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A Short Review of Pigmentation Disorders in Systemic Diseases

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Abstract

Since ages, the skin colour is an important issue for human race. Melanocyte abnormalities are mentioned during the fetal developmental stages in literature from ancient cultures. The deciding factor for the pigmentation is melanin. An old notion of melanocyte producing melanin is now obsolete. It is the epidermal unit which is responsible for the process of melanogenesis, production and distribution of the melanin. Various systemic diseases are having hyper or hypo-pigmenatation as their signs. The present review briefly describes a few of these systemic disorders.

Keywords: Hypo-pigmenatation; Melanocytes; Melanogenesis; Addison's disease

Introduction

Since ages, the skin colour is an important issue for human race. Melanocyte abnormalities are mentioned during the fetal developmental stages in literature from ancient cultures [1]. The deciding factor for the pigmentation is melanin. An old notion of melanocyte producing melanin is now obsolete. It is the epidermal unit which is responsible for the process of melanogenesis, production and distribution of the melanin. Pigment cell melanocyte surrounded by keratinocytes constitutes the epidermal unit. On one hand when exposure to the sunlight increases skin melanin content, on other melanin imparts photoprotection with its ability to absorb ultraviolet radiations specially UVB [2-4]. Melanocytes have specific distribution in the skin. In the basal layer of the epidermis at the junction of the dermis and epidermis melanocytes are located. Dendritic processes of these melanocytes help in the melanin distribution and cell signaling. Melanin pigment is also present in uvea of the eye, cochlea and vestibular region of the ear, leptomeninges of the brain, and ventricular septum and valves of the heart [5].

Melanocytes are derivative of the neural crest (NC) cells which are present on the dorsal surface of the neural fold. Both dorsolaterrally as well as ventromedially migrating part of the NC cells gives rise to melanoblasts – melanocyte precursors. Melanoblasts migrate from dermis to epidermis during the process of embryonic development and later start the melanin production [6-8]. Melanin chemically is an insoluble compound 5,6-dihydroxyindole synthesized from an amino acid tyrosine. In melanocytes it is produced in the 'melanosomes' - cytoplasmic organnels. Melanin synthesis is under hormonal and neural regulation. Initial steps are catalyzed by tyrosinase, a copper-containing oxidase, which converts tyrosine to dopaquinone. Subsequent reactions occur through nonenzymatic auto-oxidation, in the presence of zinc, with formation of the black to brown pigment eumelanin. The yellow to reddish brown, high-molecular-weight polymer known as pheomelanin and the low-molecular-weight trichromes result from addition of cysteine to dopaquinone and further modification of the products (Figure 1).

Thus melanogenesis is a complex process. When gone awry, it results into various pigmentation disorders either hyper or hypo-pigmentation. These disorders may be congenital or acquired, permanent or temporary, systemic or region restricted [9]. Pharmaceutical and cosmetic industry are getting constant boost as such disorders have a significant negative impact on the lifestyle of the patients [10,11]. In the present review hyperpigmentation and hypopigmentation disorders are discussed in association with few of the important systemic diseases.

Hyperpigmentation

Systemic diseases causing hyperpigmentation can be differentiated into metabolic, autoimmune and endocrinopathies.

In porphyria cutanea tarda the presentation is reticulate, spotty or diffuse patterns, especially localized on temporal regions, cheeks, V-shaped area and arms. The skin darkening is seen in sun-exposed areas and is a reflection of the photoreactive properties of porphyrins [12]. There are various mediators like reactive oxygen species (ROS), mast cells and fibroblasts, ecosanoids, complements and matrix metalloproteinase. ROS damages cell membrane and causes tissue injury and release of inflammatory mediators [13,14]. Complements too participate in the porphyrin mediated pigmentation through generation of ROS. Complements are found on the vessel walls and dermo-epidermal junction [15,16]. Fibroblast proliferation with metaloproteinase like MMP1 or MMP2 has degenerating action on

