VITILIGO

5.ÅRSOPPGAVE I STADIUM IV

MEDISINSTUDIET VED UNIVERSITETET I TROMSØ

SKREVET AV: SAIMAH AHMAD, KULL 97

VEILEDERS NAVN: E. S. FALK

VÅR 2002, TROMSØ.

VITILIGO

1.0 Resume

The purpose of this report was to put together all the up to date information of vitiligo. I have written on a range of topics from basic and research fields to clinical aspects, especially treatment of vitiligo. The whole report is built on literature, primarily articles published in medical journals the last ten years.

The term vitiligo may have evolved from the Latin word vitium, meaning fault, or vitelius meaning spotted calf. Vitiligo is a specific, common, acquired skin disorder characterised by well-circumscribed milky white macules due to loss of melanocytes in the epidermis. The precise pathogenesis of the disease remains unknown. But there are many hypotheses, which have been proposed to explain the loss of melanocytes. The incidence of this disease varies greatly between populations, but the worldwide incidence is considered to be between 1%-2%, and it is often heritable. The natural course of the disease is usually one of slow progression, but it may stabilize or exacerbate rapidly. Some degree of spontaneous or sun induced repigmentation is not uncommon in vitiligo. The clinical presentation includes segmental, focal, generalised and universal vitiligo. The disease is asymptomatic and does not adversely affect survival. Although vitiligo is in general a benign disorder, the cosmetic disfigurement may lead to considerable emotional distress and impair the patient's private and professional life. Although the treatment of vitiligo has improved during the last decade, therapy is still not satisfying for many patients. Several treatment modalities, such as PUVA, UVB and local corticosteroids are currently used in the treatment of vitiligo. Surgical methods intended to repigment leucoderma are a therapeutic option if patients have stable disease.

2.0 Epidemiology

Commonly it is stated that about 1% of the worlds population has vitiligo vulgaris and this prevalence is constant for all ethnic groups in all countries, however the data do not confirm these assumptions. Large studies in other countries have shown a prevalence of 0.38% in Denmark, 0.49% in rural areas in Surat, India, 1.78% in urban areas in Surat, India, and 0.2% in Calcutta, India. From studies it has been concluded that the general prevalence of vitiligo vulgaris throughout the world is about 1 per 200 individuals, and both sexes are affected equally; however it should be noted that there are locations in the world, such as isolated villages in India, where the prevalence can be much higher, as high as 8% (1).

3.0 The clinical features

The key clinical finding in vitiligo is the acquired onset of an increasing number of initially hypopigmented and then depigmented macules, patches and later even broad sheets of skin. Vitiligo can appear at any age, but starts before the age of 20 years in 50% of cases. Initially small, pale or white patches appear; they are easier to see when the adjacent skin is either dark or tanned. At first there are usually a small number of patches, ranging in size from less than 1 cm to several centimetres. Their border is very sharp and they may be surrounded by hyper-pigmented skin. As the patches increase in number they fuse, creating bizarre intersecting lesions. Patients occasionally complain of itching, but inflammation is never seen clinically. Sometimes the lesions become red and painful when sunburn is incurred (2, 33, 34).

The sites of predilection are the somewhat more pigmented skin regions, such as the backs of the hands and feet, genitalia, head, neck, axillae and nipples. The distribution is often symmetrical. The hairs may depigment or they may retain their natural colour, even if the scalp is white (2, 33, 34).

Occupational vitiligo can occur too after contact with industrial chemicals such as substituted phenols. Sometimes it is confined to the areas of exposure, but is frequently more extensive, implying systemic exposure. Occupational vitiligo can be indistinguishable from the idiopathic variety (2).

The classification of vitiligo into localised, generalised, and universal types according to distribution is widely used. Localised type includes focal, mucosal and segmental. The generalised type includes acrofacial, vulgaris, and mixed type. The universal type is defined as complete or nearly complete depigmentation. Vitiligo can also be classified into two major clinical types, type A (non dermatomal or non segmental) and type B (dermatomal or segmental) vitiligo on the basis of both the distribution pattern and physiological function. The natural courses of type A and type B vitiligo are characteristic and quite different from each other (3, 4).

3.1 Nonsegmental vitiligo

Nonsegmental vitiligo includes all cases not classified as segmental such as localised, generalised and acrofacial. It can occur at any age. Nonsegmental vitiligo spreads progressively over the whole body throughout the life of the patient. It is frequently associated with a poor prognosis. Nonsegmental vitiligo results from immunologic mechanisms (4, 5, 6).

3.2 Segmental vitiligo

Lesions distributed along the ipsilateral dermatome, whose central part does not cross the midline, constitute segmental vitiligo. In segmental vitiligo, depigmented patches are confined to a particular dermatome, the patients are generally young, and disease activity usually ceases after one to two years of rapid spread over the particular dermatome. Segmental vitiligo results from dysfunction of the sympathetic nervous system in the affected skin area (4, 5).

3.3 Trichrome vitiligo

Trichrome vitiligo is a rare type of vitiligo. In early phase, especially in dark skinned individuals, one may see trichrome vitiligo- the three colours are the white patch, the normal skin colour and the hyperpigmented brown areas between normal and diseased skin (4, 33).

3.4 Progression pattern of vitiligo

The course of vitiligo on a case-by-case basis is unpredictable. Vitiligo spreads either by appearance of new depigmented macules or by centrifugal enlargement of pre-existing lesions, or both. The natural course of the disease is usually one of slow progression, but intervals of months or years may elapse when the disease is static. At other times, vitiligo may progress rapidly. Segmental vitiligo usually spreads over the affected dermatomal area, so the progression pattern can be easily predicted; however nonsegmental vitiligo spreads progressively over the whole body, without any known specific pattern (2, 4, 5). There is no difference between the sexes where progression of vitiligo is concerned.

Definitive factors that predict progression of vitiligo are speculative, although emotional shock, physical illness, sunburn and pregnancy are often mentioned as initiating or aggravating factors by patients. These subjective experiences vary from one patient to another and cannot be used by the dermatologist to advise new patients. Objective clinical characteristics such as sex, family history, clinical type, onset age, duration, Koebners phenomen, leukotrichia, and mucous membrane involvement may be relevant in predicting the progression of vitiligo (4, 5).

