Pigmentation Disorders: A Short Review

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Abstract

Pigmentation disorders are a group of diseases caused by changes in the levels of the pigment melanin produced by melanocytes, the cells that manufacture pigment in the skin, or due to the accumulation of other pigments in the skin. These can be examined under the headings hypo-, hyper- and depigmentation. This review describes pigment disorders in the light of the current literature.

Keywords: Pigmentation disorders; Vitiligo; Albinism; Hyperpigmentation; Hypopigmentation

Introduction

Agents that give rise to skin color are skin thickness, the skin’s light refraction and absorption properties, vascular status, levels of oxidized and reduced hemoglobin, carotenoid content and, most importantly, the pigment melanin. Melanocytes, cells responsible for pigment formation, are present in the basal layer. Melanocytes are most concentrated in the central part of the face and most sparsely present in the distal part of the nail. Melanocytes have dendrites and melanin containing intracellular organelles (melanosomes). Melanin synthesis takes place inside these melanosomes through the conversion of tyrosine by the enzyme tyrosinase, first into dihydroxyphenylalanine (DOPA) and then into DOPA-quione, and subsequently into eumelanin, which bestows black-brown color, and pheomelanin, which bestows yellow-red. Pigmentation may be defined as color changes occurring in the skin, hair and eyes due to genetic heterogeneity, levels and location of melanocytes and melanin producing cells. The scope of genetic heterogeneity can range from a normal structure to pathological pigmentation phenotypes. Normal human pigmentation includes pigment distribution, which bestows color to the skin, hair and eyes. Pigmentation may be defined as color changes occurring in the skin, hair and eyes due to genetic heterogeneity, levels and location of melanocytes and melanin producing cells. The scope of genetic heterogeneity can range from a normal structure to pathological pigmentation phenotypes. Normal human pigmentation includes pigment distribution, which bestows color to the skin, hair and eyes.

Diseases involving hypopigmentation

Vitiligo: Vitiligo is a chronic, idiopathic, acquired pigmentation disorder with an unpredictable course arising in association with melanocyte destruction in affected areas and characterized by hypochromic patches and macules in the skin and mucous membranes [2,3]. The global prevalence irrespective of gender is reported at 0.5-4%, with a mean age at onset of 24 and equal prevalence between males and females [3-5]. Vitiligo was first described in Buddhist literature and sacred texts in approximately 1400 BC. Despite the disease being very ancient, the etiology is still uncertain. Researchers have proposed several theories, however. These include genetic, immunological, ototoxic, neurohormonal, viral, cytoxic, biochemical, oxidative stress, multifactorial, decreased melanocyte survival and melanocytorrhagy theories. The most popular theory in recent years is that vitiligo results from melanocyte destruction due to environmental factors against a genetic background. Environmental factors leading to the initial symptoms of the disease include puberty, pregnancy, major infections, dietary irregularities, stress and skin trauma. Vitiligo can develop as a result of all these hypotheses or pathological mechanisms [4,5].

Clinically, the disease can be classified as segmental, non-segmental or mixed. The difference between these subtypes is not solely associated with clinical symptoms (mode of formation of the first skin lesion, its size and location, accompanying autoimmune diseases and natural course of dermatosis) but also with the etiology (2,3,5). This distinction is important in terms of treatment options and prognosis. Lesions can be seen in the form of white macules of varying shapes and sizes anywhere on the body [2,3]. Recent studies have reported that vitiligo can compromise quality of life as a result of psychological impacts such as depression, social phobia and loss of self-esteem [2,5].

Although various therapeutic options are available for vitiligo, resistance to treatment is common. The most generally employed of these therapeutic options are topical corticosteroids, topical calcineurin inhibitors and ultraviolet (UV) light therapy. UV therapies can be applied in the form of phototherapy (UVB) and phototherapy with psoralen plus UVA. UV therapies are considered the most effective of these. Although systemic corticosteroids are effective in widespread and progressive cases, there are concerns over their reliability in long-term use. Several topical and systemic treatments are still being investigated. The effectiveness of TFN-α-inhibitors due to increased TFN-α levels in vitiligo has also attracted attention [6,7]. Grafting techniques supplemental to these therapies have also become popular in the last 1-2 decades. Surgical treatment of vitiligo due to melanocyte injury is possible with surgical melanocyte replacement. These surgical techniques are known as grafting methods. There are two types – tissue grafting and cell grafting. Selection of grafting technique varies depending on lesion size, the patient’s age, social status and expectations and the skill of the surgeon due to perform the procedure [8]. Autologous mini-punch grafting and needling are other surgical options due to the minimal need for equipment and ease of application [9]. One study showed that a positive improvement was identified in quality of life indices of patients with vitiligo receiving excimer laser therapy [10]. Low-level laser (LLL) therapy is a new technique that is expanding rapidly and is used in wound healing with stem cell renewal.

