ISSN (Online): 2455-3662
EPRA International Journal of Multidisciplinary Research (IJMR) - Peer Reviewed Journal
Volume: 9| Issue: 6| June 2023|| Journal DOI: 10.36713/epra2013 || SJIF Impact Factor 2023: 8.224 || ISI Value: 1.188

DESCRIPTIVE OVERVIEW OF VITILIGO

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Article DOI: https://doi.org/10.36713/epra13496
DOI No: 10.36713/epra13496

SUMMARY

Introduction: *Vitiligo is an acquired idiopathic autoimmune disorder showing non regular depigmentation of the skin, hair, or both. It may show with amelanotic, milky-white, firmly demarcated macules or patches of normal skin. Vitiligo, a common depigmenting skin disorder, with a prevalence of about 0.5-2% worldwide. Among the therapies commonly used as treatment are systemic glucocorticoids and phototherapy.*
Objective: *to detail the current information related to vitiligo, epidemiology, etiology, presentation, differential diagnosis and treatments.*
Methodology: *a total of 30 articles were analyzed in this review, including review and original articles, as well as clinical cases, of which 21 bibliographies were used because the other articles were not relevant to this study. The sources of information were PubMed, Google Scholar and Cochrane; the terms used to search for information in Spanish, Portuguese and English were: vitiligo, depigmenting, melanocytes.*
Results: *Vitiligo is present in all ethnic groups, as well as in all skin types without predilection. It is a profound disease with a genetic risk between 75% and 83%, the remaining percentage being due to environmental factors.*
Conclusions: *Vitiligo, a common depigmenting skin disorder, with a prevalence around 0.5-2% in adults and children. The disease is multifactorial with a polygenic inheritance pattern, so the individual contribution of each genetic variant to susceptibility is relatively minimal. Vitiligo is a depigmentation that can be primary, circumscribed or generalized in the skin and mucous membranes, linked to melanocyte self-destruction, genetic factors, autoimmunity, oxidative stress and cytokines. The detailed molecular mechanisms still need further investigation. Diagnosis is usually clinical, by finding acquired, amelanotic, non-squamous, chalky-white, chalky-white maccules with distinct margins in a typical distribution. The differential diagnosis is of utmost importance for this purpose Wood's lamp can be used to facilitate the diagnosis. Vitiligo presents 2 segmental and non-segmental types. As the development and understanding of the molecular mechanism improves, treatment will become more and more precise. Treatment should be individualized and take into account the location, clinical presentation and presence of activity.*

KEY WORDS: *vitiligo, skin, melanocytes, macules, hypopigmented.*

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INTRODUCTION

Vitiligo, a common depigmenting skin disorder, with a prevalence of about 0.5-2% worldwide and distinguishable by the selective loss of melanocytes that produces chalky white, non-squamous macules. The pathogenesis of this autoimmune disease is now better understood. Vitiligo occasionally presents psychologically disturbing effects on the affected individual. As of 2011, by international approval, segmental vitiligo was classified away from other forms of vitiligo, and the term vitiligo was conceptualized to refer to all variants of non-segmental vitiligo. Vitiligo is an acquired idiopathic autoimmune disorder showing non-regular depigmentation of the skin, hair or both. It may appear as amelanotic, milky-white, sharply demarcated macules or patches of normal skin. Individuals with this pathology, particularly those with darker skin tones, are often victims of stigmatization, which has a negative impact on their mental health as well as their quality of life. Among the therapies commonly used as treatment are systemic glucocorticoids and phototherapy, however, new therapeutic methods are currently being used in clinical studies. The effective therapeutic approach to this disorder remains a challenge because of the incomplete understanding of its pathogenesis(1-4).

METHODOLOGY

A total of 30 articles were analyzed in this review, including review and original articles, as well as cases and clinical trials, of which 21 bibliographies were used because the information collected was not of sufficient importance to be included in this study. The sources of information were Cochrane, PubMed and Google Scholar; the terms used to search for information in Spanish, Portuguese and English were: vitiligo, depigmenting, melanocytes.