4.0 Melanocytes

4.1 Melanogenesis / pigmentation

In normal healthy skin, melanocytes generate melanin within compartments called melanosomes that are located in the basal layer of the epidermis. Melanin containing melanosomes are a specialized lysosome of melanocytes, and are distributed among surrounding keratinocytes. Through dendrite like processes, melanin is transferred from a melanocyte to neighbouring keratinocytes. Briefly, Melanin synthesis involves multiple catalytic conversions starting from the amino acid tyrosine, a derivative of the essential amino acid phenylalanine, leading to the formation of either pheomelanin (yellow/red melanin) or eumelanin (brown/black melanin), depending on the composition of the melanosome (7, 8).

4.2 Melanocytes in normal human skin

Human epidermal melanocytes function as a protective barrier against ultraviolet (UV) radiation and oxidative stress by generating the radical scavenging pigment melanin. Melanin is transferred to keratinocytes where it forms supranuclear caps that reduce UV transmission to the nuclear content (7, 8).

Apart from responding to environmental growth factors and cytokines, melanocytes generate cytokines themselves. These cytokines assist in maturation and migration of professional antigen presenting cells such as Langerhans cells, and in the recruitment of immune infiltrates into the skin. Indeed, such cytokine production, combined with the strategic position and dendritic morphology of melanocytes, has led to the suggestion that melanocytes, in conjunction with keratinocytes and langerhans cells, are active participants within the skin immune response. Melanocytes are capable of phagocytosis, and can process and present antigens to MHC class II restricted T cells. The processing of external antigens appears to involve fusion of phagosomes with melanosomes. The presentation of antigens to CD4+ T cells is supported by the expression of several co stimulatory molecules, such as intercellular adhesion molecule 1 (ICAM-1) and leukocyte function associated molecule 3 (LFA3). These findings support the notion that melanocytes provide a protective immune barrier at the dermo-epidermal junction and thus participate in immune surveillance (7).

4.3 Melanocytes in vitiligo skin

Vitiligo is a skin disease in which melanocytes are eradicated from lesional epidermis, resulting in disfiguring loss of pigment. Melanocytes are destroyed by melanocyte-reactive T cells, as well as other non-immune and immune components (7).

In the disfiguring disease vitiligo, melanocytes are eliminated from the lesional skin in association with T-cell infiltrates. Destruction of melanocytes in vitiligo is mediated by skin homing auto reactive T cells and by additional specific and non-specific components, including antibodies, complement factors and nitric oxide (NO), aided by melanogenic metabolites such as toxic ortho quinines. In vitiligo, natural immune tolerance is over ridden such that the host immune surveillance system can orchestrate melanocyte destruction (7).

5.0 Histology

5.1 Pathological staging

Epidermal melanocyte loss has been considered as the hallmark of vitiligo. Gauthier has proposed a staging in three grades (9).

Grade I: partial depletion in epidermal melanocytes (corresponding to the possibility of repigmenting patches evenly without follicular pattern, frequent on face and neck after phototherapy).

Grade II: complete depletion in epidermal melanocytes (corresponding to the usual follicular pattern of repigmentation of pigment cells originating from the melanocyte reservoir).

Grade III: complete depletion in follicular melanocytes (with no hope of response to medical therapy).

5.2 Histopathological finding

The characteristic histologic picture of vitiligo is an absence of melanocyte and melanin pigment within the epidermis. In vitiligo with erythematous borders, only sprinkles of mononuclear cells and lymphocytes are present at the edge of the lesion. Morphologic studies have emphasized subtle changes observed in the normal appearing skin adjacent to vitiliginous skin: degenerative changes in melanocytes, mild vesiculation in the epidermis, and intradermal and epidermal infiltration of lymphocytes. These changes seem more prominent in the skin in actively spreading vitiligo than in stable vitiligo (10).

The fact that melanocytes are uniformly absent in vitiligo skin is supported by dopa and silver nitrate-negative staining and by monochlonal and polychlonal antibodies directed against melanocytes. Cultured melanocytes from the periphery of depigmented patches show evidence of degeneration with cytoplasmatic vacuolisation, aggregation of melanosomes, autophagic vacuoles, fatty degeneration, and pyknosis. Moreover these melanocytes tend to grow poorly and die prematurely. Some studies have demonstrated dilatation of the rough endoplasmic reticulum in affected cells at the periphery of depigmented macules and in melanocytes in normally pigmented skin of patients with vitiligo. Some studies demonstrated inflammatory changes in the dermis and perivascularly at the border between pigmented and depigmented areas. Electron microscopic evaluations of skin specimens from the periphery of depigmented patches found vacuolisation of the basilar layer and accumulation of extra cellular granular material, with more marked changes in rapidly progressing lesions (11).

6.0 Aetiology / pathomechanisms in vitiligo

6.1 Intrinsic pathomechanisms / immune mechanisms

6.1.1 Autoimmunity

A number of indirect and direct observations suggest vitiligo is an autoimmune disease directed to pigment cells (12).

The indirect observations include the following:

1) Vitiligo is a systemic disease. Approximately one quarter of patients with vitiligo have destruction of pigment cells in the eye, indicating that the disease is a systemic process capable of affecting pigment cells in all parts of the body.
2) Vitiligo is associated with a variety of non specific immune abnormalities which are following: Vitiligo is frequently associated with a variety of organ specific autoantibodies and is 10-15 times more common with some autoimmune disease. Most patients with vitiligo show a 2-to 10-fold increase in autoantibodies to numerous organs, particular the thyroid, the adrenals, and gastric parietal glands.

3) Most effective treatments that induce repigmentation such as psoralen and ultraviolet A (PUVA), topical steroids, and topical cytotoxic drugs are immunosuppressive, this suggests that their benefit could result from suppression of local immune reactions that damage melanocytes.

The most convincing evidence is the direct demonstration:

Vitiligo is associated with abnormal antibodies to melanocytes; these antibodies correlate with the extent and activity of the disease, and have the functional ability to kill melanocytes in vitro and in vivo. These antibodies have been confirmed by using techniques such as complement dependent cytotoxity, immunoblotting, enzyme linked immunsorbent assay (ELISA), and passive transfer experiments. Using these techniques, antibodies to melanocytes are found in most patients with vitiligo. It is unusual to find these antibodies in persons with non-pigmentary skin disease.