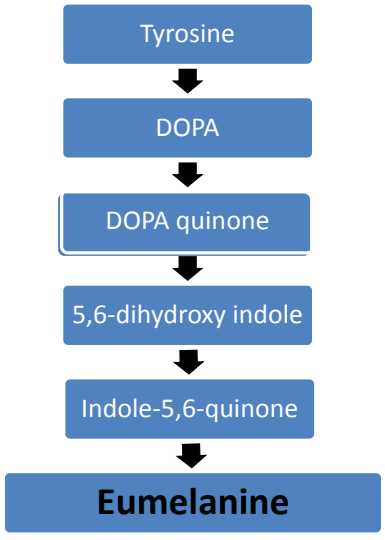

Figure 1: Melanin synthesis.

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the dermis. Eicosanoids especially the PGE2 also possibly involved in pigment changes [17,18].

In hemochromatosis deposition of excess iron in the skin stimulates melanin production leading to the bronze like hyperpigmentation [19]. Niacin deficiency is well known to cause pellagra in which area exposed to sunlight shows scaly hyperpigmented patches [20]. Similar picture is reported in the vitamin B12 and folic acid deficiency but is described as reversible in nature [21,22].

Generalized hyperpimentation is found in patients of whipple's disease along with other sign like diarrhea, weight loss, arthritis, and lymphadenopathy. Also seen in Peut-Jegher's syndrome, Cronkhite-Canada syndrome. Skin pigmentation suggests the severe form of whipple's disease [23].

Among autoimmune diseases, primary biliary cirrhosis (PBC) shows diffuse hyperpigmentation due to presence of increased amount of melanin. The ratio of melanocyte: keratinocyte is not significantly higher in PBC. However, in PBC, melanosomes persisted to unusually high levels in the epidermis and are packaged in larger membrane-bound clusters. Whether excess melanin results from increased melanogenesis or defective melanin degradation remains unclear, although there is some evidence favouring the latter mechanism [24].

Presentation of hyperpigmentation is similar in scleroderma and PBC. In biliary cirrhosis, the hyperpigmentation is accompanied by pruritus, jaundice, and xanthomas, whereas in scleroderma, it is accompanied by sclerosis of the extremities, face, and, less commonly, the trunk.

POEMS (polyneuropathy, organomegaly, endocrinopathies, M–protein, and skin changes) syndrome. The skin changes include hyperpigmentation, induration, hypertrichosis, and angiomas [25]. A few cases of Eosinophilia-myalgia syndrome are reported with the use of L-tryptophan (Table 1).

Addison's disease or primary adrenal insufficiency results in glucocorticoid and mineralocorticoid deficiency. Along with other signs and symptoms cutaneous manifestations include darkening of the skin especially in sun-exposed areas and hyperpigmentation of the palmar creases, frictional surfaces, vermilion border, recent scars, genital skin, and oral mucosa [26]. Hyperpigmentation is caused by increased levels of beta-lipotropin or Adrenocorticotropic hormone, each of which can stimulate melanocyte production [27].

Nelson's syndrome is a potentially life-threatening condition that does not infrequently develop following total bilateral adrenalectomy (TBA) for the treatment of Cushing's disease. Hyperpigmentation of skin and mucous membranes particularly on extensor surfaces, flexures, over scars and on the areolae is seen [28]. Addison's disease, Nelson syndrome and ectopic ACTH Syndrome exhibit overproduction of the pituitary hormones α-MSH (melanocyte-stimulating hormone) and ACTH can lead to an increase in melanocyte activity. These peptides are products of pro-opiomelanocortin gene and exhibit homology.

Hypopigmentation

Systemic diseases causing hypopigmentation can be classified into two groups as diffuse systemic and localized systemic.

Oculocutaneous albinism (OCA) is a classic example of the diffuse form of hypopigmentation. Oculocutaneous albinism (OCA) is a group of inherited disorders of melanin biosynthesis characterized by a generalized reduction in pigmentation of hair, skin and eyes. Worldwide prevalence is considered to be 1:17000. OCA1A being the most severe type with a complete lack of melanin production throughout life, while the milder forms OCA1B, OCA2, OCA3 and OCA4 show some pigment accumulation over time [29]. The disease is due to mutations in the tyrosinase gene (type I) or the P gene (type II); with most severe form having total lack of enzyme activity.