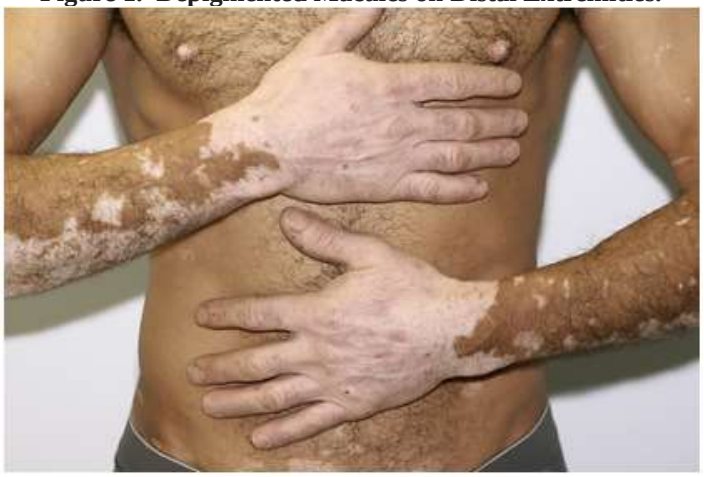
The choice of bibliography exposes elements related to vitiligo, epidemiology, etiology, presentation, differential diagnosis, evaluation and treatments.

DEVELOPMENT

Epidemiology

Vitiligo, a common depigmenting skin disorder, with a prevalence of about 0.5-2% in adults and children. Early epidemiological studies reported vitiligo to occur in 0.38% of the population. Vitiligo is present in all ethnic groups, as well as in all skin types without predilection, however it may present alterations according to geographic location, probably due to the inclusion of cases with chemical and toxic depigmentation, or possibly the disparity in prevalence data may be due to better detection and reporting in places where cultural and social stigma is normal, or in populations with darker skin predilection showing more evident skin alterations. A comprehensive review of prevalence data has presented results of prevalence of vitiligo ranging from 0.06% to 2.28%; a meta-analysis reviewing 103 studies estimated the prevalence of vitiligo, found the combined prevalence of vitiligo in 82 population-based studies to be 0.2% and in 22 hospital-based studies to be 1.8%. In some studies segmental vitiligo represents approximately 5 to 16% of vitiligo cases, other bibliographies show a prevalence between 5 and 30%, demonstrating that its incidence and prevalence are not well established. Possibly due to the instability of the classification of the disease prior to consensus, in addition to the lack of consistency in affected individuals and the variety of locations. The prevalence among men and women is almost the same, however women and girls tend to consult more frequently, possibly because of the greater negative social impact compared to men and boys. Non-segmental vitiligo usually develops between 10 and 30 years of age, however it can appear at any age. One quarter of individuals with vitiligo develop the disease before the age of 10, approximately 50% of individuals with vitiligo develop the disease before the age of 20 and approximately 70-80% before the age of 30. Vitiligo is a profound disease with a genetic risk between 75% and 83%, the remaining percentage being due to environmental factors. The disease is multifactorial with a polygenic inheritance pattern, so the individual contribution of each genetic variant to susceptibility is relatively minimal(1,5-7).

Figure 1. Depigmented Macules on Distal Extremities.



Source: Bergqvist C, Ezzedine K. Vitiligo: A Review. Dermatology. 2020;236(6):571–92 (1).

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Etiology

Of unknown pathogenesis for the moment, however, there is a hypothesis that is widely established and supported, the autoimmune hypothesis. The latter is based on the relationship with other autoimmune diseases, the elevated level of antibodies against melanocytes that are present in approximately 10% of individuals with vitiligo, the susceptibility loci linked to vitiligo that are in the genome, broadly related assays that encode immunomodulatory proteins, and the inflammatory infiltrate that is evident at the edge of active lesions. A different theory is that of melanocytorragia, which consists of defective cell adhesion leading to detachment and transepidermal decrease of melanocytes with exposure of autoantigens and activation of the immune system generating the alteration of melanocytes. Another possible etiology could be explained by the biochemical theory, in which the injury to melanocytes is due to an imbalance in oxidative stress; more hydrogen peroxide and more superoxide dismutase activity in individuals with vitiligo. Also relevant is the convergence theory viewpoint which merits a combination of multiple pathways for the development of vitiligo, among which we have susceptibility to environmental changes, genetic background, altered epidermal microenvironment, an alteration of the melanocytes themselves and autoimmune response(3,8-10).

