Vitiligo Prevalence, Causes and Updated Treatment

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Received: November 14, 2020; Published: November 30, 2020

**Abstract**

**Background:** Vitiligo disease, which is the main depigmentation disease characterized by complete deletion of the pigment cells of the epidermis, it affects both the skin and the hair and known to be progressive, idiopathic and acquired. The incidence of vitiligo is 0.5% to 1% of the people, the mean age of its onset is 24 years old, it actually affects both sexes, males and females approximately in an equal way, it could be seen more in women but this is just because reporting are more about female cases due to their caring to see the dermatologist more than males.

**Aim:** In this review, we will look into the prevalence, etiology and updated management of vitiligo.

**Conclusion:** Vitiligo is a serious dermatological disease that affect the health and the psychological state of the patients, its prevalence differs from one place to another but it falls generally within 1 - 2%, the causes for vitiligo are still not clear till now although there are many theories to explain it and the most accepted one that the disease is combination of many causes. Many treatments are available now which led to great improvement in its management.

**Keywords:** Vitiligo; Etiology of Vitiligo; Management of Vitiligo

**Citation:** Nawal Raja Alyamani., et al. “Vitiligo Prevalence, Causes and Updated Treatment”. EC Microbiology 16.12 (2020): 75-83.
The pathogenesis of vitiligo is considered to be combination of 2 main factors that work together and cause the destruction of the melanocytes that produce the pigment, those two factors are oxidative stress and autoimmune stress, going deep to understand how autoimmunity contributes in this disease we can see that cellular and humoral immunity, both of them are part of developing vitiligo, they produce antibodies mainly against the antigens of the pigment cells such as tyrosinase and tyrosinase-related protein 1 and 2 [9,10]. The histological observation of the vitiligo lesion showed presence of T-cells, neutrophils and macrophages especially in progressive cases [11].

The psychological effect of vitiligo is one of the factors that necessities developing treatment for it, as it affects the quality of the patient’s life, self-confidence, finding a job and even marriage, as most of people are confused between it and other contagious diseases such as leprosy. Patients with darker skin are the most affected owns due to the great difference between the colour of their normal skin and the affected parts [12].

Picardo and Taieb, classified vitiligo into 4 main groups: segmental vitiligo (SV), Non-segmental vitiligo (NSV), mixed NSV and SV and unclassifiable types [13], NSV is the only one that have sub categories named; mucosal, focal at onset, acrofacial, generalized and universal. Too sensitive parts of the body that is easily affected by pressure or trauma could have generalized vitiligo, which occurs mostly in late age, in contrast to this there is SV, which starts generally during childhood. We seek mainly in our treatment to stop the progression of the disease, retaining the pigmentation of the skin, we nowadays have many ways and methods for treatment, but setting the right and the perfect treatment plan is the most important step [14,15].

In this review, we will look into the prevalence, etiology and updated management of vitiligo.

Prevalence

Generally, we can divide those who get affected with vitiligo into 2 groups; group one who got the disease when they are less than 12 years old and group 2 get it after they are 12 years old. Group 1 is mostly known to have a family history of the disease and atopy while group 2 had more comorbid thyroid disease and acrofacial disease [16]. In some parts of India, the occurrence of the disease happens in early time with a mean of 6.9 years old; also the family history was very clear in about 25% of the cases [17].

Moving to Greek and Denmark, where most of the cases were similar to group 2, a study that collected 50,237 patient between 1995 to 2002 was conducted in Greece, this study showed that the prevalence of vitiligo is about 0.5%, the age were most cases occurred was 43 for men and 38 for women, also it showed that patients more than 30 years old showed higher percentage in female than male 0.6 vs. 0.3, but for those over 60 years it was the same 0.5% [18]. Ezzedine., et al. discussed that the age of the beginning of the disease is mixed in most populations also we can notice having 2 peaks most of the times [19]. Most cases of vitiligo happen mainly before 30th, statistics show that most cases show the symptoms of vitiligo when they are 20 years old [20].

Kruger and Schallreuter had collected data from 50 studies worldwide, this happened in 2012; they concluded that the prevalence of vitiligo can range between the lowest numbers which is 0.06% to the highest number which is 2.28% so we can conclude that it ranges from 0.4 - 2% [21]. In USA, a study made on 140 dermatology patients showed that 80% of the patients showed a problem with their skin pigmentation, 47.3% accepted it while 32.7% was not satisfied about it, only one case had vitiligo, so the prevalence of vitiligo in this study is only 0.7% [22]. Alkhateeb., et al. studied the prevalence using survey, he surveyed 2624 from UK and North America, and results showed that prevalence in men was 3.9% and 4.1 in women with a mean of 0.4%, also he studied the rate of family history and the prevalence was 6.1% [23].
Indian clinic of dermatology conducted a recent study, they studied 1010 diseased patients, in most of the cases, the onset of the disease was early, while after 60 years old it was only 4.3%, in 41.5% the lower limb was the starting point for the disease, face 50%, the upper limb 68.3%, and genital disease 6.7% [24]. Also, although the general prevalence of vitiligo is 0.5 - 2%, some places in India show higher prevalence of 8.8%, which make us, think about a connection to the environment and the genes [25].