Hermansky-Pudlak syndrome (HPS) is a rare autosomal recessive disease that displays genetic heterogeneity; there are 9 known subtypes. HPS is characterized by oculocutaneous albinism, a platelet storage pool deficiency and resultant bleeding diathesis, and lysosomal accumulation of ceroid lipofuscin [30]. Chédiak-Higashi syndrome is a rare autosomal recessive congenital immunodeficiency mainly characterized by a condition called oculocutaneous albinism. It has been reported due to disturbance in melanin migration because of giant melanosoms [31,32].

Phenylketonuria (PKU) is caused by deficiency of phenylalanine hydroxylase (PAH) in the liver. Patients with PKU show increased L-phenylalanine in blood, which leads to mental retardation and hypopigmentation of skin and hair [33].

Homocysteinuria is the deficiency of cystathionine beta-synthase (CBS) is a genetic disorder of transsulfuration resulting in elevated plasma homocysteine and methionine and decreased cysteine (Table 2). Homocysteine inhibits tyrosinase, the major pigment enzyme leading to cessation of pigment synthesis [34].

Sarcoidosis is a multisystemic inflammatory disease characterized by graulomas which are noncaesiating in nature. The development and accumulation of granulomas constitute the fundamental abnormality in sarcoidosis. Granulomas are compact, centrally organized collections of macrophages and epithelioid cells encircled by lymphocytes. Macrophages, in the face of chronic cytokine stimulation, differentiate into epithelioid cells, gain secretory and bactericidal capability, lose some phagocytic capacity, and fuse to form multinucleated giant cells [35,36]. In sarcoidosis, asa result of inflammation, localized hypopigmented patches are seen. Dermal nodules with surrounding hypopigmentation and macular hypopigmented areas are reported in the literature [37]. Similar picture is seen in the cutaneous T cell lymphoma (CTCL).

Waardenburg syndrome is a rare disease characterized by deafness in association with pigmentary anomalies in skin, hair and eyes. This is a type of neurocristopathy in which there is an abnormal embryonic migration or survival of two neural crest–derived elements, one of them being melanocytes. The syndrome is caused by mutations in genes that

Metabolic	Autoimmune	Endocrinopathies
Porphyria cutanea tarda	Biliary cirrhosis	Addison's disease
Hemochromatosis	Scleroderma	Nelson syndrome
Vit B12, Folate deficiency	POEMS syndrome	Ectopic ACTH syndrome
Malabsorption syndromes	Eosinophilia-myalgia syndrome	
Pellagra		

Table 1: Systemic diseases with dermal hyperpigmentation.

Diffuse systemic	Localized systemic
Oculocutaneous albinism	Sarcoidosis
Hermansky-Pudlak syndrome	Scleroderma
Chédiak-Higashi syndrome	Waardenburg syndrome
Phenylketonuria	Cutaneous T cell lymphoma (mycosis fungoides)
Homocystinuria	

Table 2: Systemic diseases with dermal hypopigmentation.

regulate the melanocytes differentiation from the neural crest during embryonic development [38,39].

Scleroderma is an autoimmune disease from rheumatic category. Clinical picture is vitiligo-like leukoderma. This resembles to idiopathic vitiligo that has begun to repigment as a result of treatment in which perifollicular macules of normal pigmentation are seen within areas of depigmentation. The presence of macules with any degree of pigmentation or macules with varied pigmentation would favor the diagnosis of scleroderma over vitiligo [40]. Vogt-Koyanagi-Harada syndrome, onchocerciasis and melanomaassociated leukoderma are some of the other disorders that have to be differentiated from vitiligo.

Conclusion

Thus there are many systemic diseases which have hyper or hypo-pigmentation as one of their presenting features. One needs to be very careful while diagnosing the disorder as some signs may overlap.

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