As previously mentioned, we defined vitiligo as a depigmentation that can be primary, circumscribed or generalized in the skin and mucous membranes, linked to melanocyte self-destruction, genetic factors, autoimmunity, oxidative stress and cytokines. Recent studies have presented that the IFN-γ-CXCL9/10-CXCR3 axis appears to play a key role in vitiligo by inhibiting melanogenesis, inducing melanocyte apoptosis and recruiting more T cells to the skin. All of these involved in the JAK/STAT pathway; likewise it has been evidenced that cytokines, HSP70i, IL-15, IL-17/23, TNF, as well as the wnt signaling pathway, Tregs, miRNA are related in the pathogenesis of vitiligo(11).

Emphasizing that vitiligo is a complex disease with pathogenesis arising from the interaction of different genetic and metabolic factors related to cellular oxidative stress, innate immunity, adaptive immunity and melanocyte adhesion to the epithelium, which result in melanocyte injury. In this disease, melanocytes are more prone to oxidative damage, generating more expression of proinflammatory proteins, such as HSP70 and less expression of epithelial adhesion molecules, such as E-cadherin and DDR1, leading to the impact on melanocytes and the display of antigens that promote autoimmunity. Activation of the type 1 IFN pathway maintains the direct function of CD8+ cells against melanocytes, facilitated by altered regulatory T cell function(6).

Diagnosis

It is usually clinical, through the finding of acquired, amelanotic, non-squamous, chalky white macules with defined margins in a typical distribution: lips and tips of distal extremities, periorificial, segmental, penile and friction areas. Laboratory tests are generally not used to confirm, however, sometimes it is necessary to do other tests or skin biopsy to exclude other disorders. Lack of melanocytes in a lesion can be evidenced noninvasively by in vivo confocal microscopy or by skin biopsy. Histology of the center of a vitiligo lesion shows complete deprivation of melanocyte pigment in the epidermis and lack of melanocytes. In addition, lymphocytes may occasionally be found at the margin of lesion progression. Wood's lamp can be used to simplify the diagnosis, it allows to identify the focal loss of melanocytes in addition to finding sites of depigmentation that are not seen with the naked eye, particularly in pale skin. When using this lamp, vitiligo lesions emit a bright blue-white fluorescence and appear sharply demarcated. Dermoscopy can be used in case of suspicion of other depigmenting disorders, as it allows differentiation from other pathologies. The disease presents residual perifollicular pigmentation and telangiectasias, which are not present in other hypopigmenting disorders. In addition, it serves to assess the activity of the disease and the evolutionary stage, for example progressive lesions present perifollicular pigmentation, while stable lesions present perifollicular depigmentation. The differential diagnosis of vitiligo is large, most of the conditions among the differentials are infrequent, Table 1 shows the most important differential diagnoses of vitiligo. It is of great relevance to rule out melanoma-related leukoderma; clinically it is similar, antibodies against melanoma antigen recognized by T-cells 1 (MART1) in melanoma-related depigmentation usually support not to confuse it with vitiligo. Nevus depigmentosus is another differential of segmental vitiligo, it is a stable segmental hypopigmentation, which appears at birth or at the first year of life, these present a normal number of melanocytes with a small melanin production, in Wood's lamp, the contrast between the lesioned skin and the normal one is less remarkable than in vitiligo(1,12).

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Table 1. Differential diagnosis of vitiligo.

