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Vitiligo

Questions and Answers

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Vitiligo. Questions and Answers.

Part 1 by Prof. Torello Lotti, MD

Question 1. What is vitiligo?

Key points

- *Vitiligo is a pigmentary disorder resulting in typically asymptomatic white macules that can appear any time during human life and can be psychologically devastating.*
- *It occurs in all skin types and at all ages and with equal frequencies between men and women.*
- *Vitiligo is considered to be an autoimmune disease with underlying genetic predisposition in majority of cases.*
- *Vitiligo is not caused by poor medical care.*
- *Personal behavior or state of mind may play an important role in the disease management.*
- *Vitiligo is never a contagious disease, but infective agents may apparently play an indirect role in some cases.*
- *Vitiligo is not related to wrong diets, but correct diet may help.*
- *Vitiligo seems not to be directly related to pollution, but the environment plays a major role in vitiligo development.*
- *Vitiligo is not clearly genetically transmitted.*
- *Progression of the disease can be halted in about 90% of cases, if requested.*
- *A cure is not yet known for each and every case, but adequate medical and /or surgical therapies may treat satisfactorily over 75% of the affected subjects.*
- *Be optimistic! It is not true that there is nothing to do for vitiligo. In fact, just the opposite is true and research is going on all over the world to find the cure for vitiligo.*

Answer

Vitiligo is an acquired sudden loss of the inherited skin color. Despite its long recognition, the cause of this disorder is still unknown. The loss of skin color yields white patches of various sizes, which can be localized anywhere on the body. The disease affects people of all races, men and women, and all age groups. It may appear at any age; cases have been reported as early as 6 weeks after birth and after 80 years of age.

Vitiligo is not a contagious disease. Vitiligo can be rarely tolerated, being more often a psychologically devastating disease, especially in darker skinned individuals, in whom it is more easily noticeable. The actual cause of vitiligo is under debate and has been attributed to autoimmune causes, oxidative stress, and/or a neurogenic disturbance. These terms will be explained later on.

In other terms, vitiligo is a skin and/or mucosal disorder characterized by white patches, often, but not always, symmetrical, which usually increase in size with time, corresponding to a substantial loss of functioning epidermal and sometimes hair follicle melanocytes. It may occur in a unilateral distribution or may be generalized.

Vitiligo lesions may rarely itch and have a high

propensity to sunburn. Vitiligo is a chronic persistent and often progressive disorder; spontaneous repigmentation is uncommon and usually occurs around the hairs in a perifollicular pattern. Many patients are poorly educated about their illness. In one study, 51.3% of patients believed that their vitiligo was caused by poor medical care, 30% thought personal behavior played a major role, 25% - wrong diet, 21.3% - altered state of mind, and 20% blamed only pollution or environmental alterations.

All the believes mentioned above are considered by the scientific community to be "per se" unfounded and misleading, even if all of them may bring some true indications for understanding the disease and for finding the cure.

Vitiligo is a disease that presently cannot be cured, but still can be treated successfully with many different approaches. Its progression can be halted in almost 90% of cases with appropriate therapy, most frequently by combining different treatments. More than 75% of subjects affected by vitiligo respond satisfactorily to active treatments (medical or surgical).

Thus, it is not true that there is nothing to do for vitiligo. In fact, just the opposite is true.

Question 2. Is vitiligo a common disease?

Key points

- Nearly 100 million people worldwide are affected by vitiligo.
- Vitiligo is not common in some countries and is very common in other countries: in China 0.09% of the population is affected, while in Gujarat (India) 8.8% have vitiligo.
- In females, vitiligo starts mainly in the first decade of life.
- In male, the peak prevalence occurs in the fifth decade of life.
- Presently, no convincing explanations are given to this wide variation of prevalence in different countries.

Answer

The prevalence of vitiligo is believed to be between 0.5% and 2% of the world population on average, but local numbers may vary greatly. Large studies in China, India, and Denmark have found the prevalence to be 0.093%, 0.005%, and 0.38%, respectively. Gujarat, India is considered to have the highest prevalence in the world with 8.8% of the local people affected by vitiligo. Men and women are equally affected, but women are more likely to seek treatment.

In most studies, 20% of vitiligo subjects report about a first-degree relative suffering from vitiligo.

The mean age of onset is earlier in those patients having positive family history, which ranges from 7.7% to more than 50%. Vitiligo is significantly more prevalent in young women (≤ 30 years of age) than young men.

The peak in females occurs in the first decade of life.

Male peak prevalence is in the fifth decade of life.

Vitiligo is more frequently diagnosed in spring and summer (64.4%).

Question 3. What causes vitiligo?

Key points

- The cause of vitiligo is unknown.
- There are different types of vitiligo.
- The different types could have different origins and causes.
- The most widespread forms of vitiligo seem to be related to the immune system disorder with production of antibodies against melanocytes. Life stressing events, infections, and the accumulation of toxic compounds in the body are under investigation.
- The limited forms of vitiligo seem to be related to alteration of skin nerves.
- The autoimmune hypothesis is the best documented theory: it seems that the immune system reacts against the cells which produce melanin pigment.
- The neurohumoral, cytotoxic, and oxidative stress theories have moderate evidence (All medical terms will be explained in the following pages.)
- New theories focus on melanocytorrhagy – i.e. melanocytes are discharged by the skin – and on decreased melanocyte survival in the skin.

Answer

It remains unclear what causes damage to melanocytes and their subsequent total inactivation and/or disappearance in vitiligo skin. There are several theories; the most prominent are autoimmune, neurohumoral, related

to abnormal detachment of melanocytes from the epidermal layers and autotoxic. None are mutually exclusive, and it is likely that each of them partially contribute to the disease development.

The current thought is that vitiligo represents a group of different disorders with a similar outcome: the appearance of white patches on the skin.

The convergence theory states that stress, accumulation of toxic compounds, infections, autoimmunity, genetic predisposition, altered cellular environment, and impaired melanocyte

migration can all contribute to the vitiligo initiation process. Autoimmune mechanisms are likely to underlie generalized vitiligo, while a more localized phenomenon (i.e. the altered activities of sensitive nerves in the skin) may be responsible for segmental or focal vitiligo. A site of a skin physical trauma may develop vitiligo; it is called a "Koebner phenomenon".

Question 4. I have vitiligo: will my children have vitiligo too?

Key points

- *Be optimistic! If you have vitiligo, most probably your children will not have vitiligo.*
- *Genetic component in vitiligo is weak and quite inconsistent.*
- *If I have vitiligo, it is possible that all my relatives may have increased probability of developing vitiligo.*
- *Identical twins have only 23% concordance of developing vitiligo: this means that the pure genetic component of the disease is not really dominant.*
- *Most cases of vitiligo are sporadic, thus it is not necessary that children of parents with vitiligo will also develop vitiligo.*
- *In less than 20% of vitiligo patients their close relatives may be affected.*

Answer

Although most cases of vitiligo are sporadic, familial clustering is not uncommon, and up to 20% of patients report on the affected relatives. In whites, the lifetime frequency of vitiligo among patients' siblings is 6.1%, an 18-fold increase over the studied population. The frequency of vitiligo among first degree relatives in white, Indo - Pakistani, and Hispanic populations is 7.1%, 6.1%, and 4.8%, respectively, compared to an estimated worldwide frequency of 0.14% to 2%.

Epidemiologic studies indicate that vitiligo is inherited in a multifactorial pattern. Identical twins with identical DNA have only a 23%

concordance in developing vitiligo, suggesting a significant non-genetic component in the disease.

Familial clustering of generalized vitiligo with other autoimmune diseases is a compelling evidence for an autoimmune predisposition, a common underlying genetic susceptibility to an immunologic aberrancy. Among vitiligo patients, 20% report on thyroid disease (an 8-fold increase over the general population), particularly hypothyroidism. Similarly, there is an increased frequency in other forms of autoimmune diseases and autoimmune disorders of the endocrine system (see later on).

Question 5. Is it true that my quality of life will be affected by vitiligo?

Key points

- *Vitiligo may impair one's quality of life mainly because it is poorly understood in many communities.*
- *It is often confused with leprosy or sexual infections, and even seen as a sign of a sin or a sort of punishment sent by God.*
- *Women are generally more psychologically affected by the skin disorder than men.*
- *For doctors, it is important to assess the patient's quality of life during encounters, and take initiatives.*
- *The dermatologist must always inform the vitiligo patients of the possibility of successful treatments: this will change the patient's mood immediately.*

- *Observation of re-pigmentation over the white patches always brings optimism to the vitiligo patient.*
- *Psychotherapy can be of help in selected cases, but only after careful consideration.*
- *Regional Vitiligo Support Groups and VRF are committed to eradicate all discriminating attitudes against vitiligo subjects all over the world.*

Answer

It is true that vitiligo can be a psychologically devastating disease, especially in darker skinned individuals and in case of improper management by the dermatologist.

