patients are anxious to get rid of he disease

and this sometime leads them to make incorrect decisions.

Misconceptions

It is commonly believed that the disease could be acquired from others or could be caused by taking certain foods such as milk or talking fish with milk or some foods such as citrus fruits, pickles etc are also believed to interfere with treatment. Even intake of vitamin C has been prohibited by some physicians. Another misconcept among physician is the use of corticosteroids. Stopping this drug inappropriately could interfere with recovery of patient.

Clinical Aspects

Vitiligo manifests as asymptomatic depigmented or hypopigmented granules. There is no other change like scaling, atrophy, hair loss or sensory impairment. The disease can start at any age and rarely may be present at birth. It involves both sexes equally. In a large majority of patient vitiligo starts as a single lesion but the further spread of the disease varies in different patients. In some it may be slowly progressive in other cases there may be rapid exacerbation. Sometimes the disease may become static there may even be spontaneous repigmentation of the lesion.

The degree of the loss of pigmentation in different lesions varies from faint hypopigmentation to complete depigmentation with varying shades in between. The size of the lesion may vary from 1-2 m to very large area covering almost the whole limb, trunk or entire body. Some patients have lesion confined to only the mucosal areas like lips or genitalia (mucosal vitiligo).

TREATMENT

The approach to the treatment of vitiligo should include the following:

1. Controlling activity of disease.
2. Repigmentiaon of vitiliginous area.
3. Surgical treatment of vitiliginous area.

1. Controlling activity of disease

For this a detail history about the time of onset of disease, its response to treatment taken previously and its latest course is required. It is better to photograph all lesions before starting treatment for further comparison.

1. **Levamisole Pulses:** Levamisole acts as an immunmodulator. It is given in pulses of 150mg orally on two consecutive days per week for at least a year or even more until either all the lesions disappear or there is no further repigmentation of any of the lesions. Results are better if combined with conrticosteroids.[9] The does is 100mg for children between 6-12 years and 50 mg if the patient is less than 6 years of age. The drug may cause variable degree of nausea and loss of taste but these symptoms could be ignored. Rarely patient may develop serious side effects which may include joint pains and fever but mostly no serious toxicity occurs even if the drug is taken for years.
2. **Corticosteroids:** Corticosteriods orally in a dose of 2 mg betamethasone orally on alternatere days provide adequate results. But most of the patients tend to develop side effects. To prevent this, mini pulse therapy has been devised. It consists of 5mg betamethasome orally with morning breakfast on two consecutive days per week. With this schedule 90% of the patients show complete control of disease activity. Few patients who are not completely controlled respond to increasing the dose to 7.5mg betamethasone or the addition of 50mg cyclophosphamide orally per day on all days of week.

3. Augmentation of repigmentation

1. **Topical corticosteroids:** Moderately potent corticosteriods are used with one application a day till repigmentation develops. Exponsure to sunlight is not necessary.

2. **Photochemotherapy:** Long wave length ultraviolet radiation, called psoralens photochemotherapy (PUVA) is used in the treatment of vitiligo. Psoralens owe their therapeutic efficacy to the photosensitizing effect of these compounds. They are at present considered to be the most effective for the treatment of vitiligo. 8,Methoxypsoralen is most widely used psoralens. The recommended dose varies between 0.3-0.8 mg/kg body weight orally. Maximum concentration in the skin is reached in 2-3 hours and this level is maintained for another 2 hour so the best time for exposing the skin to UVA is 24 hours after oral dose. One can use either sunlight (PUVA-SOL) or an artificial source of UVA like UVA lamp. The dose of radiant light from the lamp can be adjusted and started from $2J/cm^2$ and increased till maximum tolerable does is reached, which is usually less than $6J/cm^2$ for Indians. Increase in UVA dose can be stopped once lesions show initial repigmentation. The optimum time for exposure to sunlight is between 12 noon to 2 pm. when its intensity is maximum. The duration of exposure to sunlight on first day should be 10-15 minutes increasing by 2-5 minutes per week to a maximum duration of 30 minutes. Generally, the PUCA/PUVASOL therapy is given 2-3 times per week and continued till the lesions get repigmented. If there is no repigmentation in any of the lesions in spite of proper treatment for 6 months the treatment may be considered to have failed. Contraindication for PUVA/PUVASOL therapy include children below 12 years of age, pregnancy, lactation, photosensitive dermatoses, melanoma or history of melanoma, patients receiving arsenic or ionizing radiation and severe cardiovascular, renal and hepatic disease.[11,12] Care is necessary if the patient is concomitantly receiving photosensitizing drugs.

Acute side effects of psoralens include, pruritis, nausea, vomiting, headache, dizziness and depression. But the major problem with PUVA/PUVASOL is phototoxicity.

Psoralens can also be used topically, especially when the disease is limited,[13,14] and can also be used in children.

Other medicinal modalities apart form psoralen and corticosteroids include.