6.1.2 Humoral immune response

Humoral immunity to melanocytes is supported by the finding that antibodies to melanocytes are more abundant in active phases of the disease and also by the observation that melanocytes are destroyed in normal skin engrafted onto nude mice injected with vitiligo patient sera (7).

Antibodies reactive against melanocyte-derived antigens have been demonstrated in the serum of vitiligo patients. Several authors reported that the principle antigen recognized by these antibodies is tyrosinase. Others melanocyte differentiation antigens that are recognized are gp 100 / Pmel 17, and tyrosinase related proteins (TRP-1) and (TRP-2). These differentiation antigens all localize primarily to the melansomes, where as it has been well established that antibody-mediating killing requires membrane expression of the target antigens. Surprisingly, however it was observed that patient's sera can induce in vitro damage to melanocytes via the classical pathway of complement activation and by antibody dependent cellular cytotoxity, and that at least some of the antibodies recognize membrane expressed melanocyte antigens (8).

6.1.3 Cellular immune response to pigment cells in vitiligo

Cellular immunity to melanocytes is supported by the consistent presence of immune infiltrates in marginal skin from progressing lesions in inflammatory and generalized vitiligo. Inflammatory cells, a marker for involvement of cellular immune mechanisms, are usually sparse in lesions of vitiligo but not completely absent. When present they are most prominent at the periphery of active lesions. The infiltrate consists of CD3+ (T cells), CD4+ (helper T cells), and CD8+ (cytolytic cells) and macrophages (7, 12).

The T cells are activated, as evidenced by increased expression of class II HLA antigens. T cells are often found close to the remaining melanocytes, next to the lesional margin, and recent data shows that the majority of these skin homing receptor (CLA+) T cells are cytotoxic, as determined by their granzyme/ perforin-staining pattern. Most convincingly, the involvement of T-cell-mediated immunity is supported by the presence of increased numbers of CLA+MART-1-reactive CD 8+Tcells in peripheral blood from progressive vitiligo patients (7, 12).

Further evidence for involvement of cellular mechanisms is provided by the rare cases of inflammatory vitiligo, in which pruritis and erythema are present at the periphery of active lesions and the vitiligo proceeds at all times in the direction of skin that still contains melanocytes. The inflammatory cell infiltrate in these patients again consist of T cells that are concentrated at sites of melanocyte destruction and macrophages. The CD8/CD4 ratio is increased (12).

Several other observations suggest that cellular mechanisms can be involved or activated in vitiligo. One is the abnormal expression of class II HLA and ICAM-1 by perilesional melanocytes. Another is an increased proportion of peripheral T lymphocytes that express HLA-Dr in patients with vitiligo, an indication that peripheral T cells are activated (12).

6.2 Extrinsic Pathomechanisms

6.2.1 Viral infections

Does a virus cause vitiligo? The presence of cytomegalovirus DNA has been detected in the depigmented and uninvolved skin of some patients with vitiligo and its absence in control subjects suggest that vitiligo may indeed be triggered by a viral infection in selected patients (9, 13).

6.2.2 Phenolic agents

Exposure to phenolic agents contributes to the development of occupational vitiligo. Proposed as a causative factor for leukoderma in vivo, the para substituted phenol 4-tertiary butyl phenol was chosen to investigate early cellular events responsible for selective disappearance of melanocytes from the epidermis of individuals sensitive to such agents. Results showed altered gene expression in melanocytes exposed to 4-tertiary butyl phenol (9, 14).

6.2.3 Koebners phenomen

The role of pressure and friction which occurs during every day cleansing and dressing has been emphasized by Gauthier, who has produced a body chart correlating vitiligo patch distribution and corresponding harmful mechanic stresses (9).

The prospective assessment of Koebners phenomen was done after experimental injury and found in 61% of a series of consecutive non-segmental vitiligo patients. There was some correlation between the activity of vitiligo and the presence of experimentally induced Koebners, suggesting that this tests may function well as a clinical factor to assess present disease activity, and may also predict the responsiveness to therapy (9, 15).

6.2.4 Stress and coping

Little scientific attention has been paid to the psychological impact of vitiligo or to the effects of psychological status on the illness itself. Compared to controls suffering from disfigurement, vitiligo patients endure a significantly higher

number of stressful life events than do controls, suggesting that psychological distress may have contributed to the onset of their condition (9, 16).

6.2.5 Neural theory

A hypothesis is that vitiligo results from a neural dysfunction, because vitiligo sometimes has a segmental distribution or stops abruptly at the midline, can spare denervated areas in patients with lesions of the central nervous system, can be associated with decreased sweating within lesions of segmental vitiligo, or with mild degenerative and regenerative changes in a small proportion of axons and Schwann cells supplying vitiligo lesions (12).

An ultra structural study of the dermal nerves was performed recently. Subtle ultra structural differences were observed between biopsies taken from marginal and central parts of vitiliginous skin and nonvitiliginous skin. The most consistent feature, seen in all biopsies from vitiliginous skin, was an increased thickness of the basement membrane of Schwann cells. This change was seen in approximately three quarters of dermal nerves in vitiligo biopsies and in about one quarter of dermal nerves in normal control biopsies. About half of the abnormal dermal nerves showed minor axonal damage, whereas indicators of regeneration predominated in the others; in addition, communication between the nervous system and epidermal melanocytes has been recently proved (10).

6.2.6 Self destruction theory

This hypothesis holds that vitiligo results from self destruction of melanocytes by toxic products made by these cells. There are several variants of this hypothesis (12).

1) One is that there is an overproduction or an inability to inactivate certain enzymes or intermediate products of melanin synthesis that are toxic to melanocytes.
2) A second is that multiple defects in catalase activity and in tetrahydrobiopterin and catecholamine synthesis in the epidermis of patients with vitiligo leads to the accumulation of toxic levels of hydrogen peroxide.

3) A third is that melanin fails to function as a scavanger of toxic free radicals, the accumulation of which kills the cells.