The assessment of quality of life should always be made during the first consultation, because there may be a difference between patient's and physician assessment of severity, and it should be followed during treatment to assess patient's satisfaction. Studies suggest that vitiligo imparts mental and emotional burden comparable to that of chronic hand eczema or psoriasis, and that women tend to suffer more than men. Vitiligo patients also experience sexual difficulties and a variety of psychological problems, such as adjustment disorder, sleep disturbance, depression, anxiety, and so called "dysthymia".

Clinical variables, such as duration, facial or chest involvement, unsuccessful previous treatment, darker skin type, and extent of disease may predict a poorer quality of life.

In fact, vitiligo may be, or may become, a psychologically devastating disorder. The fact that it typically occurs in exposed areas (face and hands) has a major impact on self-esteem and perception of the self. In many societies, vitiligo is poorly understood and is believed to be a sign of leprosy or sexually transmitted infection. In these societies, women with vitiligo have difficulty getting married and finding educational and vocational opportunities according to their skills. Many patients worry about the disease worsening, have their social life affected, and feel embarrassment, depression, and shame.

Correct information on vitiligo (extended to non-affected subjects, media system and to the Authorities) will rapidly change this outrageously and incredible discriminated attitude against the alteration of the color of the skin. The vitiligo support groups and the VRF are committed to fight against all irrational feelings and behaviors which negatively impact the quality of life of vitiligo patients all over the world.

Question 6. How can I be sure that I am really affected by vitiligo?

Key points

- *Uniformly white patches surrounded by normal skin, not painful and usually not itchy: this is the most usual presentation of vitiligo.*
- *Vitiligo is usually discovered during the spring and summer months in the sun-exposed areas. The white patches will not pigment after sun exposure and will have a tendency to sunburn.*
- *The dermatologist should always make a full body examination for vitiligo.*
- *A handled device (Wood's lamp) emitting ultraviolet light is usually used to increase visibility of white patches: this can be enough for the correct clinical diagnosis.*
- *Biopsy of the skin is usually not required.*
- *After the examination, appropriate blood test can be requested and then the appropriate treatment will be selected according to blood test result.*
- *Rare types of vitiligo are possible and, thus, an assessment by an expert dermatologist is advisable.*

Answer

Discrete, uniformly white patches with convex borders and surrounded by normal skin, not painful and very rarely itching: this is the usual presentation of vitiligo. White hair can be associated or not with these white patches. Any kind of trauma of the skin may induce white patches of vitiligo in any part of the skin surface: it is called Koebner Phenomenon, and is quite common.

The diagnosis of vitiligo is usually made clinically and with the use of Wood's lamp, a handheld device emitting ultraviolet rays (at 365 nm) which makes the color of white patches even more white.

Vitiligo is usually discovered during the spring and summer months in sun - exposed areas: normal skin becomes tanned while vitiligo skin remains white, with tendency to sunburn. When presentation of vitiligo is atypical, a biopsy can be taken from the skin, in order to show the complete absence of melanocytes in the white patch. A full body examination is necessary to detect all skin areas affected, including mouth mucosal and genital depigmentation.

Question 7. I have vitiligo: which blood tests or other examinations are necessary?

Key points

- *After a full body skin examination, specific forms of vitiligo may require blood examination or other medical investigations.*
- *Vitiligo can be generally divided into three classification types: localized, generalized and universal (involving more than 80% of the skin): according to this, different blood tests or specific examinations are necessary.*
- *Thyroid disorders and autoimmune diseases should be investigated in generalized and universal forms.*
- *Ophthalmologic and auditory investigations can be useful in generalized and universal forms.*
- *Localized vitiligo usually does not require blood tests or further medical examinations.*
- *In conclusion, generalized and universal vitiligo per se requires the investigation of thyroid disorders and other autoimmune diseases, as well as ophthalmologic and auditory investigations.*

Answer

After the diagnosis of vitiligo, a full body skin examination is necessary in order to evaluate the specific form of the disease. Thyrotropin (thyroid-stimulating hormone) levels, antinuclear antibody titer, and a complete blood count should be considered for all generalized forms of vitiligo, especially when prompted by signs or symptoms. Antithyroidperoxidase antibodies and/or antithyroglobulin antibodies may also be worthwhile. They are mandatory, if any signs of thyroid disease are present.

The evaluation of possible associated disorders is mandatory in all generalized forms of vitiligo. In these cases all autoimmune diseases should be screened, as well as atopic dermatitis, psoriasis, pernicious anemia and diabetes. Ophthalmologic and auditory investigations can be useful, because melanocytes are present both in the eye and in the inner ear.

Question 8. Is it true that vitiligo can be a part of one of the most complex multisystem organ dysfunctions of the human body?

Key points

- *Vitiligo may be associated with other disorders.*
- *The Dermatologist, in cooperation with Geneticists and Experts in related fields will manage properly each and every associated/isolated condition.*
- *Subjects with vitiligo may also be affected by a multisystem organ dysfunction.*
- *The latter are named “vitiligo systemic syndromes”.*
- *Usually these cases are discovered at birth or during infancy.*

Answer

Disorders and syndromes possibly associated with vitiligo (in alphabetical order)

More common associations	Less common associations	
Addison disease	Acrokeratosis paraneoplastica	Lymphoma
Alopecia areata Atopic dermatitis	Bazex Alezzandrini syndrome	Melanoma
Autoimmune thyroid disease	APECED* syndrome (*Autoimmune	MELAS syndrome
Chronic urticaria Diabetes mellitus	PoliEndocrinopatya Candidiasis	Morphea
Halo nevi Hypoacusis	Ectodermal Dysplasia) Asthma	Multiple sclerosis Myasthenia
Hypoparathyroidis m	Ataxia-telangiectasia	gravis Nonmelanoma skin cancer
Ichthyosis Morphea Ocular abnormalities	Deafness	Nail dystrophy Pemphigus vulgaris Sarcoidosis
Pernicious anemia Psoriasis	DOPA-responsive dystonia	Schmidt syndrome Systemic lupus erythematosus Turner syndrome
Rheumatoid arthritis	Dysgammaglobulinemi a	Twenty-nail dystrophy
	Hemolytic Anemia (autoimmune)	Vogt-Koyanagi- Harada syndrome
	Hepatitis C	
	HIV	
	Inflammatory bowel disease	
	Kabuki syndrome	
	Kaposi sarcoma	

Question 9. Is there a full list of white patches on skin, which are not associated with vitiligo?

Key points

- *Not all white patches on the skin are a sign of vitiligo. White patches not diagnosed as vitiligo are named leukodermas.*
- *A list of the so called leukodermas is hereunder available for Dermatologists who face the problem of a differential diagnosis of vitiligo.*
- *The expert Dermatologist should recognize all cases of leukodermas.*
- *Different kinds of leukoderma require different treatments.*

Answer

Not all white spots appearing on the skin is vitiligo. White patches that are not diagnosed as vitiligo are named leukodermas.

Here is a list of leukodermas for dermatologic use:

Differential diagnosis in vitiligo: the Leukodermas

Chemically-induced leukoderma (often occupational)

Arsenic
Phenols and other derivatives,
catechols

Infections

Leishmaniasis (post kala-azar)
Leprosy
Onchocerciasis
Secondary syphilis
Tinea versicolor
Treponematoses (pinta and syphilis)

Genetic syndromes

Chediak-Higashi syndrome
Hypomelanosis of Ito
Oculocutaneous albinism
Piebaldism
Tuberous sclerosis
Vogt-Koyanagi-Harada syndrome
Waardenburg syndrome

Postinflammatory hypopigmentation

Atopic dermatitis/allergic contact dermatitis
Nummular dermatitis
Phototherapy- and radiotherapy-induced hypopigmentation
Pityriasis alba
Postraumatic hypopigmentation (scar)
Psoriasis
Sarcoidosis
Systemic lupus erythematosus
Topical or systemic drug-induced depigmentation

Neoplastic

Amelanotic melanoma
Halo nevus
Melanoma-associated leukoderma
Mycosis fungoides

Idiopathic

Idiopathic guttate hypomelanosis
Lichen sclerosus et atrophicus
Lichen striatuslike leukoderma
Morphea
Melasma (caused by contrast between lighter and darker skin)
Progressive (or acquired) macular hypomelanosis

Malformations

Nevus anemicus
Nevus depigmentosus/hypopigmentosus

Nutritional

Kwashiorkor

Selenium deficiency

(Adapted from Alikhan et al. (4))

Question 10. Whitish and depigmented patches on skin: how can I know what they are?