Children also show similar prevalence to the elder ones, as in a clinic in Nepal, the incidence was estimated to be 2% [26] a school in Taiwan was also tested and the prevalence was 0.09% [27], so as what happens with children when they grow up, here it is suggested in very sunny and hot places; as Sinai the incidence decreased in such places to 0.18% [28], generally the prevalence of vitiligo in children worldwide ranges 0 to 2.16% [29]. Studying the prevalence of vitiligo based on the type of it revealed that generalized vitiligo is the most common type, the prevalence differs by location, 85% of patients in India have generalized vitiligo, 6.6% of Segmental disease, universal 6.9%, generalized vitiligo accounts to 35 - 70% of the cases [30,31].

Head and neck are the most parts of the human body included in the disease, in a study of pediatric cohort from Chicago, the percentage was up to 36.5% [32], another study in India showed that legs were the most parts included in half of patients also Pajvani., et al. study the percentage of those affected in their head and neck in Korean children and results was up to 58.8% had head and neck vitiligo [33]. Family history also contributes to the prevalence as 15 - 20% of cases had a family history of vitiligo [34], 20.4% was the percentage of family history in Gujarat survey, while In a Chinese survey it was 15.7%. Mumbai showed the lowest percentage that was 3.43% [35].

Etiology

Many hypothesis were made trying to predict how vitiligo occurs, although none of these hypothesis totally explain all the clinical presentation, there are some hypothesis that are acceptable, here we discuss these hypothesis [36].

Genetic hypothesis: Genes and environment interact together and most of the diseases come out due to their interaction, understanding how the genes could affect the occurrence of vitiligo is the first key to understanding the disease itself. This hypothesis lead us to think of vitiligo as complex genetic disease because of many reasons (i) the severity of symptoms and the onset of the disease differs between individuals, which restrict us from finding a general definition of the disease, also most of cases where vitiligo occurred early, there was a familial history of generalized vitiligo and comorbidity of other severe diseases (ii) the mechanism of the disease is not clear till now, and all what we have is some suggested theories (iii) genetic diseases mostly have many genes responsible for it with each gene contributing to the disease with one way different than the other [37,38].

Studies of Ando., et al. [39] showed that there is a connection between HLA-B46 and familial non segmental vitiligo, the study was carried on 131 patients from japan, research found about 50 genes suspected to participate in the occurrence of the disease such as HLA associated genes, including HLA-A2, HLA-DR4 and non-HLA genes, including DDR1, XBP1 [40]. Finally, we conclude that genes have an important role of the pathogenesis of vitiligo also it is not full clear till now.

Autoimmune hypothesis: This theory is the most common and important one, it suggest that the immunity attacks the melanocytes causing its damage, this is shown more when following the pathway and mechanism of the disease which reveals the big similarity between it and other autoimmune diseases such as thyroid disorders [41]. Both cellular and humoral immunity are in responsibility for vitiligo, in 5 - 10% of patients, high level of IgG was found [42], which support this theory as autoantibodies circulating in high level in vitiligo patients, on the other side another theory suggest that this could be secondary to the damage of melanocytes and keratinocyte.

Immune histochemical studies of the lesions of active vitiligo showed the infiltrations in this lesion is rich with T-cells which suggest that it plays important role in the disease pathogenesis [43], also, mononuclear cells of the blood showed abnormalities, levels of natural killer cells CD 4+ and CD8+ could be increased or decreased or normal which depends on many other factors [44].

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Neural hypothesis: This hypothesis was first set by Lerner [45], suggesting that some neurotransmitter mediators that nerve endings secrete are toxic to melanocytes, this hypothesis came with some evidences such as (i) presence of local vitiligo, that is localized in specific part of the body and does not respond to the normal treatment of vitiligo but respond to agents that act by modulating the neural function. (ii) vitiligo is connected to emotional stress although the mechanism of how this cause the disease is not clear. (iii) some patients with neurological diseases such as multiple sclerosis have vitiligo [46].

Growth factor defect hypothesis: Puri., et al. Proposed in 1987 that faulty melanocyte growth arose from non-lesional and peri-lesional skin. By more studying, investigators found that in vitro supplementation of growth factors derived from foetal lung fibroblast has corrected the defects partially. These results suggest that the defect in growth factors play a vital role in the pathogenesis of vitiligo. However, more studies are needed to prove the use of growth factors as part of vitiligo repigmentation therapy [47].

Auto cytotoxic hypothesis: Dopachrome, dopa, and 5, 6-dihydroxyindole are precursors to melanin which are formed during melano genesis, this theory suggests that these precursors are toxic to melanocytes, normally our body have protective mechanism against these precursors and other free radicals, in vitiligo patients, this protective pathway is destroyed which lead to accumulation of free radicals and toxic indoles and finally melanocytes destruction [48].