6.2.7 Biochemical factors in vitiligo

It has been proposed that vitiligo is a disease of the entire epidermis with a complex biochemical imbalance that leads to direct inhibition of tyrosinase and melanin bleaching by hydroxyl radicals. In normal skin, L-tyrosine is the common substrate for melanin biosynthesis by melanocytes and catecolamines biosynthesis by keratinocytes. L-tyrosine production from L- phenylalanine by phenylalanine hydroxylase is rate limited by the co factor (6R)-5,6,7,8 tetrahydrobiopterin (6-BH4). 6BH4 is recycled from 4a-OH-BH4 by an enzyme, the 4a-OH-BH4 deshydratase. In vitiligo patients, it is suggested that activity of 4a-OH-BH4 deshydratase is low, resulting in a build up of 7-BH4 and of hydrogen peroxide in the epidermis. A result of 7-BH4 build up is inhibition of phenylalanine hydroxylase, leading to a defective synthesis of melanin. Furthermore, catalase activity is very low in the epidermis of vitiligo patients, leading to increase in the toxity of hydrogen peroxide. Therefore, a sudden burst of hydrogen peroxide can be very cytotoxic and may explain active depigmentation (10).

6.2.8 Composite theory

Elements from other theories are brought together.

7.0 Genetic factors and associated diseases

Vitiligo seems to have a predilection for kinships, although its transmission does not follow Mendelian genetics. Environmental factors can not be ruled out, although it seems more likely that vitiligo is caused by a group of several genes, possibly four sets of alleles, that make the individual more likely to be affected by environmental factors that cause the vitiligo to be expressed. Factors might include chemicals in the work place, but they also could comprise foods, including the spices and seasonings that are known to contain phenolic compounds. Some families seem especially prone to vitiligo with or without other disorders (1).

The extent of familial aggregation of vitiligo is statistically significant. The pattern of the relationship between relative risk and degree of kinship indicates that the disease is associated with genetic loci on different chromosomes, which points to a polygenic nature of the disease. Further, several positive human leukocyte antigen (HLA)-associations for vitiligo have been reported: HLA-A2, HLA-Dw7, HLA-DR4, B13, Bw35, Cw7, and DR6 (8).

A wide variety of illnesses may be associated with vitiligo. Thyroid disorders are the most common associated factor, being found in as many as 30% of the patients. Both hyperthyroidism, including Graves disease, and hypothyroidism, along with Hashimoto thyroiditis, may be found. Other possibly related endocrinologic disorders includes Addison disease and both insulin-dependent and adult onset diabetes mellitus. A wide range of other autoimmune disorders are also associated with vitiligo. They include pernicious anemia, lupus erythematosus, systemic sclerosis, myasthenia gravis, Crohn disease, primary biliary cirrhosis, Sjøgren syndrome, alopecia areata, uveitis and atrophic gastritis (8, 33).

8.0 Mechanisms of repigmentation

Some vitiligo patients show spontaneous repigmentation, but most patients have permanent melanocyte loss. About 50% of these patients will repigment with photo chemotherapy (psoralen with ultraviolet light). Repigmentation usually occurs in a perifollicular pattern, suggesting that follicular melanocytes colonize vitiliginous skin. In most cases of repigmenting vitiligo, studies also argue for a proliferation of follicular melanocytes followed by their migration; however less commonly, repigmentation might occur from residual intraepidermal melanocytes (10).

Based on the perifollicular pattern of repigmentation, the existence of a melanocyte reservoir in human hair follicles has been postulated. Recently, the existence of a population of intraepithelial cells that have immunophenotypic characteristics of mature melanocytes within the upper epithelial regions, but lack the differentiated melanocytic phenotype within the deeper follicular regions, has been demonstrated (10).

During vitiligo repigmentation, melanocytes migrate from the outer root sheath of the follicle to the basal layer of epidermis just above the basement membrane. Because keratinocytes are attached together through desmosomes and to the basement membrane by hemidesmosomes, migration of melanocytes supposes several complex processes that are not yet understood (10).

9.0 Treatment of vitiligo

Today, as never before, we have an acceptable spectrum of many treatments for vitiligo; however, the best repigmentation rates do not reach figures beyond 70-75% (17). The treatment of vitiligo is unsatisfactory and in those who respond the risk of relapse persists indefinitely. Treatment options are listed beginning with the most readily available. The long list of suggested therapies for vitiligo simply confirms that there is no good approach (33).

9.1 Sunscreens

Sunscreens with sun protection factor values of 15 or greater are recommended to prevent sunburn on exposed sites (2). Even though patients hardly think of sunscreen application as therapy, it is essential for two reasons. One, vitiligo skin has risk of skin cancer development. In addition, by using a sunscreen, the normal skin does not tan as much, so the contrasts are less apparent (33).

9.2 Fake tan products

Fake tanning preparations are useful in extensive vitiligo and actually bind to the stratum corneum; the active ingredient is dihydroxyacetone. The colour builds up over 2-3 days and then disappears over a few days if application ceases. However the colour match is often poor, the fake tan tending to be orangey yellow (2).

9.3 Cosmetic camouflage

Cosmetic camouflage can give a very good result indeed, especially in facial vitiligo, but is time consuming and the preparations rub off on clothing (2). In the USA the best known is Covermark but there are many worthy competitors (33).

9.4 Topical corticosteroids

Low-, mild-, and high-potency steroids are often used to treat vitiligo, and for many reasons they should probably be considered as initial treatment (18). This offers almost the only way to treat children (33).

Topical corticosteroids may be effective, and are most useful on small patches of recent onset. A potent topical agent such as 0.1 % betamethasone valerate (Betnovate) may be used on the face, and a super potent agent such as 0.05% clobetasol propionate (Dermovate) on the body. Follow-up every 1-2 month is recommended, and if no

response has been seen within 3 months, treatment should be stopped. If some repigmentation has begun, it may be continued under close supervision. Full response, if it occurs, may take many months (2).

9.5 Vitamin D analogues

In a study it was shown that the combination of PUVA sol (psoralen-sun therapy) and calcipotriol is highly effective and works faster and may be used for shortening the therapy with PUVA in the treatment of patchy areas of vitiligo depigmentation (19). In another study topical calcipotriol appeared to be an effective and well-tolerated treatment for vitiligo and it can be safely used in conjunction with PUVA (20).

9.6 Phototherapy

Several sources of ultraviolet light have been utilised in the treatment of vitiligo. The oldest, dating to centuries ago, is of course the sun. In the last century, up until the 1980s, different types of mercury lamps were widely used, which emitted ultraviolet light mainly in the UVB region but reaching UVA and visible light. In 1969, long wave UVL was used and in 1974 high intensity UVA fluorescent bulbs were manufactured. Since then, fluorescent lamps emitting different regions of UVL have been used, e.g. broadband UVB (290-320 nm), selective UVL (295-335 nm), narrow band UVB (311 nm) and UVA 1 (340-400 nm). Several types of psoralen have been tried, 8-methoxy-psoralen being the oldest and most widely used, but in oral and topical form (21).