Key points

- *Not all whitish patches on the skin are vitiligo.*
- *Depigmented patches on the skin other than vitiligo are named leukodermas, they can be “occupational”.*
- *Occupational and drug-related forms of depigmentation can be manifested as vitiligo.*
- *Common disorders with similar manifestation include Nevus Depigmentosus, Piebaldism, etc.*

Answer

No, not all white patches are vitiligo, but white patches resembling vitiligo are not unusual on human skin. They are called leukodermas. Chemical leukoderma can be induced by dyes, perfumes, detergents, cleansers, insecticides, rubber condoms, rubber slippers, black socks and shoes, eyeliners, lipliners, lipsticks, toothpaste, antiseptics with phenolic derivatives, and mercuric iodide-containing "germicidal" soap.

Occupational vitiligo may occur in those individuals who work with depigmenting substances, such as hydroquinone, para-tertiary butyl catechol, para-tertiary butyl phenol, para-tertiary amyl phenol, and hydroquinone monomethyl ether.

Depigmentation has also been reported in shoemakers and after contact with arsenic - containing compounds. Nevus depigmentosus is a segmental hypopigmentation detectable in the first year of life and stable in size in proportion to the child's growth. With a Wood's lamp, the contrast between lesional and normal skin is less marked than in vitiligo. Piebaldism is an autosomal dominant disease presenting at birth with anterior midline depigmentation and a white forelock (poliosis). Many other types of leukoderma have been described. The diagnosis and treatment of leukodermas needs expert approach. The only way to know if a depigmented patch on the skin is vitiligo or not is to consult a Dermatologist with special interest in Pigmentary Disorders of the skin.

Question 11. How can I treat vitiligo?

Key points

- *Many different modalities may be used to treat vitiligo.*
- *Treatment should always start with efficacious and safe approaches and at the same time with less aggressive and cost/effective modalities.*
- *A targeted UVB therapy (308 or 311 nm) alone or associated with topical steroids or with topical calcineurine inhibitors represents the most efficacious and safe approach if less than 15% of the skin is affected.*
- *Second-, third- and fourth-line therapies must be discussed by the dermatologist and vitiligo-affected subject in an open and constructive way, keeping in mind that the less aggressive and the most cost/effective modalities are always the first choice.*
- *Don't feel frustrated if you don't achieve the goal with the first-line treatment: discuss other options with your dermatologist and go on according to your new treatments.*
- *Be always optimistic: you have very many chances to find the right treatment for your vitiligo!*

Answer

Choosing a treatment for vitiligo can be difficult, sometimes overwhelming. In general, first-line therapy should be safe, effective, minimally invasive, and cost efficient. More complex, invasive, and time- consuming options should be reserved for subjects with recalcitrant disease. Each therapeutic modality should be tried for a sufficient period of time because the initiation of pigmentation varies and is in general rather slow. An effective therapy should be continued as long as there is an improvement or the lesions repigment completely.

We are in need of consistent data on maintenance regimens or the long-term

persistence of pigmentation with any of the recommended therapies.

How to treat vitiligo:

First-line. There are many topical and some oral agents that are inexpensive, easy to use, and effective at halting disease progression and inducing repigmentation. Corticosteroids (CSs) are consistently reported as the most effective single topical agent, with Calcineurine Inhibitors (CIs) being always a close second. Due to the possibility of local side effects of CSs, scheduled drug holidays are recommended.

In our experience focused micro- phototherapy (using 308 or 311 nm emission device) is the recommended treatment either when used alone and in combination with topical therapy. Topical CIs are effective as monotherapy in patients who do not tolerate topical CSs.

They are also effective for recalcitrant lesions on the extremities when applied nightly under occlusion. Current data does not support monotherapy with topical vitamin D3 analogs, but Vitamin D3 can augment the effect of topical steroids even in previously steroid non-responsive patients. Topical L-phenylalanine, topical antioxidants and mitochondrial stimulating cream, associated with natural sunlight with oral khellin have all been suggested as efficacious alternative first-line therapies.

When administered in patients with an active disease, a short course of oral or intravenous steroids can arrest vitiligo progression and induce repigmentation in the majority of patients. However, the optimal dose to maximize benefits and reduce the incidence of side effects has yet to be determined.

Second-line. A second - line treatment is considered when “first-line” one fails. Given the cost, time commitment required by patients and staff, and higher incidence of side effects, phototherapy is recommended as a second-line therapy for patients who fail conservative first - line treatment(s). Focused micro- phototherapy (308 or 311 nm) should be electively offered when cutaneous involvement is less than 15%. Narrow Band Ultra Violet type B (NBUVB) phototherapy produces the greatest clinical improvement compared to other forms of light therapy; combinations with topical therapy work better than either alone.

Topical C Is with NBUVB phototherapy have the best clinical outcomes compared to other topical adjuvant therapies. It is uncertain whether adding a vitamin D3 analog to NBUVB phototherapy enhances the effects. While inferior to NBUVB in terms of clinical response, both UVA and broadband UVB phototherapies with various adjuvant therapies are beneficial as alternative second-line treatments.

Third-line. Targeted phototherapy with the 308 nm Monochromatic Excimer Laser (MEL) is an effective as monotherapy, superior to NBUVB

phototherapy when compared side by side. However, it should be reserved for those patients, who fail NBUVB phototherapy, except in very limited disease, or in patients, who can afford the time and cost of the therapy. MEL works best in combination with topical CSs or CIs.

Fourth-line. Surgery should be offered when lesions persist despite appropriate therapy. There are many different surgical techniques available. While the specific technique will depend on individual patient characteristics and the custom practice of the expert surgeon, it can provide excellent cosmetic results for limited lesions recalcitrant to other modalities.

Special populations. Although patients with Segmental vitiligo (SV) have been studied alongside those with Non-Segmental Vitiligo (NSV), it is unclear how applicable study results refer to this population. SV tends to be more stable and recalcitrant to treatment. The He-Ne laser seems to be more effective in this population. Generalized/universal vitiligo may also require tailored treatment. The extent of the disease can be so great that it may be nearly impossible to provide cosmetically pleasing repigmentation. For these patients, depigmenting agents should be offered and discussed extensively for their non-reversible effects.

Considerations. At all stages of therapy, keep in mind that vitiligo can be a lifelong disease that may extensively damage one’ s psychosocial sense of wellbeing. Acknowledging this hidden impact of the disease on quality of life and offering support for dealing with it will improve the physician - patient relationship greatly and promote a positive outcome. Camouflage can always provide temporary cosmetic relief, and psychotherapy should be offered to help patients deal with the psychological disease burden.

An approach to treating a patient with vitiligo (treatment algorithm): we have divided treatment options into first-, second-, third-, and fourth-line options. The treatment order was determined by the level of evidence in literature for each treatment. Treatment options for special cases are also included.

Focused Micro-Phototherapy (PMP)

– 308 or 311 nm – has been included for efficacy and safety reasons in the “first-line” offer.

Question 12. Is it possible to stop the progression of vitiligo?

Key points

- *Localized vitiligo usually stops its progression in 1-2 years after its first manifestation.*
- *Generalized vitiligo is progressive in 73% of the cases.*
- *Administration of oral or intravenous corticosteroids may lead to cessation of the disease progression in 85% of cases.*
- *Vitiligo progression could be stopped in 4 out of 5 cases by the use of potent systemic corticosteroids, but due to possible relevant side effects, the decision must be taken by expert dermatologists after careful evaluation.*

Answer

Vitiligo is progressive in 73% of cases and regressive in 1.3%. We usually explain to the patients that progression depends on the modality of the disease spreading: localized or generalized forms have different behavior. In 89% of localized vitiligo cases, disease activity ceases after 1-2 years of rapid spreading over the affected skin area, while generalized vitiligo shows less progression only when it starts on the face (52% of the cases).

In 89% of cases we can arrest patch extension in widespread vitiligo with oral minipulse corticosteroid therapy (5 mg betamethasone on 2 consecutive days per week). Use of corticosteroid

methylprednisolone 8 mg/Kg intravenously for 3 consecutive days in patients with generalized vitiligo led to temporary cessation to the disease progression in 85% of cases and repigmentation in 71% of cases. Other steroids used intravenously showed a similar degree of limiting the disease progression.

Thus, it is true that vitiligo progression could be stopped in 4 out of 5 cases by the use of potent systemic corticosteroids. However, systemic corticosteroids might have possible relevant side effects, hence, the decision of their use for limiting vitiligo progression must be taken by expert dermatologists and after careful evaluation of the individual clinical situation.

Question 13. Depigmentation: when and how?