Chemically-induced leukoderma (occupational)
Phenols and other derivatives
Topical or systemic drug-induced depigmentation
Genetic syndromes
Hypomelanosis of Ito
Piebaldism
Tuberous sclerosis
Vogt-Koyanagi-Harada syndrome
Waardenburg syndrome
Hermanski-Pudlak syndrome
Menke's syndrome
Ziprkowski-Margolis syndrome
Griscelli's syndrome
Postinflammatory hypopigmentation
Pityriasis alba
Atopic dermatitis/allergic contact dermatitis
Psoriasis
Lichen planus
Toxic drug reactions
Posttraumatic hypopigmentation (scar)
Phototherapy- and radiotherapy-induced
Neoplasm-related hypomelanoses
Melanoma-associated leukoderma
Mycosis fungoides
Infection-related hypomelanoses
Leprosy
Pityriasis versicolor
Leishmaniasis
Onchocerciasis
Treponematoses (pinta and syphilis)
Idiopathic
Idiopathic guttate hypomelanosis
Progressive (or acquired) macular hypomelanosis
Congenital
Nevus anemicus
Nevus depigmentosus
Others
Lichen sclerosus et atrophicus
Melasma (caused by contrast between lighter and darker skin)

Source: Bergqvist C, Ezzedine K. Vitiligo: A Review. Dermatology. 2020;236(6):571–92 (1).

Classification

The grouping of the different types of vitiligo was made in consensus in 2011 giving rise to two types:

- Segmental.
- Non-segmental.

Management and treatment

Management and treatment criteria seek to stop the disease, as well as to provide repigmentation and prevent relapse. Roughly speaking, it has been shown that the combination of therapies generates better results.

Vitiligo is usually managed with topical therapies such as glucocorticosteroids, calcineurin inhibitors, immunosuppressive agents and vitamin D, in addition to various phototherapy modalities and surgical techniques. Current treatments for this disease are not good enough, however targeted therapies, such as biologics targeting cytokines and small molecule inhibitors targeting intracellular signaling molecules, show promising results. As the development and understanding of the molecular mechanism improves, treatment will become more and more precise(11,13,14).

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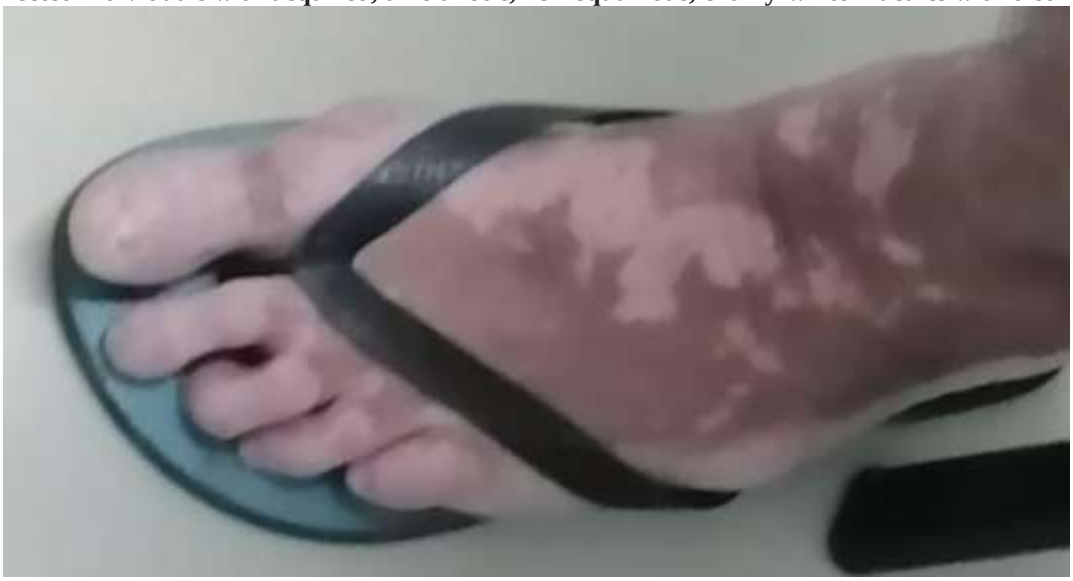
Figure 2. Affected individuals with acquired, amelanotic, non-squamous, chalky-white macules with distinct margins.



Source: The Authors.