Although it has been documented that the absorption spectrum of 8-methoxy-psoralen (303nm) lies within the UVB range, the action spectrum lies within the UVA range of 320-360 nm. The combination of psoralen with different types of UVL sources in the treatment of vitiligo has led to different reports of success (21).

9.6.1 UVB

Recently, narrow band (311nm) UVB fluorescent lamps seem to be gaining a strong foot in phototherapy. The long-term carcinogenic risk of narrow band UVB is unclear (21).

A study have suggested that the treatment of patients with vitiligo with 311-nm UV-B radiation (narrow band (TL01) UVB) is as efficient as with oral PUVA and has fewer adverse effects (22).

Another study has shown that narrow-band ultraviolet B phototherapy is a useful and well-tolerated treatment for vitiligo. This treatment resulted in rapid repigmentation in many patients, including those with skin photo types IV and V (23).

9.6.2 PUVA

Photo chemotherapy using psoralen and UVA (PUVA) is most useful for extensive vitiligo. The psoralen is used either in a bath preparation for 10 min, or orally as a single dose of 0.3 mg/kg of 8- methoxypsoralen (Oxsoralen-Ultra) taken 90 minutes before exposure to artificial fluorescent UVA lamps (315-400 nm), two or three times a week. If not tolerated, 0,6 mg/kg of trimethyl-psoralen can be taken 2 hours before exposure. Repigmentation may occur gradually in a perifollicular fashion, although sometimes it may develop evenly over the whole area. If there is no response within 3 months, treatment should be stopped; otherwise treatment may be continued for a year or so as the pigmentation gradually expands; marked repigmentation occurs in up to 30% of patients. Relapse may then begin in up to 75 % within 1-2 years. Initial dose of 1-2 J/cm^2, increasing by 1 J each treatment. Two treatments weekly, often up to 100-300 in total (2, 33).

9.6.2.1 Mechanisms of action of PUVA

PUVA therapy is probably beneficial via a variety of mechanisms. Psoralens form monofunctional and bifunctional photoadducts that suppress DNA synthesis. Studies have demonstrated that PUVA stimulates hypertrophy and proliferation of follicular melanocytes residing in the outer root sheath of hair follicles as well as melanocytes at the borders of vitiliginous skin. Therefore repigmentation is the result of the migration of these stimulated melanocytes into the depigmented epidermis.

PUVA significantly impacts immunologic responses. It causes suppression of delayed hypersensitivity and contact allergy, and it

alters the distribution and function of T lymphocytes. In addition, PUVA stimulates selective cytotoxity of mononuclear cells and inhibits degranulation of mast cells. The aforementioned mechanisms may indeed synergistically create a favourable local milieu, conducive to melanocyte growth and survival (24).

9.6.3 PUVB

A study has compared oral 8-methoxy-psoralen plus UVA (PUVA) and oral 8-methoxy-psoralen plus UVB (broadband, 290-320 nm; PUVB) in the treatment of vitiligo. It showed that the use of psoralen plus broadband UVB is as effective as PUVA in the treatment of vitiligo. However the long-term side effects of psoralen plus UVB are unknown (21).

9.7 Depigmentation

The presence of residual pigmented skin areas, especially when they are located on the face, may also cause cosmetic disfigurements and psychosocial problems. These patients may benefit more by receiving depigmentation therapy, which is designed to remove the remaining pigment rather than to regain new pigment in the skin (25). Bleaching the remaining, normally pigmented skin may be the most practical approach to therapy in patients having vitiligo involving considerable areas of the body surface (18).

In many institutions worldwide, depigmentation therapy consists of the application of a bleaching agent containing monobenzylether of hydroquinone (MBEH). Although the use of MBEH may lead to a satisfying degree of depigmentation in most patients, several disadvantages and cutaneous and ocular side effects have been reported with this drug. Moreover, recurrence of the pigment is sometimes observed (25).

Even though chemical depigmentation is useful in widespread vitiligo but must only be undertaken after very careful assessment and a full explanation of the implications. Permanent depigmentation may be achieved within 1 year by the use of hydroquinone-containing preparations, 20 % monobenzyl ether of hydroquinone being the most used. Occasional use thereafter may be required. Hydroquinone may be absorbed and cause depigmentation at distant sites. Ochronosis is a rare complication (2).

Laser treatment has also been used to achieve depigmentation in widespread vitiligo. Ruby laser treatment can be effective, fast, and safe method for removing cosmetically disturbing remnants of normal pigmentation in vitiligo patients with a positive Koebner phenomen (26).

9.8 Pseudocatalase

It has been shown that patients with vitiligo have an extremely low catalase activity (18). Topical application of pseudocatalase (a low-molecular-weight inorganic complex of unknown formula with catalase activity), topical calcium preparation used in combination with short term UVB light exposure has been reported in an open study to show repigmentation. Complete repigmentation on the face and dorsum of the hands appeared in 90 % of those treated (2, 27).

9.9 Cognitive behavioural therapy

Vitiligo is a chronic skin disease that can have a profound impact on patient's lives. It can affect lives in a variety of ways consistent with having perceived stigma and many patients experience substantial psychological distress (28).

Papadopoulos L and other authors have examined the effect of cognitive behavioural therapy on coping with vitiligo and adaptation to the negative effects on body image, quality of life, and self esteem in adult patients. Two matched groups of vitiligo patients were compared, one of which received cognitive behavioural therapy over a period of 8 weeks, while the other received no changes to their treatment status. Result suggests that patients can benefit from cognitive behavioural therapy in terms of coping and living with vitiligo. There is also preliminary evidence to suggest that psychological therapy may have a positive effect on the progression of the condition itself, and the authors advocate incorporating psychological counselling into patient care and management (28).

Skin disfigurement, however, may be a barrier to privileges and opportunities because of the profound social significance of appearance and the attitudes and prejudices of society toward one whose appearance is atypical. The cosmetic disfigurement, which accompanies skin disease, may have profound effects on a patient's self-esteem and social relationships. The social effects of skin diseases may cause more hardship than the physical limitations.