Key points

- *If after consistent treatment(s) for vitiligo, satisfactory repigmentation is not achieved, one can consider depigmentation to avoid the skin color contrast.*
- *Chemicals, such as hydroquinone and monobenzone, have been used as topical agents, with increasing doubts as for their safety profile.*
- *Many types of lasers (including Q-switched, alexandrite and Ruby Laser) have been used successfully alone or in combination with topical chemical depigmentary agents.*
- *Cryotherapy has been used with promising results, but pigment recurrence is always possible.*

Answer

Depigmentation is an option for vitiligo management that can be used when all repigmentation treatments have failed. The scope of cutaneous depigmentation is to reach a uniform (white or very fair) skin color.

Depigmentation is a process that destroys the remaining cutaneous melanocytes in the skin: patients should be aware that they will stay for the rest of their life with the skin that is not "their own skin".

It may happen that one cannot cope with extreme photosensitivity.

The ideal candidates for depigmentation are adult patients with few residual dark spots scattered over the face or on other visible areas of the body.

Children should not be considered eligible for depigmentation treatments.

Question 14. What are the individual factors associated with propensity to vitiligo?

Key points

- *Heridity: 20% of people with vitiligo report about a first degree relative as the one suffering from vitiligo.*
- *Human Leukocyte Antigen (HLA) haplotype may contribute to vitiligo susceptibility.*
- *A number of pathological conditions have been associated with vitiligo: their presence might be considered a propensity to disease development.*
- *The disease onset is frequently associated with stressful life events.*
- *Physical trauma of skin may induce vitiligo (Koebner phenomenon).*

Answer

It is well known that heredity is an issue in vitiligo propensity. In fact, around 20% of people with vitiligo report about a first degree relative as the one suffering from the same disorder. Children of a vitiligo-affected subject have a 1.7-fold increased risk of developing vitiligo compared with other family members. HLA haplotypes may contribute to generalized vitiligo susceptibility, i.e. HLAs -A2, -DR4, -DR7 and -DQB1 0303.

NALP-1 gene (NACHT leucine rich- repeat protein 1) is a major susceptibility gene that is epidemiologically linked to generalized vitiligo and other autoimmune diseases (i.e. thyroid disease, pernicious anemia, and lupus erythematosus).

Patients already affected by the following diseases are more prone to develop vitiligo (and vice versa):

Alopecia areata
Pernicious anemia
IgA selective defect

Thyroid autoimmune disease

Addison's disease

Congenital melanocytic nevi
MELAS syndrome (mitochondrial encephalomyopathy, lactic acidosis, and stroke episodes syndrome).

Stressful life events, probably interfering with the psycho-neuro-endocrine-immune system, and physical traumas of skin, including solar burns, may easily promote vitiligo onset in predisposed subjects.

Question 15. Surgical therapy for vitiligo: when and how?

Key points

- *Surgical therapy is usually introduced when medical or physical treatments of vitiligo fail.*
- *It consists in bringing melanocytes from pigmented skin area onto white patches of the same subject.*
- *Many different treatments are available including simple skin punch grafting, split thickness grafting, blistering roof grafting and the most sophisticated melanocytes or keratinocytes-melanocytes suspensions.*
- *The graft failure, scarring, infection, irregular pigmentation, cobble stoning appearance and vitiligo kobnerization phenomenon are always possible and limit the use of surgery in vitiligo.*

Answer

The surgical option in vitiligo is always possible, at least on selected/ limited depigmented areas.

Two main conditions are required:

– the white vitiligo lesion to be treated should be stable (i.e. avoid surgical procedures in lesions which are progressing – no progression of lesions or appearance of additional depigmentation must be evident for at least 2 years).

– the white area should be recalcitrant to the main and most effective medical and physiotherapeutic UV-based treatments (lights or lasers).

A number of surgical procedures are possible. Among these are the following:

- punch grafting and mini-grafting
- epidermal grafting
- dermo-epidermal grafting
- suction blisters grafting
- autologous melanocyte suspension transplant

– treatments with tissue - engineered skin

– cultured epidermis with melanocyte

They are considered to be the most popular procedures.

Neo-melanogenesis usually begins shortly after melanocyte graftings or transplantation and continues for a few months at a slow rate.

UV exposure (with lamps or natural sunlight) induces faster and deeper repigmentation after surgery. Surgical techniques offer repigmentation that is not often comparable with normally pigmented skin. They are always invasive procedures. Final results vary considerably from patient to patient.

The psychological aspect of the subject who requires surgical/invasive procedure must be always evaluated and patient's expectations must be clearly discussed.

Thus, the decision of starting a surgical procedure for vitiligo must be always a well balanced and informed decision.

Question 16. Tattoo for vitiligo patches: when and how?

Key points

- *Cosmetic tattoo represents the standard treatment for achieving permanent camouflage in vitiligo areas.*
- *It is especially helpful for mucosal vitiligo.*
- *Adverse effects must be considered.*

Answer

The tattoo is currently adopted by the general population for ritual or symbolic reasons. It consists in introducing micropigments into dermis, i.e. inerting iron oxides that are considered to be unable to migrate. The micropigment implanted into skin cannot be washed off, but its colors fade naturally in 24-36 months.

Cosmetic results depend on doctor's or technician's skill in matching the color of the tattoo with the color of the surrounding normal skin.

Dark skinned people usually have better results than fair skinned individuals.

Adverse effects that have been reported include recurrences of herpes simplex infection, chronic granulomatous reactions to implanted pigments, allergic reactions, koebnerization, imperfect color matching and, in our experience, also cutaneous pseudolymphomas.

Question 17. Should I take topical or oral antioxidants for vitiligo?

Key points

- *There is some growing evidence supporting oral antioxidants supplementation, specifically associated with UVB irradiation of the skin.*
- *There are no defined dosing parameters and side effects profiles studies on antioxidants oral supplementation in vitiligo subjects.*
- *Polypodium Leucotomos (a fern of the American subtropics), Ginkgo Biloba, cucumis melo, alpha lipoic acid, vitamins C and E, polyunsaturated fatty acids, phenylalanine and other natural substances have been assumed per os with the sake of elevating systemic catalase activity in blood and, thus, decrease the levels of reactive oxygen species. Recently curcumin alone or in combination with capsaicin and resveratrol have been shown to contrast vitiligo actively.*

Answer

There is a clear inclination of the experts in the field of vitiligo research toward considering that appearance and progression of white patches are related to a global unbalanced activity of the scavenger mechanism (s), which decreases the levels of reactive oxygen species (ROS) both in blood and in skin of the vitiligo patients.

Thus, both local and systemic use of substances that are able to decrease the levels of reactive oxygen species have been repeatedly proposed.

Most of these substances are mentioned in the Key points section of this paragraph.

In general, while some studies show remarkably good results in repigmentation after

the use of local or systemic “natural antioxidants”, other studies show no benefits.

The Dermatological Scientific Community seems to encourage both per os and local use of the “natural antioxidants” for treating vitiligo.

Nevertheless, defined dosing parameters, double blind consistent studies on efficacy and safety profiles of these natural substances are not clarified yet.

A book on “Natural Antioxidants in General Medicine and in Dermatology” co-edited by the present Authors will be available soon for the VRF audience.

Question 18. What does “treating vitiligo with catalase” mean?

Key points

- *Established medical treatments for systemic vitiligo are usually chosen for inducing local and/or systemic reduction of the immune system (=immune depression).*
- *An alternative therapeutic option is based on the concept that instead of inducing local and/or systemic immunodepression in vitiligo subjects, one can introduce substances rich in catalase activity in order to protect melanocytes against the excessive oxidative stress.*

Answer

Catalase is a substance well known for its antioxidant properties.

It belongs to the group of oral and local antioxidants, which have been listed and discussed in the previous chapters. The subject is exhaustively discussed in the book “Natural Antioxidants in General Medicine and in Dermatology” , available as e-book for the VRF audience.

This substance is usually of natural origin and its use is combined with ultra violet irradiation of the skin.

The Dead Sea climatotherapy associated with topical pseudocatalase seems to be as effective as the use of potent local corticosteroids in inducing repigmentation.

Thus, this issue should be discussed by the patients with their dermatologist before starting any active treatment with chemical drugs, which induce immune depression, keeping in mind that unfortunately defined dosing parameters and possible side effects have not been fully elucidated yet for those substances with catalase activity.

Question 19. What are the main side effects of vitiligo treatments?

Key points

- *Topical and systemic treatments of vitiligo may have different side effects in different subjects.*
- *Topical potent corticosteroids are considered to be first-line therapy. Erythema, acne-form lesions, atrophy of the epidermis, teleangiectasia, striae distensae and increased hair growth are commonly reported.*
- *Topical calcineurine inhibitors (Tacrolimus, Pimecrolimus) commonly induce erythema, burning, and irritation. In spite of some circulating information, to date there is no convincing evidence suggesting that there is any increase in skin cancer after their use in vitiligo subjects.*
- *Vitamin D3 analogs may only produce mild irritation on the treated skin.*
- *Topical psoralens are highly phototoxic even in very low concentrations after UV exposure: blistering and skin necrosis may be seen.*

Answer

Treatment of vitiligo is a complex issue which always requires a clear and exhaustive explanation of side effects of both systemic and local treatments.