Adhesion defect theory: Melanocytorrhagy theory; is known as chronic detachment of melanocytes generally by trauma or mechanical rubbing of the skin this was suggested by Gautier., et al. [49], in 2003. Gauthier., et al. also suggested that dendritic cells and T-memory cells cause autoimmune activation which detects the auto-antigens in the basal epidermal cells [50].

Convergence theory: As the presentation of the disease is different among patients in onset, history or clinical presentation, it suggested that not one single hypothesis that explain the disease, but many hypothesis combine together to explain it such as infection, cytotoxicity, stress, genetic factors, mutations, environmental factors and impaired distribution of melanocytes all contribute to the phenomenon of vitiligo [51].

Updated management

Advances in vitiligo are not only regarding the understanding of the pathophysiology of the disease, but also in the therapeutic methodologies and techniques, that makes us in better position of the treatment; the updates in the management of vitiligo will be discussed here.

Medical management

The advances in the treatment such as Narrowband Ultraviolet B (NB-UVB) therapy targeted Ultraviolet B (UVB), topical immuno-modulatory treatment, laser therapies, UV light combined with topical Vitamin D.

Narrowband ultraviolet B (NB-UVB): It is considered the first line of treatment for generalized vitiligo and pitched vitiligo, it is based on using UV lamp that emits light with a peak of 311 nm [52,53], Westerhof and Nieuwbor-Krobotova were the first ones to detect the usage of NB-UVB in 1997[54], it act by inducing the growth of melanocytes at skin and hair follicles, also it cause local immunosuppression at the site of infection. The proliferation is due to activating melanogenesis and production of melanocyte stimulating hormones (MSH) [52]. Comparing NB-UVB to another therapy mainly Psoralen and Ultraviolet A (PUVA) [55], showed that NB-UVB has more efficacy and less side effects.

Other advantages of NB-UVB in comparison to PUVA are high efficacy, very low side effects especially the systematic ones, it is safe in pregnancy and can be used with children, the acceptance of the patients is also better as it does not need eye coverage within the treat-
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ment, a double blind study [56]. Showed that repigmentation achieved with NB-UVB is much better than that achieves by PUVA regarding persistence and colour matching to the other skin segments [56].

**Laser therapy:** It is another modern treatment of vitiligo that uses Xenon-Chlorine (Xe-Cl) gas to generate monochromatic laser light that has wavelength of 308 nm [57]. It produces local effect and also could be used alone or in combination with other treatments such as PUVA therapy or topical immunomodulators [58], for both localized and segmented vitiligo, laser can give rapid and effective results. A study that included 18 patients [57], they had 29 affected areas, 57% of these areas showed improvement after 6 exposures within 2 weeks, the result was 87% after 12 sessions of treatment.

The conventional UVB therapy is less effective than laser therapy, this because in laser therapy targeted treatment could be achieved so non-infected areas are not involved I the treatment and also the repigmentation occurs faster with Excimer laser therapy than UVB.

**Targeted UVB therapy**

It is based on using UVB light in high intensity which is targeted to the affected area only that makes the patient receive less amount of UVB light and also thought to improve the efficacy. A study on 8 patients who had segmental; vitiligo showed that using targeted UVB light led to repigmentation of more than 75% in efficacy, this proved that targeted UVB therapy is effective in both segmental and focal types of vitiligo [59]. Comparing this therapy to Excimer laser shows that targeted UVB therapy is almost the same efficacy and less cost while comparing it to conventional UVB therapy It is more effective and much safer than it [60].

**Systemic immune-modulator therapy**

Since vitiligo is an immunity-mediated disease, so immunosuppressive agents are effective in treating it. An example of immunosuppressant is systemic steroids, but steroids have the disadvantages of serious side effects especially in children and to overcome this we give it in mini-pulse form. A study that involved 14 patients, they were given high doses of methylprednisolone pulse therapy, in 10-60% of patients the disease stopped progression [61].

**Topical vitamin D analogues**

The usage for it is based mainly on the fact that vitamin D3 has a role in the proliferation of melanocytes and keratinocytes, this had been shown by presence of receptor for 1- alpha dihydroxy vitamin D3[62], the most important member of this group is Calcipotriol, and they can be used in combination with NB-UVB and topical steroids. The results are variable within all the studies [63].

**Surgical management.**

It is used when this condition is found; the patient's condition is stable for one year at least and the patient is not responding to the treatment. The biggest advantage of the surgery is the high percentage of repigmentation 90 - 100%, and also the development in this field makes it easier to perform these surgeries. Different types of surgery are available such as split-thickness grafting, smash grafting, autologous suction blister grafting, single follicular unit grafting and autologous melanocyte culture grafting [64].

**Conclusion**

Vitiligo is a serious dermatological disease that affect the health and the psychological state of the patients, its prevalence differs from one place to another but it falls generally within 1-2%, the causes for vitiligo are still not clear till now although there are many theories to explain it and the most accepted one that the disease is combination of many causes. Many treatments are available now which led to great improvement in its management.

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