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and several skin diseases, such as acne scarring. In vitiligo, however, it has been shown to reduce depigmentation with melanocyte stimulation and autoimmunity inhibition and to increase pigmentation [11]. Two separate studies have also reported that Polypodium leucotomos extract (PLE), a tropical fern found in South and Central America, can also be included among the alternative therapies. PLE has been used by indigenous populations for various skin diseases for many years. PLE has been determined to have antioxidant, anti-inflammatory, antitumor and photoprotective effects, and the gel, cream and oral forms have been shown to be beneficial in pigmentation diseases, including vitiligo [12,13].

Vogt-Koyanagi-Harada syndrome (VKHS): VKHS is a rare autoimmune disease involving melanin containing skin, meninges, inner ear and eyes. It is more common among black-skinned women aged 20-50. The classic appearance includes bilateral panuveitis, hypoacusia, poliosis with meningitis, vitiligo and alopecia. The cause is uncertain, although the role of genetic factors has been stressed. Attacks may be seen in some patients despite the early use of high-dose systemic steroids [14].

Idiopathic guttate hypomelanosis (IGH): IGH is a leucodermic dermatosis more commonly seen in middle-aged or elderly women with a familial disposition. Although the cause of IGH is uncertain, actinic and iatrogenic injury triggered by photoaging and ultraviolet light have been implicated in the pathology. Macules with sharp margins 2-10 mm in size are seen in clinical practice. These are most commonly seen on the extensor surfaces of the extremities, and also in other regions such as the abdomen and chest. Non-ablated laser, fractionated carbon dioxide laser, 88% phenol and topical tacrolimus and pimecrolimus can be used in treatment [15].

Albinism: A disease characterized by little or no pigmentation in the skin, eyes and hairs due to inherited deficiency of the enzyme tyrosinase involved in the biosynthesis of melanin. Albinism can be seen in all ethnic groups with a worldwide prevalence of approximately 1/17-20,000. Prevalences may vary among the different forms. This may be attributed to different gene mutations. Clinical differentiation is problematic, however. Generally, there are 11 types exhibiting autosomal recessive transmission, and the severity of the disease is different in each. In the most severe form, Type 1 (oculocutaneous) albinism there is a complete absence of tyrosinase due to a defect in the coding TYR gene. The skin and hair are completely white, and subjects never tan, even if they go out in the Sun. The most common of the forms with partial tyrosinase activity is Type II (oculocutaneous) albinism. Melanin synthesis occurs, albeit at a low level. The hair is cream or light brown in color, and they eyes gray-blue or light brown [16,17]. Varying degrees of congenital nystagmus, iris hypopigmentation, decreased retinal pigment in the epithelium, loss of visual acuity, photophobia, strabismus and loss of hearing may also be seen in albinism in clinical practice. Patients with albinism exhibit normal development, intelligence and fertility. Sun glasses and photochromic lenses are generally sufficient for photophobia and visual acuity. Regular skin examination is very important for these patients in terms of early diagnosis and treatment of skin cancers [18].

Pityriasis alba (PA): One of the most common pigmentation disorders, this is a chronic, benign, inflammatory dermatosis characterized by widespread hypopigmented lesions. The condition is frequently recurring and troubling to patients in esthetic terms. It is seen in 1% of the general population and 9.9% of the pediatric population. It is the most common skin disease among children aged 6-16. Clinically, irregular, hypopigmented macules with ill-defined margins are observed. These lesions may be 0.5-6 cm in size. They are generally seen on the face, on the lateral aspects of the arms and on the trunk. Sun light, dry skin and exposure to light and moisture and implicated in the pathogenesis. Moisturizers, corticosteroids, Sun protectors and antiseptics can be used in treatment. Studies have recently reported perfect results with local immunosuppressive agents such as pimecrolimus and tacrolimus [19,20]. Moreno-Cruz et al. compared the use of calcipotriol and tacrolimus in PA and reported similar results in terms of repigmentation. They also reported that calcipotriol might represent a therapeutic alternative since this lacks the long-term side-effects of immunosuppressives [20].

**Diseases involving hyperpigmentation**

**Melasma:** Melasma (chloasma) is an acquired pigmentation disease arising due to melanogenesis dysfunction. It is more common in females than in males. The disease is also known as the mask of pregnancy or chloasma. The cause is still unknown, although there are known to be triggering factors, such as pregnancy, menopause and oral contraceptive use. Clinically, brown macules with distinct and irregular margins are seen. These are generally symmetrical and often on the face when exposed to the Sun. There are two subtypes of facial melasma depending on the site of involvement, centrofacial and peripheral. It may also be seen in extracutaneous sites such as the arms, forearms or cervical and sternal regions. The course involves irregular, symmetrical hypochromic skin discoloration. Involvement in these regions is generally seen in advanced age in patients undergoing the menopause or receiving hormone replacement. Diagnosis is generally clinical. Wood’s light and histopathology may be employed on rare occasions [21-23].