Each vitiligo patient should ask the dermatologist about the length of the treatment(s) as well as possible side effects.

The discussion of any systemic treatments of vitiligo requires always a discussion in private between the vitiligo patient and her/his dermatologist in a most empathic and cooperative setting based on clear questions and clear answers.

Hopefully, this mini-book will help the patient(s) in rising clear answers to the dermatologist to achieve better understanding and treating vitiligo.

Question 20. Camouflage: when and how?

Key points

- *Cover-ups should be considered in global approach to vitiligo, mainly in those cases when vitiligo subjects cannot overcome the emotional stress deriving from their skin change.*
- *Corrective cosmetic products used for camouflage can be cover creams, instant self-tanning topicals, stains and dyes.*
- *Camouflage can be just temporary (make-up), semi permanent (self-tanning topicals) or permanent (tattoo).*
- *Camouflage and active treatments for vitiligo may be combined.*

Answer

Most therapies for vitiligo may require treatment periods lasting for months or years before repigmentation eventually occurs.

Thus, palliative treatments could be used in the meantime, with considerable improvement in quality of life of vitiligo-affected subject .

Sunscreens are usually added to most of those cosmetic products in order to avoid sunburn.

The vitiligo patients should know how many different topicals are available for them on the market, and should become familiar with different methods of application and cleaning.

Cover creams, stick correctors, tinted cover creams and fixing spray applications on the vitiligo-affected areas require expert recommendations in order to get optimal results.

Permanent camouflage is obtained with cosmetic tattoo, usually done by implanting iron oxides pigments into the dermis.

Colors of the tattoos naturally fade over years, thus, they require periodic maintenance, usually every 30 months.

The quality of life of vitiligo subjects is usually improved significantly by use of cover-ups, which can temporarily cancel vitiligo areas and give vitiliginous skin a natural color.

Unfortunately, reliable clinics devoted to acknowledgeable application of camouflage in vitiligo are not always available.

Question 21. Psychotherapy: when and how?

Key points

- *Vitiligo is a distressing disease because of its perceived stigma, cosmetic disfigurement and chronic relapsing course.*
- *In certain cases treatment of psychological rebound may both improve the self-esteem and clinical outcome: this must be started in the "liaison consultation" room where the subject will be simultaneously in contact with the dermatologist and the psychotherapist.*
- *Cognitive behavior therapy may be appropriate in certain cases.*

Answer

Vitiligo is often considered to be emotionally triggered both by the affected subjects and doctors.

An incubation period of 2-3 weeks between the stress event and clinical manifestation of vitiligo patches is reported by over 70% of patients.

Even the localization of white patches has been anecdotally but significantly reported as related to specific affective relationships.

Thus, according to some reports men who had been betrayed developed vitiligo on the genital areas, women who did not accept their pregnancy developed vitiligo on their abdomens.

It is illuminating as for the case of a woman who developed vitiligo on hands in a few hours after cleaning the sheets where her son's girlfriend had been aborted.

These are obviously anecdotal reports in medical literature, which are of very limited "per se" value, but are clearly disclosing possible general psycho-somatic pathways, which could drive the researchers onto the causes and to the cure of vitiligo in not yet explored psycho - neuro - immune endocrine territories.

Nobody ignore the burden of somato-psychic rebound of vitiligo into the psyche of the affected subject.

Vitiligo subjects may adopt (more or less consciously) different behaviors to cope with vitiligo.

Some will adopt the "mastery active" psychological mechanism consisting in reading, studying and researching actively the causes of the disease.

Others will behave as "natural acceptors" showing good self-esteem and not trying to hide their skin lesions.

Others instead will make heroic attempts to hide their white spots, will be always embarrassed and often depressed. These subjects could limit their social contacts and could lose their job because of vitiligo.

While examining any vitiligo subject and discussing therapeutic options, each skilled dermatologist will try to understand both the psycho-somatic mechanism inducing the appearance of vitiligo patches (if any) and the somato-psychic rebound of the disease over self-esteem and quality of life of each individual subject.

Thus, should the dermatology always or often refer each and every vitiligo patient to the psychologist or the psychiatrist?

Hard to say no, but it is harder to say yes.

If the vitiligo patient has chosen the dermatologist for "superficial and deep" assistance regarding understanding of his/her surface and depths, the dermatologist cannot give up.

The dermatologist must always respond to the request of the patient by giving the complete full care which has been requested, including supplying proper counseling.

"Forcing" the patient to visit another (non-skin) specialist is, in fact, dangerous.

Immediate insensitive referral of skin patients to a psychiatrist can even lead to suicide ideas in too sensitive subjects, as it has already been reported in literature.

Thus, when a psycho-intervention will be considered "necessary", the dermatology should use the "liaison consultation" practice of getting the patient into close collaboration with the psychiatrist-psychologist. It will be a direct contact of two to one: the vitiligo subject, the dermatologist and the psychiatrist.

Only later on, the two experts will have the full right to treat the same patient separately, with expected excellent results.

In this context, it seems that the cognitive behavior therapy will give fair results versus different psycho approaches.

Future trends. New concepts in vitiligo treatment

Key points

- *Is vitiligo a single disease and will the cure be identified as such?*
- *Or, conversely, does vitiligo include a spectrum of different disorders with different causes, all manifested by white patches on skin but requiring different treatments?*
- *Will genetic studies bring to discover the cure for vitiligo?*
- *Will vitiligo patients have access and financial support to cope with the inherent cost and effective treatment modalities?*
- *What will be the role of Cloud Medical Research Management (MRM)?*
- *What's new on the horizon of vitiligo therapy and cure?*

Answer

This is the only section of this booklet in which all key point sentences are followed by a question mark.

The statement “the cause of vitiligo still remains unknown” should always be followed by the sentence “because in each single vitiligo patient a different process may be involved in the production of white patches onto his/her skin”.

In other terms, the same white spots on the skin of different subjects, which will be diagnosed by the dermatologist as “vitiligo”, most probably are related to several different mechanisms affecting melanin production, release and removal in the skin. Vive la difference!

According to this, there will be not one form of “vitiligo”, but more forms of “vitiligos”, affecting different subjects, and all manifested similarly or identically as white patches on skin and/or on mucosal areas.

This concept excludes “leukodermas”, i.e. those white patches of the skin of known origin.

It is implicit that different forms of vitiligo will require different treatments and, eventually, different cures.

It is also implicit that today “combined treatments” are the most rationale choice for treating any individual case.

It is hard to say if genetic studies will bring to the direct discovery of the vitiligo cure. Most probably, this will not happen soon. Identical twins with identical DNA have only 23% concordance in developing vitiligo, suggesting a significant environmental and non-genetic component of the disease.

Genetics will probably help us in identifying different subpopulations of the subjects affected by “white patches on skin and/or mucosal areas” and diagnosed by the dermatologist as “vitiligo” which will need different investigations, different treatments and probably completely different cures. This could be the best current goal of genetic testing in vitiligo subjects, with excellent perspective. In addition, genetics might be helpful in predicting treatment success, thus, allowing to choose the best therapy for a particular individual.

The cost and accessibility of therapy must be considered when choosing a treatment plan for vitiligo. Presently, a vast majority of the vitiligo subjects have heavy financial limitations for proper treatment according to already existing treatment protocols.

This problem will probably become more acute in the nearest future, due to the progressive recession in the economy of many countries and relative increase of the cost of the effective treatments for vitiligo.

Thus, on the horizon of vitiligo therapy and possibly of vitiligo cure we see a complex interaction of different overlapping ingredients including identification of the specific form of vitiligo (classification and genetics), evaluation of the inherent biological pathways that have produced white skin patches in any individual case (pathophysiology) and, finally, selection of the proper treatment (treatment and, hopefully, cure).

This last issue is already showing (and probably will be more in the future) how cost and accessibility of therapy must be considered when dealing with a lifelong (presently) disease which affects “democratically” all populations in the world.

Most of the affected subjects will probably have financial limitations for proper treatment/cure of «their» vitiligo.

On the horizon of vitiligo therapy and cure we see a complicated puzzle with some essential bricks already well positioned and installed in their right places.

For the rest, the Scientific Community, the Vitiligo Patients Associations and the Foundations devoted to vitiligo are requested to coordinate and harmonize their strategies and efforts for winning the battle against vitiligo, by completing the puzzled image.