Treatment should be individualized and take into account the location, clinical presentation and presence of activity. All therapies for vitiligo are limited, more research is needed to better understand the pathogenesis(3).
Within the pharmacological management we have:
Topical treatment corticosteroids that present a significant response in vitiligo as they regulate and suppress the inflammatory response. They are the first line, using corticosteroids such as betamethasone valerate or clobetasol propionate. The therapeutic effects are more noticeable in sun-exposed areas(12,15).

Topical calcineurin inhibitors, generally directed to the head and neck, here we have tacrolimus and pimecrolimus, which do not present many adverse effects, especially no risk of atrophy. It could be used for at least six months, twice a day, although the management can be extended according to the results. It is advisable to accompany the treatment with moderate daily sun exposure(12,16,17).

Topical vitamin D3 analogues (D3A) are not effective as a solitary treatment, their immunomodulatory components reduce the function of T cells, stimulate the creation of melanocytes and induce melanogenesis, they can be used as an adjunct to other treatments. The dose of 100g is optimal in a time of four weeks in ointment and eight weeks when the cream is applied on 30% of the body surface, it is useful to mix with calcipotriol at 0.005% and betamethasone at 0.05%(12,18).

Methotrexate; 5-fluorouracil; apremilast; prostaglandin F2 alpha analogues; Janus kinase inhibitors, a peptide derived from the primary basic fibroblast growth factor; systemic therapy corticosteroids; etc. are other promising pharmacological treatments with the use of antibiotics such as minocycline(12,18,19).

Within the physical therapy used in vitiligo we find:
Narrowband UVB phototherapy: ultraviolet irradiance seems to present some systemic results, such as stimulation of the central hypothalamic-pituitary-adrenal hypothalamic axis, immunosuppressive effects, initiation of the propiomelanocortin pathway in the arcuate nucleus of the hypothalamus, and opioid gene results. UVB irradiance is more prominent than UVA. NB-UVB photodynamic therapy lowers the immune system, stimulates melanocyte segmentation, increases melanin synthesis and generates the displacement of melanocytes from the perilesional skin to manage the disease(12,19).

PUVA: PUVA irradiation generates melanin production by decreasing the immune system and creating an ideal environment for melanocyte creation. This treatment involves placing psoralen topically or ingesting it and then placing it under the UVA rays. Psoralens are given orally 1 to 3 hours prior to UV exposure. Other physical management therapies include combined Fraxel Erbium and UVA1 lasers, as well as excimer laser therapy(1,12,20).

Surgical Treatment
Currently there are some methods to improve the appearance of the skin. Surgery is a good alternative when other treatments have been tried. Both the development of new techniques and alterations to the already available treatment of cell and tissue transplantation offer future hope in the management of the disease. The different surgical techniques present advantages and disadvantages, which should be thoroughly analyzed by a physician and discussed with the affected individual. Surgical interventions may be a good option for individuals with a stable

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form of vitiligo, however side effects such as the Koebner phenomenon, which is the appearance of unseen changes in the damaged skin, may occur(21).

CONCLUSIONS

Vitiligo, a common depigmenting skin disorder, with a prevalence of about 0.5-2% in adults and children. The disease is multifactorial with a polygenic inheritance pattern, so the individual contribution of each genetic variant to susceptibility is relatively minimal. Vitiligo is a depigmentation that can be primary, circumscribed or generalized in the skin and mucous membranes, linked to melanocyte self-destruction, genetic factors, autoimmunity, oxidative stress and cytokines. The detailed molecular mechanisms still need further investigation. Diagnosis is usually clinical, by finding acquired, amelanotic, non-squamous, chalky-white, chalky-white maccules with distinct margins in a typical distribution. The differential diagnosis is of utmost importance for this purpose Wood's lamp can be used to facilitate the diagnosis. Vitiligo presents 2 segmental and non-segmental types. As the development and understanding of the molecular mechanism improves, treatment will become more and more precise. Treatment should be individualized and take into account the location, clinical presentation and presence of activity.

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Conflict of Interest Statement

The authors report no conflicts of interest.

Funding

The authors report no funding by any organization or company.