Treatment must primarily be directed toward the underlying cause. Additionally, local treatments such as hydroquinone, tranexamic acid, 4-n- butylresorcinol, oligopeptides, silimarin, an extract of the plant *Silybum marianum* and orchid extract can be used, as well as chemical peeling gents such as tretinoin, trichloracetic acid (TCA), glycolic acid (GA), kojic acid and the novel agent amino fruit acid, as well as Q switched (QS) laser therapies. Local hydroquinone is still the most important gold standard treatment for melasma. This prevents tyrosinase enzyme inhibition and the conversion of dopamine into melamin. Another foreseen mechanism is destruction in melanocytes with RNA and DNA synthesis inhibition. Hydroquinone used in concentrations of 2-4% in combination with tretinoin and dexamethasone (Kligman’s formula) increases its effectiveness. Recent studies have shown that microcapsules containing 4% hydroquinone in combination with 0.15% retinol and antioxidants causes a marked decrease in the color and size of lesions. One percent tretinoin used for chemical peeling has been found to achieve similar success to 70% GA. Peeling with TCA, which can be used at a level of 10-20%, produces results within 4 weeks, although recurrences can be seen after 12 months. Amino fruit acid peeling is a novel agent reported to represent an effective therapy with its powerful antioxidant and photopigmentation-preventive effects. QS lasers can be used in the form of neodymium:yttrium aluminum garnet-532 nm (Nd:YAG), QS ruby-694 nm, Q switched alexandrite-755 nm or QS Nd: YAG-1064 nm [19]. QS Nd:YAG-1064 nm is the most commonly employed laser therapy for melasma. One study used laser therapy in combination with 30% GA peeling and reported that this was more effective than sole use [24].

**Post-inflammatory hyperpigmentation:** This refers to hyperpigmentation that may be seen as a response to cutaneous inflammation following trauma (physical or chemical injury), skin...
irritation and acne, and to dermatoses such as atopic dermatitis, lichen planus and psoriasis. It can be seen at any age and in any individual. Studies have shown a greater number of melanocytes released as a response to inflammation and a resulting increase in pigmentation due to increased melanin production associated with an inherited disposition in some individuals. It is characterized by lesions being restricted to a pre-existing area of inflammation and has indefinite margins. Pigmentation gradually returns to normal with resolution of inflammation. The underlying primary dermatosis must first be brought under control and treated if possible. It is also very important to avoid exposure to the Sun and to use solar protectors. Additionally, 0.1% tretinoin cream, 2% hydroquinone, 10% GA peeling and combinations thereof can also be used [25,26].

**Erythema dyschromicum perstans (EDP):** EDP was first described by Ramirez in 1957. It is also known as ashy dermatosis. This hyperpigmentation disease is characterized by slow progressing, asymptomatic ash-colored macules. Some authorities consider it to be an antithesis of lichen planus pigmentosus. The condition is still controversial because of its clinical and histopathological characteristics. The etiology is still uncertain. It is more common in dark-skinned individuals. Slowly proceeding gray, gray-brown or gray-blue macules and plaques similar to pityriasis rosea are seen on the trunk, neck, arms and faces in most cases. It is seen in advanced stages of generalized hyperpigmentation disease. Diagnosis is made on the basis of histopathological tests in addition to clinical findings. Histopathological are typical but not pathognomonic. Vacuolization in the basal layer and varying degrees of lichenoid lymphocytic infiltration and colloid bodies are observed. Avoiding the Sun, chemical peeling agents and topical and systemic steroids have been used in treatment but found to be ineffective. Use of dapsone, clofazimine and griseofulvin has been shown to exhibit partial effects [27,28].

**Prurigo pigmentosa (PP):** PP is a disease of uncertain etiology first described by Nagashima in 1971. Several studies have shown no other underlying disease in patients with PP. However, some studies have reported that it may be associated with diabetes mellitus, ketonemia, diet, weight gain, pregnancy and menstruation. The condition is an inflammatory dermatosis characterized by symmetrically located, powerfully itching, erythematous urticarial papules on the trunk and neck accompanied by reticular pigmentation. Histopathological tests are needed to exclude other inflammatory dermatoses in diagnosis. Hyperplasia and parakeratosis in the epidermis and hyperpigmentation with melanophages in the upper dermis without pathognomonic findings may be determined. First-step treatment is generally 100 mg/day oral minocycline. Doxycycline, dapsone, potassium iodide and antibiotics from the macrolide group have also been reported as thereof can also be used [25,26].

## Conclusion

This review discusses pigmentation disorders, a disease group that occupies an important place among diseases of the skin and that is particularly distressing in cosmetic terms. Enhancing dermatologists’ and other physicians’ experience and knowledge concerning differential diagnosis and treatment will greatly assist correct management of these diseases.

## References