The Vitiligo Research Foundation (www.vrfoundation.org; www.vitinomics.net) is committed to keep you always informed on the ongoing research and on treatments available for vitiligo.

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Vitiligo. Questions and Answers.

Part 2 by Prof. Antonio Salafia, MD

Introduction

Vitiligo is an acquired skin pigmentation disorder, which causes both physical defect and psychological distress in patients, more often in dark-skinned individuals. It has been known for several thousands of years. Apart from aesthetic changes, vitiligo is not life-threatening or contagious. However, it can change a patient's quality of life.

Vitiligo is a multifactor disease, i.e. many

factors are involved in causing this disease. Some authors think that it is hereditary, but there is no definite proof for it. I agree that in some patients, there might be a congenital predisposition to the disease, but it will be discussed in detail later. Occasionally, there may be other diseases associated with vitiligo, however, it is rather an exception than the rule. At the same time, similar to many other diseases, there can be accompanying ones.

Chapter 1. Introduction. Skin color

The normal skin color appears to be the dark one; the light color is a mutation. There are more genetic differences in the African race than in the White race, and there is a larger gamma of hues in "darks" than in "whites"; it also speaks in favor of the theory that "Black hair, brown eyes and dark skin color must be considered the primordial state for humans".

Final skin color is determined by interaction of four pigments:

- a) Yellow: produced by carotenoids (called as they are found in large quantities in carrots).
- b) Brown: due to melanin.
- c) Red: this is the color of oxygenated hemoglobin in capillaries.
- d) Blue: the color of hemoglobin – with less oxygen – in venules.

Among all, melanin is the major component of skin color, which depends on the number, type, and distribution of melanosomes and even their size.

Other elements contributing to skin color include: thickness of the skin, of its top layer in particular, the velocity of blood flow, oxygenation level of the circulating hemoglobin and exposure to UV light. Finally, the color of skin depends not only on the production of melanin, but its transport, too. Any cell capable of producing

melanin can be called a melanocyte, but in current use, the name melanocyte is used for those cells that originate from the neural crest (the area in the fetus from which the spinal cord develops) and possess tyrosinase enzyme.

We already know that hair acts as a depot for melanocytes and, clinically, we notice that hairy parts of the body undergo repigmentation earlier and faster. Melanocytes are not equally distributed in all anatomical areas of the same individual. There are between 1,000 and 3,000 melanocytes per one square mm of skin area, with higher density in forehead, cheeks, nasal skin, face, lips, penis and scrotum. Thus, it is evident that areas that contain more melanocytes have better chances for earlier repigmentation than those with lower melanocyte concentration.

Blood supply is also related to the rate of repigmentation – as it has been already noted by Protá. Blood supply in fingers and toes is about 25% less than in other parts of the body. Our face has the highest blood supply and it is not surprising that almost in all patients it is their face that repigments the earliest and fastest.

Exposure to sunlight (or artificial UV light) increases skin color, and for this reason in case of vitiligo exposure to sunlight – in moderation – is not optional, but an integral part of treatment. Too much sunlight, however, can damage our skin, which will be discussed later.

Chapter 2. The first question coming to mind: who gets vitiligo?

The answer is not simple or straightforward. At present, there is no sufficient evidence to say that the disease is more common in certain races, communities or geographical areas. One thing is certain: vegetarian and non-vegetarian diet does not make much of a difference, except that vegetarian diet may be poor in certain important vitamins. However, as I consider vitiligo to be primarily a metabolic disorder, the possibility that diet, fasting, intestinal parasitosis, and presence of any other metabolic disorder – like diabetes mellitus – can complicate and aggravate the problem. Let us examine various epidemiological parameters one by one.

To my knowledge, no systematic epidemiological studies have been done in vitiligo; most of the statistics are done by dermatologists and the percentages reflect one of vitiligo patients out of all dermatological cases.

Therefore, we cannot be absolutely certain about the Prevalence (the total number of patients at any given moment) and Incidence (the number of new cases per year) of vitiligo in a given population.

Conclusions of the Epidemiologists are often biased by limited experience and/or relatively small number of patients examined.

The prevalence is variously quoted at 0.5% – 2.00% worldwide; 1% in the USA. It is said to be 1% in Europe, 4% in India, and 0.38% in Denmark.

Nobody knows how much these statistics are worth; there is exaggeration in both directions, by

those who underestimate the problem and by the ones who overrate it.

My statistics are also a percentage of all skin cases registered at Vimala Dermatological Centre (VDC), other charitable hospitals and my own consulting room. Due to the fact that my treatment is totally different from the one usually prescribed by other dermatologists, it arises that at VDC there is a different and effective treatment, which is true.

As a consequence, I see a large number of vitiligo patients. Many records are lost due to various reasons, however, at present in my computer I have complete records of more than nineteen thousand patients. About 20% of my patients are from various parts of India, and a few hundred are from abroad. Having evaluated the records of the previous 15 years, I can say that the prevalence is about 8% and the annual incidence is 11.7%. To reflect the national average, my statistics have to be downsized for the reasons just mentioned.

I consider prevalence of 4-5% a figure more close to the reality of India. However, it does appear to be that the incidence of vitiligo is increasing slowly but steadily for reasons yet unknown; I can venture to say that pathogenesis of vitiligo is contributed by free radicals (as we'll see later), as well as pollution, adulterated food and edible oils, certain diets, stressful life... All of them may contribute to the frequency of the disease.

Chapter 3. General prevalence

The prevalence in general population depends on various factors:

1. Awareness of the patient and the doctor, level of patient's concern, which, in its turn, is influenced by the relatives, society on the whole, and the volume of patient's psychological trauma.

2. Possibility of access to medical care; it is evident that in many remote areas – and there are a few of them in India, Africa and Australia –

2. there are no doctors, and people, by and large, are not concerned about their color when there are many more serious diseases to deal with. Let us have a look at some reports from different parts of the world.

AFRICA: in Nigeria the rate quoted is 6% for the period of 1980 –1983. Approximately 70% were aged under 30. Again in Nigeria in 1985 – 1998, Benin City, only 3.2% out of 351 dermatological cases, were vitiligo.

INDIA. The first comprehensive study was done in Calcutta by Das et al., and they found a prevalence rate of 1:1000 in 15,685 patients. In Saurashtra it was said to be 2 % in 400 skin patients. At the same time another author gives a prevalence of 1.13% in Surat. In Pondicherry the prevalence is quoted as 2.6%. Shajil says, "The incidence of vitiligo is found to be 0.5-2.5% in India with high prevalence of 8.8% in Gujarat and Rajasthan states".

BANGLADESH. Khan is right to say that the incidence of vitiligo varies from country to country; the prevalence in his country is 0.4%.

KUWAIT. While analyzing 10,000 patients, Nanda has found that vitiligo is quite low against Atopic Dermatitis.

KOREA. Ahn investigated Korean vitiligo patients and healthy Korean volunteers. Compared to normal controls, patients with lighter skin color had much lower prevalence than the ones with 'darker' skin type.

SAUDI ARABIA. One paper quotes a prevalence of 5%.

EUROPE. A study done in older population in north Europe revealed that vitiligo had a prevalence of 1.2% against 2.9% of Psoriasis. A few years ago one author said that there were 500,000 cases of vitiligo in the whole UK. In Denmark, out of 47,033 cases examined, the prevalence of vitiligo was 0.38 %.

Chapter 4. Age at onset of the disease

The age of onset of the disease has also been a subject of many papers. Here again the observation made at the beginning of the chapter is valid. I quote only a few authors.

Onset at birth has been reported. Handa reports the mean age of 25 years. Cho says that the mean onset age is 5.6 years. Prcic gives the mean age of 7 years. Handa in his study involving 182 elderly patients, found the mean age of 55. Bleehen, in the UK, says that it is present before the age of 20, and this has become a sort of leitmotiv with other authors, who keep on quoting him without saying whether they themselves have done a survey in their country or not.

I have 4 cases of onset at birth, 8 cases of patients aged 80 and one patient aged 97!

From all these papers, which, in many cases, are representative of a small number of patients, we conclude, in a more practical and pragmatic way, by saying that the disease can start at any age; in my series the highest incidence is in the age group of 20-30.

A detailed analysis of my data shows a crescendo for female-child till the age of 17, after that the male patient's prevalence surpasses the female one. In brief, sex, religion, and socioeconomic status do not seem to have any influence. Occupation, in some patients, is a precipitating factor, as we will see later on.

Chapter 5. Familial incidence

The studies of the Italian author Frati are of great interest: he has found a familial incidence.

Alkhabeet writes about family in a non-Mendelian pattern suggestive of multifactorial, polygenic inheritance. Some Indian authors say that it is as high as 13.8%, while others put it at 2.55% (Apte in Mumbai). Such a considerable difference!