- Placental extracts.
- Khellin: it also has photosensitizing effect.
- Phenylalanine: a precursor of tyrosine is useful when used in doses of 50mg twice a day. It has also been used successfully with oral minipulse corticosteroids therapy.
- Topical flurouracil: Used as 5% cream.
- Clofaimine: Gives short-lived effect.
- Pseudocatalase: A topical preparation containing pseudocatalase and calcium chloride applied twice a day followed an hour later by total body exposure to UVA twice a week arrests the disease activity and produce pigmentation of vitiliginous areas.

Surgical treatment

Surgical treatment is for certain lesions, which do not repigment inspite of all medical therapeutic modalities. The two basic approaches are:

- To cover the entire lesion with a normal skin graft.
- To implant small graft of normal skin (Melanocytes) and then expect perigraph spread of pigmentation. For the surgical procedure to be under taken the disease should be static for at least 6 months. The size of the lesion should be within a certain limit and keloidal tendency of the patients should be considered.

The surgical methods used are:

PUNCH GRAFTING

This technique consists of transplanting pieces of normal skin obtained from the donor site with the help of skin biopsy punch to the recipient vitiliginous areas after removing the affected skin with a slightly smaller sized biopsy and punched. The distance between the grafts should be such that after the perigraft spread of pigmentation. There is no intervening depigmented area. The spread of pigmentation begins in 4-6 weeks and reaches to maximum in 6 months. It may be augmented with PUVA/ PUVA SOL.

SPLIT THICKNESS SKIN GRAFT

The technique consists of removing a piece of skin comprised of epidermis and superficial portion of dermis and transferring this sheet to the recipient vitiliginous area which has been prepared with dermabrasion. The complications include hyper pigmentation, hypertrophic scarring, graft rejection or peripheral depigmentation.

SUCTION BLISTER GRAFTING

The procedure is time consuming and blister formed are very painful. It can also occasionally lead to haematoma formation.

SURGICAL EXCISION OF THE LESION

If the residual vitiliginous area is very small single surgical excision can be done.

AUTOLOGOUS MELANOCYTE GRAFTING[13,14]

A small piece of normal skin obtained from the patient by skin biopsy can be cultured on artificial media for multiplying the melanocytes. These sheets can then be transferred to the recipient vitiliginous area prepared with dermabrasion.

CAMOUFLAGE

Along with specific treatment for the disease camouflage may have to be used to conceal lesions till they regain pigment, especially if located on exposed parts. It can also be used for the lesions that persist in spite of treatment.

The most commonly used approach for camouflage consists of covering the depigmented area with an opaque cream that has the colour of the patient's normal skin. Such cream consists of a basic masking cream and a taning agent for exact colour match. But the creams get removed easily and have to be applied several times a day.

The second approach consists of staining the skin with chemical substances, which can conceal the depigmented area.

TATTOOING

This is another method of camouflage in which an opaque dye either of black colour or a mixture of red, yellow, black and brown area deposited in the superficial dermis to compensate for the absence of melanin. The dyes have to be inert. It must be ensured that the diseases has become inactive.[15]

DEPIGMENTATION

Depigmentation of the skin can be offered to patients who have about 90% depigmentation of skin. Rest of the 10% area may be depigmented by applying 20% monobenzylether or hydroquinone cream twice a day. The process may take 1-4 months to start and complete depigmentation may be achieved in 4-12 months. The

skin should be protected from sunlight by sun creams because pigmentation can sometimes recur.[16]

RECENT ADVANCES IN THE TREATMENT OF VITILIGO

Topical Application of Novitil

Novitil is a topical product having no side effects. First sign of pigmentation appears within a month of daily use followed by exposure to sunlight. In most people results are achieved after six months of regular use. It is a nontoxic drug having no side effects, cost effective and having no irritant properties. This compound contains: Lipoprotiens, polypeptides, distilledwater, glycerine, aloebarbadenses, carboxy methylcellulose, camphor, menthol, kathoneand oligoelements.

It controls microscopic inflammatory skin process, stimulates melanocytes to produce melanin and enhances the skin melanocytes to respond to light, both artificial and UVA.[17]

CONCLUSION

In short it is concluded that vitiligo is a noncontiguous, curable disease. Though there are multiple hypothesis for the cause of vitiligo. But basically there is some defect or deficiency of melanocytes in epidermis. There is a genetic predisposition. Certain trigger factors e.g. chemical, pressure or trauma may be involved. Clinically it presents as a symptomatic hypopigmented skin, its site, size, and progression varies from person to person.

Its treatment includes.

1. Controlling the activity of disease by Levamisole pulses and corticosteroid therapy.
2. Inducing repigmentiaon by topical steroids and Photochemotherapy.
3. Surgical treatment, which basically approach to cover the lesion with normal skin graft or to implant small grafts of normal skin, which regenerate melanocytes. It is also necessary to evaluate the response to the treatment from time to time so that procedure can be modified whenever necessary.

And needless to say that the earlier the treatment is started the better is the end result.

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