9.10 Surgical techniques for vitiligo

9.10.1 Selection of patients

All surgical techniques have the same basic principle: to transplant autologous melanocytes from a pigmented donor skin to regions without melanocytes. Although this is theoretically possible in all patients with a pigmented donor area, some prerequisites are necessary for vitiligo patients to be eligible for transplantation. The vitiligo has to have been stable for more than 1 year and resistant to conventional treatment. The patient should have no positive koebners phenomenon and no history of hypertrophic scars in the past. Because a good result can never be guaranteed, patients should be highly motivated to both endure such a surgical procedure and follow the postoperative management.

Appropriate selection of patients is one of the most important of the criteria to be brought into consideration. A number of aspects need careful evaluation for example emotional stability, patients expectations, side effects, size and location of leukoderma, selection of technique, age of the patient, minigrafting test, donor area, cost and timing (29).

9.10.2 Tissue grafts

9.10.2.1 Full-thickness or punch-grafts

According to this method punch grafts from normally pigmented skin are implanted in leucodermic defects. Repigmentation is based on the pigment-spread phenomena by the grafted piece of normal skin. The grafts will be implanted into perforations previously made at the recipient site using a biopsy punch under local anaesthesia. The grafts should be placed 4-8 mm apart because apparently pigment cells seem not to migrate beyond 5 mm. This probably depends upon the individual skin type (30).

The grafted area will then be covered with petrolatum gauze or a transparent adhesive tape and secured with bandages to give compression and fixation for at least 1 week. According to several authors surgical methods with full thickness grafts seem the treatment of choice for localized or unilateral forms of vitiligo. Good repigmentation has been achieved in 68-82%. The response of bilateral and generalised vitiligo to full thickness graft transplantation varies. Pigment spread occurs gradually after grafting within 1

month after surgery and full repigmentation can be achieved in 3-6 months. Difficult area as the lips could be treated successfully too (30).

Disadvantages. This method is time consuming. Postoperative treatment is often required to hasten the pigment spread. The grafts may sometimes appear hyper pigmented. Punch grafting is not suitable for areas such as body folds. If grafts are not trimmed properly, uneven thickness can result in either a cobblestone or pitted appearance. Furthermore the donor sites heal by superficial scar formation in about 40 % (31).

Other complications are observed of which colour mismatch and hyper pigmentation of the acceptor areas are the most frequently described. Another disadvantage is that regrafting between the transplanted grafts can be necessary (30).

Advantages. This is believed to be the easiest and least expensive method of surgical repigmentation. It does not require any special equipment or laboratory set-up. Very good results can be achieved in cases of segmental vitiligo and vitiligo involving the palms and soles. With full thickness grafts, a larger number of melanocytes are available for transplantation as compared to epidermal or split thickness grafts (30, 31).

9.10.2.2 Split-thickness skin grafts

After obtaining a split thickness skin graft using a dermatome it can be applied directly to the derma braded recipient area. This technique has a high success rate of 78-91%. Success area depend on using a very thin graft to prevent additional cosmetic damage to both recipient and donor areas. With these technique difficult areas such as the eyelids, lips, vagina and penis can be treated as well. Partial to near total repigmentation of leucotrichia after transplantation has been described. Temporary small epithelial milia like cysts can be observed in the recipient area during the first months, especially on the face and neck. Scar or keloid formation at the donor site is reported in 12% of the patients treated with split thickness grafts. Donor tissue is limited so more than one split skin grafting session can be necessary (30).

Disadvantages. Taking split thickness grafts of uniform thickness requires skill and dexterity. Even a fraction of dermis gives it a stuck-on appearance. A

thick graft always leaves behind an ugly scar or even depigmentation at the donor site. Most of these grafts appear hyperpigmented for a few months and stand out, which is not cosmetically acceptable. It is not possible to cover areas such as the palms, soles, or body folds. Split thickness grafts are not suitable for depigmentation caused by burns, as they may result in hypertrophic and hyper-pigmented scars (31).

Advantages. This is the best method to cover multiple lesions and large areas at one time, especially over the extremities, giving immediate result. Very thin grafts of desired length can be harvested using motorized dermatomes (31).

9.10.2.3 Suction blister grafts

After harvesting the graft, the grafts are carefully removed with sharp scissors and forceps. This epidermal sheet is then grafted onto the denuded recipient site. Repigmentation occurs gradually within a few weeks. The success rate is 73-88%. Pigment spread after epidermal blister grafting can be enhanced by pre- operative radiation therapy of the donor site using PUVA. Temporary hyper pigmentation can be seen in the grafted sites in 2- 65% (30).

Disadvantages. This technique of harvesting blisters is time consuming. It requires a minimum of 90 minutes for separation of the epidermis. This varies from person to person and also depends on the anatomic site. Obtaining large epidermal sheets are not feasible with this technique, therefore it requires repeated procedures to cover large areas. The epidermal graft has to be handled very delicately, because it rolls up and tears easily. Postoperative treatment may be required for rapid spread and coalescence of the grafts. This technique is not suitable for treating areas such as body folds, palms and soles. The hairs grow rapidly over the scalp and can raise the epidermal graft from the recipient site. It is advisable to pluck the hairs at the recipient site when treating lesions on the scalp (31).

Advantages. Being a purely epidermal graft, there is no stuck on effect. Excellent cosmetic results are seen in cases of segmental vitiligo, and vitiligo involving the face, eyelids and lips. It has also proven effective in treating patches of vitiligo with leukotrichia. Since the dermis is unharmed, the donor site heals without scarring or depigmentation and can be utilized again in the

future. Epidermal grafting can be used for treating depigmented scars caused by thermal or chemical burns. It can also be used for lesions over bony prominences, provided the treated area is immobilized with a splint. Epidermal grafting by suction has proven to be an easy, safe, inexpensive and effective treatment modality for stable localized vitiligo (31).

9.10.3 Cellular grafts

9.10.3.1 Non cultured keratinocytes and melanocytes

Transplantation technique with a suspension of non-cultured keratinocytes and melanocytes in the treatment of depigmented lesions. Donor skin is obtained from the occipital area and immersed for 18 hours in 0.25 % trypsin solution. The following day the epidermis of the donor skin can be separated from the dermis in vitro using fine forceps. After several procedures a cellular suspension is obtained. Liquid nitrogen is used to induce blisters in the recipient area. The cellular suspension from the donor site is injected into each blister at the recipient area after aspiration of the viscous blister fluid. The intact blister top is a natural dressing that holds the transplanted cells in place. It is important not to separate keratinocytes from melanocytes before grafting because factors furnished by keratinocytes sustain melanocyte growth (30).