In the 1930s and 1940s it was sustained that vitiligo is not hereditary. More recent authors believe that there is a strong familial relation.

However, the majority of modern authors have drawn their conclusions basing on a small sample and the one limited to a particular geographical area or community. There is a report in medical literature of vitiligo present in two dizygotic twins (= false twins). Further, there is a recorded occurrence of a different variety of vitiligo in two monozygotic twins (= true twins). There are cases of monozygotic twins where only one of the siblings was affected by vitiligo. I have recently come across two monozygotic male twins aged 12; only one of them has vitiligo

and the other – even 3 years later – does not show any sign of vitiligo; and another example of two female uniovular twins: only one of them has vitiligo for 2 years. Alkhabeet says that there is a certain genetic component, but the concordance of vitiligo in monozygotic twins is only 23%, indicating that a non - genetic component also plays an important role”. Neumeister reports on a case of vitiligo that developed in a 50- year - old man 9 months after transplantation from his identical sister who had had this disease for several years. There are authors who believe that childhood vitiligo is mostly associated with family history.

My series, which is representative of almost all Indian States, and a few hundred from other parts of the world (Saudi Arabia, Dubai, Muscat, South Africa, Italy, the UK and the USA), shows a low familial incidence, in fact it works out at 2.94%, which is even lower than the prevalence quoted in general population in certain parts of India. However, I adhere to the opinion of congenital predisposition, which is not necessarily genetic, or if it is genetic, it has to be a polygenic inheritance, as suggested by Alkhabeet and other authors.

Chapter 6. Precipitating factors

A large number of patients claim that the disease appeared – or spread – from one tiny patch to a wide pattern, after severe physical and / or mental stress. These are called ‘precipitating factors’, because they are not the cause of the disease, but induce its development. Stress, in this case, cannot be considered to be the ‘cause’ of the disease, but rather a contributory factor or a ‘precipitating factor’.

The list of precipitating factors is long and can be divided into four sections, such as:

1) Physiological

a) Menarche or first occurrence of menses. This could justify high incidence in young girls.

b) Pregnancy, delivery and menopause. In all these cases the female body undergoes stress, and, moreover , there are certain hormonal changes. Oestrogens are known to increase skin color; decreased level of these hormones – as it occurs during menopause – could explain the increased rate of vitiligo patches in menopausal ladies.

2) Pathological

Parasities, like Helminths , Amoeba and Giardia Lamblia. It is rather evident that intestinal parasites upset normal functioning of the digestive system.

b) Bacteria and fungi. Many young girls with vaginal vitiligo have a history of a fungal infection called candidiasis. The same is true in case of penile vitiligo . Vitiligo is known to be a consequence of Tinea Versicolor

(another fungal infection), which does interfere with melanogenesis.

c) Viral disease. I do have a number of cases where vitiligo developed in patients previously affected by Herpes Zoster. There are a few patients who have developed a white patch on their lips after Herpes labialis.

d) Typhoid fever, malaria, jaundice. These diseases are stressful to such an extent that it is not surprising to have other diseases arising as consequences of these major body alterations.

e) Chronic gastritis and low level of gastric acid have been found in some patients. Here we also can see impaired absorption of important and vital elements.

f) Hepatitis. The relation is not clear, though there are authors who believe that the evidence is compelling. A few years ago I met a general practitioner who achieved good results in vitiligo control (if not cure) by using Essentiale, a liver-protector.

g) Thyropathies. This, in theory, can make vitiligo worse, as it has been explained earlier.

3) Psychological factors

Death of one’s dearest, loss of job and/or family unhappiness are all stressful, often to the extreme. In this case Interleukins are involved and some clarifications will be given later.

The role of stress has been highlighted by various authors, however there is no consensus yet. Some of them say that stress may alter the immune system and, hence, plays an important role in precipitating autoimmune diseases in patients predisposed to them. Fisher reports on a case of vitiligo as a consequence of persecution.

Several authors have reported on poor quality of life in vitiligo patients. It is self-evident that vitiligo, or any other disfiguring disease, would have a certain impact on the patient's life. This is more so in dark-skinned individuals, where any vitiligo patch shines like a star; in India there is one more problem: common people confuse vitiligo with leprosy and this adds a certain amount of scare, because leprosy is a 'curse from God'. I have seen young girls forced to divorce because of this disease, and I have seen young men contemplating suicide because they could not find a life-partner.

4) Chemically-induced Vitiligo

A number of chemicals can be blamed for causing and/or precipitating a Vitiligo patch in a patient who has a disposition to the disease. Vitiligo due to para-tertiary butylphenol was reported in 1971 from St Johns Hospital of Dermatology in London and soon after that in Germany by Rodermund who reported vitiligo associated with hepato- and splenomegaly and goitre in three patients working in a factory producing para-tertiary butylphenol. From then on, a number of authors have found a causal relation between a form of chemical vitiligo, indistinguishable from vitiligo vulgaris, and para-tertiary butylphenol.

Various dyes have been reported to cause vitiligo, such as:

1. Azo dye in Alta; Alta is a scarlet-red solution used by Indian women as a cosmetic colorant for their feet.

2. Hair dye.

3. Rubber, in various industries, tyre assemblers, in particular, as they often deal with a rubber antioxidant. Rubber footwear has been also blamed for chemical vitiligo. In these cases chemicals have been identified as typical allergenic accelerators in children's rubber shoes, ladies' rubber boots and ladies' canvas shoes. Rubber and plastic chappals are a well-known cause of vitiligo in India.

Therefore, a possibility of penis vitiligo development can be, in part, due to rubber condoms, at least in patients who are predisposed to vitiligo. The same can be said about contact with plastic purses and plastic glass-frames.

4. Cinnamic aldehyde in toothpaste and the adhesive used to stick Bindi. Epoxy resin in dental acrylic materials. Nickel gives rise to contact dermatitis manifested as vitiligo.

5. A large number of drugs have been associated with vitiligo:

- a) Chloroquine.

- b) Hydroquinone, present in photographic developer, and monobenzene.

- c) Alpha-Interferon, used in treatment of active hepatitis C.

- d) Even corticosteroids have been blamed and it is common experience – I have 19 such cases of chemical vitiligo developed after extensive and long-term use of Betnovate cream.

- e) Levodopa used in treatment of Parkinson's disease.

- f) Beta blocking drugs (such as Atenolol) may exacerbate vitiligo

- h) Proton Pump inhibitors, such as Lansopran, used to treat gastric problems.

Chlorine-induced Vitiligo is not a rarity. Chlorine is found in excess in swimming pools which are not scientifically purified and maintained; I have three young girls and two boys – without family history of vitiligo – who clearly ascribe the development of vitiligo to the swimming pool used on daily basis for 2-3 months. A patient of mine attributed his vitiligo of lips to Alum, used to clean teeth!

Alum was used as a base in skin whiteners during the late 16th century.

Ghosh et.al. have recently done an interesting and detailed study of some of the chemicals known to cause leukoderma, and individuals at risk. They list among others: hair dyes, deodorants / perfumes, adhesives (bindi), rubber sandals, black socks / shoes, eyeliners, lipliners, rubber condoms, lipsticks, cuddly toys, toothpaste, and insecticides.

Most common and generally used items include:

Rubber gloves	12%
Lubricants and motor oils	6.8%
Detergents	5.3%
Printing ink	3.6%
Chemical laboratory agents	1.5%

Every dermatologist in India has come across a vitiligo patch localized on the left breast in some women: often ladies hide their money-purses in the brassiere. Vitiligo due to Bindi (the beauty spot Indian ladies like to wear in the middle of the forehead) is common experience, and when patients are told to avoid it, not all of them agree

because of pressure from relatives and in-laws: married young girls in Maharashtra have to wear a Bindi.

Patients often ask: "When do I stop getting white patches?" Well, it is difficult to predict the course of this disease; in a good number of patients – as I have noted – the disease goes on for 3-4 years and then it settles down, with one or two stubborn patches and the clearance of the others, but there are patients in whom the disease has certain periods of stability and then suddenly starts increasing. And there are patients – very few indeed – who gradually and inevitably turn completely white, some of them porcelain-white, others - white similar to Caucasian skin color. The natural course of vitiligo is unpredictable.

Chapter 7. Treatment and management. Introduction

Treating vitiligo is not always easy and sometimes it is an 'art'. It is very exacting to the attending doctor, the patient and his/her family. Both, the patient and the doctor have to appreciate the difficulty, as this disease is a complex one, so is its treatment, moreover, though it looks like one disease, in reality there are various forms of the same disease and they need to be treated differently. It is not only a question of tablets and creams, moral and psychological support are also needed, as well as the will and confidence, on the part of the patient, that cure is possible.

Nothing boosts the moral of the patient like some fast changes. If the patient does not see any

noticeable changes after 2-3 months of therapy, he/she is bound to get discouraged and discontinue the therapy.

As there are various forms of the disease, treatment cannot be uniformly the same; human face and hands cannot be treated with the same creams, as we will see later on.

Vitiligo requires much motivation in the patient because treatment is sometimes long and demanding; sun exposure is not always possible, in women in particular, and, hence, the major component of the treatment is missing. Dietary restrictions are not always possible, especially for those who live in a hostel or a boarding school.

Chapter 8. Treatment and management

First of all, let us have a critical look at various types of treatment and after that I will express my opinion and make some suggestions.

1. Steroids. Either locally or orally have been suggested. Steroids alone are not curative, they are used only for one purpose: to stop the inflammation, which is often present in vitiligo, and suppress antibodies (if present), but taken alone they do not cure the disease. However, steroids along with my treatment have given good results as I will describe later on. Steroids applied as creams/lotions do give good results, but cannot be used for too long because of their side effects like thinning of the skin, stretch marks, etc.

2. PUVA. PUVA stands for Psoralen+Ultraviolet light A, while PUVASOL means Psoralen+Sunlight. Psoralens have been used, in India, by el-Mofty the Ayurveda doctors from times immemorial. During the late 1950s American dermatologists, started using Psoralens and soon they realized that the beneficial effects of Psoralens were enhanced by exposing the patient to sunlight for 15-20 minutes after the intake of a psoralen tablet. PUVA does have some common side effects and some rare ones. Common side effects include liver damage and cataract.

TREATMENT

After trying, for years, Psoralens and other modalities – with disappointment – I went into search of other forms of treatment. In 1983 I came across the studies of Frati, who proposed the theory of 'metabolic disorder' and showed the importance of Vitamin B6 in Vitiligo. At the same time I came to know that in a leprosy-hospital in Andhra Pradesh, they were using Dapsone for leprosy treatment.

The importance of Copper – as a component of Tyrosinase enzyme – and Iron have been highlighted by many authors. A research worker, Prota, has written extensively on the role of Peroxidase. Putting together all this information and ideas I worked out a protocol, which is included into my book, and is available now from me, but soon can be also purchased through the Internet.

SUGGESTION FOR TREATING VARIOUS AREAS OF THE BODY

Face: Hydrocortisone butirate 0.1% should be applied in the morning followed by an exposure to sunlight and also at bed time. It is good both in children and adults. If this does not work, you can try TACROLIMUS 0.1% (not 0.03%) in the morning plus sunlight and again at bed time.

Neck: I advise the same as above.

Body: Daivonex and UVB should give good results. You can also try Tacrolimus with NBUVB.

Arms: Clobetasol along with Salicylic acid 4% can give good results, but should not be used for more than 2-3 months. Results are better with NBUVB along with Clobetasol.

Fingers and toes are difficult to treat, but I am still working on it and I hope to give you a different modality of treatment soon: in about 3-4 months I will be able to offer you an effective treatment for these difficult areas. Surgery is the last resort.

I prefer free skin grafting, which gives good/ acceptable results. Punch graft has proved to be good, if the area is small, but it is not good for big patches and at any rate the results depend a lot on the experience and technique capability of the surgeon.

Melanocytes transfer – whether cultured or non cultured melanocytes - is a good choice, but it does not come cheap, a laboratory is required, as well as specialized personnel.

Concluding remarks

The pathogenesis of vitiligo is still a puzzle awaiting for its solution.

Recent research has demonstrated lacunae in each of the hypotheses so far proposed. Therefore, a unifying theory that will take into account older hypotheses and contemporary findings about the role of T-cell, cytokines, Langerhans cells and various other factors, is needed. Segmental vitiligo most likely represents a localized form; chemical vitiligo is an entity in itself, so is the Palmo-plantar vitiligo, so often noticed in India.

The treatment should be aimed at correcting the disorder more than 'tanning the skin'. For all these years, 24 or so, I have tried a great number of therapies and finally have made my choices and completed my protocol; but I am still open to new suggestions. With my protocol the results are excellent in about 80 % of patients, provided that they follow all the instructions, including sun exposure.

There are some failures, like in any branch of medicine. There are patients who do not seem to respond to any therapy and this is a drawback that stimulates us to continue our study and try new avenues. It is a fact that even though the disease appears to be one and the same, there are certain varieties, like segmental and palmo-plantar ones, that require a different treatment.

Patient's co-operation and his/her will to cure is extremely important. I can say that today there are thousands of patients who have taken my treatment faithfully and are totally cured. So, there is a hope, there is a treatment; both patients and doctors must be willing to follow the instructions religiously and 'be patient'...there are no miracle cures. Surgery, related to vitiligo, is an interesting development and many dermatosurgeons are trying to improve on old procedures, while exploring new paths. Today, dermatosurgeons have a wide choice of procedures, but training, experience and appropriate equipment (for some procedures) are required to achieve good results. However, when all is said and done, surgery is not the first choice, and this should be clear to the doctor and explained to the patient. I have seen, over the years that medical treatment – in those patients who respond to it – gives the best results in color matching, which surgery can hardly achieve. That is why, when patients come to me requesting a surgical intervention, I insist on trying a medical approach first. If, after 6 months or so, the medical treatment does not give any significant results, then and only then I suggest a surgery.



About Prof. Torello Lotti, MD

Prof.Lotti is Full Professor and Chairman of the Dermatology and Venereology Division at the University of Florence School of Medicine, Florence, Italy.

He graduated in Medicine and Surgery cum laude in 1978 from the University of Florence School of Medicine, Florence, Italy. He completed residencies in Dermatology and Venereology (cum laude) in 1981 at the same School. He postgraduated in 1983-84 as Resident Medical Doctor at the Dermatology Institute, London, UK. He is currently Full Professor of Dermatology, Dept. of Critical Medical Surgical Area, University of Florence, Italy, and Chair, Resident Program in Dermatology, University of Florence, Italy

The fields of his principal scientific investigations are Neuropeptides, Vitiligo, Vasculitis, Psoriasis, Cosmetic Dermatology, Dermatologic Fisiotherapy.

He is Visiting at: Thomas Jefferson University, Philadelphia (PA, USA), Charles University (Prague, Czech Republic), Bowman Gray University (NC, USA), University of Louisville (KY, USA), Medical University of South Carolina (SC, USA).

His past activities in serving Dermatology have been numerous, among which are: Past-President of the Italian Society of Dermatology and Venereology (SIDeMaST , 2009-2010) and the Past President of the International Society of Dermatology (ISD, 2009-2010)

President of the European Society for Cosmetic and Aesthetic Dermatology (2003-2004)

Editor in Chief of the Journal of the European Academy of Dermatology and Venereology (1992-2002)

President of the 13th Congress of the European Academy of Dermatology and Venereology (2004)

Chairman Congress Forum of the American Academy of Dermatology (1999-2006)

Editor in Chief, "Psoriasis", 2006-

Chief Editor of the Giornale Italiano di Dermatologia e Venereologia (2010-2020)

Section Editor "Dermatologic Therapy", 2007-

Regarding scientific publications, he has authored 1054 papers (393 peer reviewed articles, 288 books chapters, 363 abstracts).

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About Prof. Antonio Salafia, MD

Prof. Antonio Salafia graduated from St.Johns' Medical College in Bangalore and soon after came to Mumbai to work, on a honorary basis, in a NGO dedicated to leprosy patients. In Bombay he studied, for 4 years, Dermatology under Prof. Rui J. Fernandez and Plastic Surgery under Dr.J.Shah. In 1983 went to Istituto Dermatopatico dell'Immacolata, in Rome, for a stage in advanced Dermatology. There he got in touch with Dr. C. Frati who passed onto him his experience with Vitiligo. In 1981 Vimala Dermatological Centre (VDC) started reconstructive surgery for leprosy patients; Prof. Salafia joined as assistant to Dr.J.Shah. Again in 1984 he was in Italy studying Hand-surgery, under Prof. E. Morelli, and microsurgery with Prof. G. Brunelli. On his return he continued his work as assistant surgeon at VDC. As Dr. Shah retired from VDC, Prof. Salafia took over as reconstructive surgeon, while carrying on his duties as dermatologist. VDC is first and foremost a referral centre for leprosy patients.

Over the years VDC has become well-known in and around Mumbai for its Skin-OPD and it was here that Prof. Salafia started experimenting with new creams and lotions for Vitiligo; gradually the protocol – based on Dapsone, Vitamin B6, Folic Acid was refined and now – for the last many years - this is the standard treatment for Vitiligo at VDC.

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25 June

Over 100 million of people suffer from this skin disease daily, but there is no cure in sight. With focus on collaboration efforts, we can bring that number closer to zero.

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