Olsson and Juhlin introduced a comparable technique by using a basal cell layer enriched suspension. However they applied the cellular suspension directly onto the derma braded vitiligo lesions. The cell suspension was covered with a thin collagen film, moistened gauze and Tegaderm. After 1 week the bandages were removed. The success rate in 20 vitiligo patients was 85% (30).

9.10.3.2 Transplantation of cultured melanocytes

Lerner et al first described the use of cultured pure autologous human melanocytes. They expanded pigment cells of a shave biopsy from normally pigmented skin in vitro with addition of several growth factors and chemical media (30).

Disadvantages. Although this method seems to be fascinating and promising, it is still in the developmental stage. It requires ultramodern equipment,

laboratory set up, specialized personnel, culture media, and growth factors, which makes it expensive. The procedure is time consuming and, transplantation and application of bandages can take up to 6 hours. Dermabrasion has to be accurate so that the cell suspension is placed over the basal cell layer. The culture media containing tumour promoters could be a risk factor (31).

Advantages. This treatment seems to be most promising, as it can repigment large achromic areas using a very small shave biopsy specimen (31).

9.10.3.3 Cultured epidermal grafts

A shave biopsy of normally pigmented skin is the source for epidermal cell culture. After separating the epidermis from the dermis the cells are seeded in a medium that allows co-cultivation of melanocytes and keratinocytes. After a week a cultured sheet is obtained, released by treatment with dispase and attached to a petrolatum gauze as support. Subsequently the gauze to which the epithelium adheres will be applied onto the derma braded recipient site and covered with occlusive dressing (30).

After grafting a repigmentation can be seen in 33 –54% of patients. The greatest advantage of this technique is the potential expansion of the cells in culture, which permits treatment of a wide area of hypomelanosis with a small sacrifice donor skin. Because only superficial dermabrasion is performed, the procedure is non-scarring (30).

9.10.4 Stability in surgical repigmentation of vitiligo

Surgical repigmentation of vitiligo involves various procedures as described above. The single most important criterion to select the patient is the stability of the disease. Even after almost three decades of implementing surgery in vitiligo, there seems to be little consensus among workers regarding the optimal required period of stability.

After several years of experience in surgical repigmentation of vitiligo, some interesting observations are creeping up. These observations are quite unsettling in so far as the fundamental concept of stability of vitiligo is concerned. The observation is that even after test grafting, the pigment spread from successive

sessions of grafting can be unpredictable; perigraft spread of pigment may be minimal or absent and in some cases even depigmentation of grafts is noted (32).

10.0 Conclusions

That vitiligo is a common disease seems clear. In order to cure this chronic disease, there have been many studies about epidemiology, pathogenesis, immunology, genetics, clinical progression, and treatment of vitiligo. The prevalence from the best studies seems to be about 0.5%, or one per 200 individuals (1). It spares no sex, age, or race. The social and emotional consequences of this disease are especially damaging for darker skinned individuals as hypomelanotic lesions frequently appear initially on sun-exposed skin. Vitiligo is probably a heritable condition with melanocytes of some individuals being genetically abnormal and predisposed to destruction and development of vitiligo. The prevalence of a positive family history of vitiligo has been reported to be 30% in the literature (5). Environmental factors can not be ruled out, although it seems more likely that vitiligo is caused by a group of several genes, that makes the individual more likely to be affected by environmental factors that cause the vitiligo to be expressed.

Vitiligo remains a challenging disease to researchers and clinicians. The pathogenesis is still unknown and constitutes a huge research field for those interested in melanocyte biology and pigmentation disorder. Research is a priority in vitiligo in order to find the complete sequence of pathogenic events leading to depigmentation. The present time is one of the more exciting periods for vitiligo and melanocyte research. While additional information has been gained, many new questions have also been raised.

Vitiligo is a multifactorial illness with diverse biomolecular alterations, and with different clinical manifestations, sometimes associated with endocrine or immune disorders. Established vitiligo is due to the destruction of melanocytes. Various theories such as autoimmune, neural, and self-destructive theories have been suggested for the aetiology of vitiligo.

A great deal of evidence supports the model in which autoimmunity, in particular that mediated by autoantibodies, is implicated in the vitiliginous depigmentation. Besides, there is significant evidence that many different biologic factors other than autoimmunity alone contribute to the pathogenesis of vitiligo. Though the cause of vitiligo remains unknown, immune mechanisms are clearly involved. Abnormal antibodies specifically directed to melanocytes are associated with vitiligo. The presence and level of these antibodies correlates

with the extent and activity of the disease. Unravelling the pathogenesis of vitiligo will lead in the direction to find a treatment for arresting completely the mechanisms of depigmentation and to convert vitiligo into a definitive stable condition.

Vitiligo has various clinical features. Understanding these characteristics can give us some valuable information in differentiating vitiligo from other hypopigmentary disorders, in treating vitiligo with the proper method, and to predict the prognosis of vitiligo to some extent.

Treating this disease forms a challenge to the clinician who is armed with only few medical therapies. Each patient with vitiligo should be individually assessed and the treatment planned accordingly. Education, support groups, counselling, and psychotherapy can be important in the management of many patients, as can cosmetic camouflage. Of the myriad therapies reported to repigment vitiliginous skin lesions, maximal results are most often achieved with oral or topical PUVA. The route of administration of PUVA therapy should be adjudicated by age, severity and progression of disease. Significant cosmetically acceptable repigmentation can be achieved in many vitiligo patients treated with PUVA. An effective therapeutic alternative to topical or systemic PUVA has not yet been found. Topical steroids are probably first-line therapy for most patients. In selected cases depigmentation with monobenzyl ether of hydroquinone gives excellent cosmetic results. There are a number of other therapies such as surgical techniques that seem promising; however, further studies are both necessary and eagerly awaited.

Vitiligo is a dermatologic disease that merits special attention. It is one of several dermatologic disorders that are easy to minimize because it is often dismissed as a cosmetic problem. In this era of medical cost containment, vitiligo is in danger of being left behind. While it is easy to reassure patients that vitiligo will not shorten their lives or lead to physical disability, it is very difficult to fix the problem. Often patients endure extreme psychological stress as a result of their illness. Therapy has not been satisfying for vitiligo patients. But now the time has come to offer patients therapy and hope. However the treatment of vitiligo remains a challenge.

11.0 References

Articles from medical journals:

1. Nordlund JJ. The epidemiology and genetics of vitiligo. Clinical Dermatology. 1997; 15(6): 875-878.
2. Shaffrali F.C.G, Gawkrodger D. Management of vitiligo. Clinical and Experimental Dermatology. 2000 Nov; 25(8): 575-579.
3. Zaima H, Koga M. Clinical course of 44 cases of localized vitiligo. Journal of Dermatology 2002 Jan; 29(1): 15-19.
4. Hann SK, Park YK, Chun WH. Clinical features of vitiligo. Clinical Dermatology 1997; 15(6): 891-897
5. Hann SK, Chun WH, Park YK. Clinical characteristics of progressive vitiligo. International Journal of Dermatology; 1997; 36(5): 353-355.
6. Chun WH, Hann SK. The progression of nonsegmental vitiligo. International Journal of Dermatology; 1997; 36(12): 908-910.
7. Das PK, Van den Wijngaard RM, Le Poole IC. A symbiotic concept of autoimmunity and tumour immunity. Lessons from vitiligo. Trends in immunology. 2001 Mar; 22(3): 130-136.
8. Van den Wijngaard R, Wankowicz Kalinska A, Pals S, Weening J, Das P. Autoimmune melanocyte destruction in vitiligo. Laboratory investigation. 2001 Aug; 81(8): 1061-1067.
9. Taieb A. Intrinsic and extrinsic pathomechanisms in vitiligo. Pigment Cell Research. 2000; 13 Suppl 8: 41-47.
10. Castanet J, Ortonne JP, Pathophysiology of vitiligo. Clinical Dermatology. 1997; 15(6): 845-851.
11. Kovacs Stephen O. Vitiligo. Journal of the American Academy of Dermatology. 1998; 38(5): 647-666.
12. Bystryn JC. Immune mechanisms in vitiligo. Clinical Dermatology. 1997; 15(6): 853-861.
13. Grimes PE, Sevall JS, Vojdani A. Cytomegalovirus DNA identified in skin biopsy specimens of patients with vitiligo. Journal of the American Academy of Dermatology. 1996; 35(1): 21-26.

14. Le Poole IC, Yang F, Brown TL, Cornelius J, Babcock GF, Das PK, Boissy RE. Altered gene expression in melanocytes exposed to 4-tertiary butyl phenol (4-TBP). Journal of Investigative Dermatology. 1999 Nov; 113(5): 725-731.
15. Njoo Md, Das Pk, Bos JD, Westerhof W. Association of the Koebner phenomen with disease activity and therapeutic responsiveness in vitiligo vulgaris. Archives of Dermatology. 1999 Apr; 135(4): 407-413.
16. Papadopoulos L, Bor R, Legg C, Hawk JL. Impact of life events on the onset of vitiligo in adults. Clinical and Experimental Dermatology. 1998 November; 23(6): 243-248.
17. Flabella R. What is new in the treatment of vitiligo? Journal of European Academy of Dermatology and Venerology. 2001; 15(4): 287-289.
18. Mandel AS, Haberman HF, Pawlowski D, Goldstein E. Non Puva Nonsurgical Therapies for Vitiligo. Clinical Dermatology. 1997; 15(6): 907-919.
19. Parsad D, Sainio R, Verma N. Combination of Puva sol and topical calcipotriol in vitiligo. Dermatology. 1998; 197(2): 167-170.
20. Ameen M, Exarchou V, Chu AC. Topical calcipotriol as monotherapy and in combination with psoralen plus ultraviolet A in the treatment of vitiligo. British Journal of Dermatology. 2001; 145(3): 476-479.
21. Mofty ME, Zaher H, Esmat S, Youssef R, Shahin Z, Bassioni D, Enani GE. PUVA and PUVB in vitiligo- are they equally effective. Photodermatology Photoimmunology Photomedicine. 2001 Aug; 17(4): 159-163.
22. Westerhof W, Nieuweboer-Krobotova L. Treatment of vitiligo with UV-B radiation vs topical psoralen plus UVA. Archives of Dermatology. 1997 Dec; 133(12): 1525-1528.
23. Scherschun L, Kim JJ, Lim HW. Narrow-band ultraviolet B is a useful and well-tolerated treatment for vitiligo. Journal of American Academy of Dermatology. 2001; 44(6): 999-1003.
24. Grimes PE. Psoralen Photochemotherapy for vitiligo. Clinical Dermatology. 1997; 15(6):921-926.
25. Njoo MD, Vodegel RM, Westerhof W. Depigmentation therapy in vitiligo universalis with topical 4-methoxyphenol and the Q-switched ruby laser. Journal of American Academy of Dermatology. 2000; 42(5): 760-769.
26. Thissen M, Westerhof W. Laser treatment for further depigmentation in vitiligo. International Journal of Dermatology.1997; 36(5): 386-388.

27. Schallreuter KU, Wood JM, Lemke KR, Levenig C. Treatment of vitiligo with a topical application of pseudocatalase and calcium in combination with short term UVB exposure. Dermatology.1995; 190(3): 181-192.
28. Picardi A, Abeni D. Can cognitive behavioural therapy help patients with vitiligo. Archives of Dermatology. 2001; 137(6): 786-788.
29. Flabella Rafael. Surgical therapies for vitiligo. Clinical Dermatology. 1997; 15(6): 927-939.
30. Van Geel N, Ongenae K, Naeyaert JM. Surgical techniques for vitiligo. Dermatology. 2001; 202(2): 162-166.
31. Mutalik S, Ginzburg A. Surgical management of stable vitiligo: A review with personal experience. Dermatologic Surgery. 2000; 26(3): 248-254.
32. Malakar S, Lahiri K, Malakar RS. How unstable is the concept of stability in surgical repigmentation of vitiligo? Dermatology. 2000; 201(2): 182-183.

Textbooks in Dermatology:

33. O. Braun Falco, G. Plewig, H.H.Wolff, W.H.C.Burgdorf. Dermatology. Second completely revised edition.
34. Rook, Wilkinson, Ebling. Textbook of Dermatology. Fifth edition by R.H.Champion, J.L.Burton and F.J.C. Ebling.