Melasma Clinical Features, Diagnosis, Epidemiology and Etiology: An Update Review

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ABSTRACT

Melasma is one of the commonest dermatological challenges that facing dermatologists in the whole world. Most of the previously published articles regarding melasma usually focused on its management and the newly discovered drugs; however, the understanding of the suspected etiology and the pathogenesis is very critical to treat this skin disorder in a correct manner. Therefore, this review is an attempt to do a comprehensive updating on the present understanding of the melasma epidemiology, etiology, its role in pregnant, post-menopausal women, and in males, besides its clinical features and diagnosis through searching in many scientific databases including EMBASE, Cochrane Library, PubMed, Pubmed Central (PMC), Medline, Web of Science, and Scopus.

This review approaches recognizing the pathogenesis that can provide ideas to solve the therapeutic problems which connect to melasma. Therefore, this article is entirely established on previously performed studies so that no new studies on animal or human subjects were conducted by the author.

Keywords: Melanin; melanocortin; melasma (Siriraj Med J 2021; 73: 841-850)

INTRODUCTION

Melasma is one of the common acquired hyperpigmentation conditions, mostly affects the face, with a high prevalence among females and the darker skin phenotype individuals.[1] Many etiologies, including family history, hormonal influence, and sunlight exposure, have been involved in its pathogenesis.[2] The overall prevalence reports wide ranges (1-50) %, because the values are usually determined in a particular ethnic group within a specific geographical area.[3] Histologically, melasma may reveal enlarged melanocytes, increased dermal or/and epidermal pigmentation, increased melanosomes, dermal blood vessel, solar elastosis, and rarely perivascular lymphohistiocytic infiltrations.[4]

Methodology

Melanogenesis

Melanogenesis is a process that occurs inside the melanosomes. There are two forms of melanin pigments are produced within the melanosomes; pheomelanin and eumelanin. Pheomelanin is a soluble sulfur-containing bright red-yellowish polymer, while eumelanin is an insoluble dark brownish-black polymer.[5] Tyrosinase is a copper-containing enzyme; however, before tyrosinase can act on tyrosine two cupric atoms present in tyrosinase must be reduced to cuprous atoms. Tyrosinase is responsible for the first 2 stages in the synthesis of melanin; the L-tyrosine hydroxylation into L-dihydroxyphenylalanine (L-DOPA) with the following stage of oxidation for this o-diphenol into the related quinone (L dopaquinone).[6] It is worth noting that the L-tyrosine concentration required for melanogenesis is determined by the conversion of L-phenylalanine which is an essential amino acid through the action of the intracellular enzyme phenylalanine hydroxylase (PAH). The L-phenylalanine significance in melanogenesis is elucidated in phototypes of the skin I-VI as the epidermal PAH actions are linearly correlated.[7]

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Following the dopaquinone synthesis, the melanin pathway is split into the synthesis of red-yellowish pheomelanin and brownish-black eumelanin with spontaneous conversion into dopachrome and leucodopachrome. In the eumelanin formation pathway, the dopachrome consider as either spontaneously transformed into 5, 6-dihydroxyindole or it is enzymatically transformed into 5, 6-dihydroxyindole-2-carboxylic acid via dopachrome tautomerase (DCT), besides pointed out as tyrosine-related protein-2 (TRP-2). The tyrosinase-related proteins are of two types, TRP-1 and TRP-2 that are structurally associated with tyrosinase.[8,9]

TRP-1 and TRP-2 are melanosomal proteins that extend to the membrane of the melanosome like tyrosinase. There is a suggestion that TRP-1 elevates the eumelanin to pheomelanin ratio. Also, they may be explaining the high tyrosinase stability. Ultimately, the quinones and indoles polymerization results in eumelanin synthesis.[10]

The pathway of pheomelanin branches from that of eumelanin at the step of L-dopaquinone and it depends upon the cysteine existence that shows active transporting through the membrane of melanosomes. The L-dopaquinone interacts with cysteine to produce cysteinyl-dopa, which is then converted into the quinoleimine and alanine-hydroxyl dihydrobenzothazine that polymerized to pheomelanin. Besides, the tyrosinase enzyme may be indirectly triggered by the tyrosine hydroxylase isoenzyme 1 (TH1) which exists in the melanosomes that catalyze L-dopa formation. In turn, the latter L-dopa may play a role as the tyrosinase substrate.[11]

Redox (Reduction Oxidation Reaction) status within melanosomes is important for the equilibrium between the pheomelanin and eumelanin synthesis. This pheomelanin or eumelanin synthesis is directly affected by the glutathione (GSH) level, the low GSH level related to pheomelanin, and the high related to eumelanin. Therefore, the functional and expressional activities of the antioxidant enzymes like glutathione reductase, glutathione peroxidase, thioredoxin reductase, and catalase are most likely modifying the melanosomes pathway.[12]

Each melanocyte that establishes at the basal layer of epithelium together with its dendrites reacts with about thirty-six keratinocyte cells to transmit melanosomes and cause skin protection from the ultraviolet radiation and photo-stimulated carcinogenesis. Besides, the type and amount of melanin synthesized and transferred into the keratinocyte cells with successive aggregation, incorporation, and degradation affects the epidermis coloration.[12]

The ratio of eumelanin to pheomelanin varies dramatically in the various skin phenotypes, found at the lowest level in type I and II and highest in type V and VI; and these types are:-

1. Type I :- (score ranges 0-6) never tans, always burns (pale white; red hair or blond; blue eyes; with freckles).

2. Type II :- (score ranges 7-13) minimally tans, usually burns (white; fair; red hair or blond; hazel, green or blue eyes).

3. Type III :- (score ranges 14-20) uniformly tans, sometimes mildly burns, (creamy white; fair; with any eye or hair colour).

4. Type IV :- (score ranges 21-27) always tans, minimally burns (moderate brown).

5. Type V :- (score ranges 28-34) very easily tans, very rarely burns (dark brown).

6. Type VI :- (score ranges 35-36) never tans, never burns (deep pigmented darkish brown to darkest brown).[13]

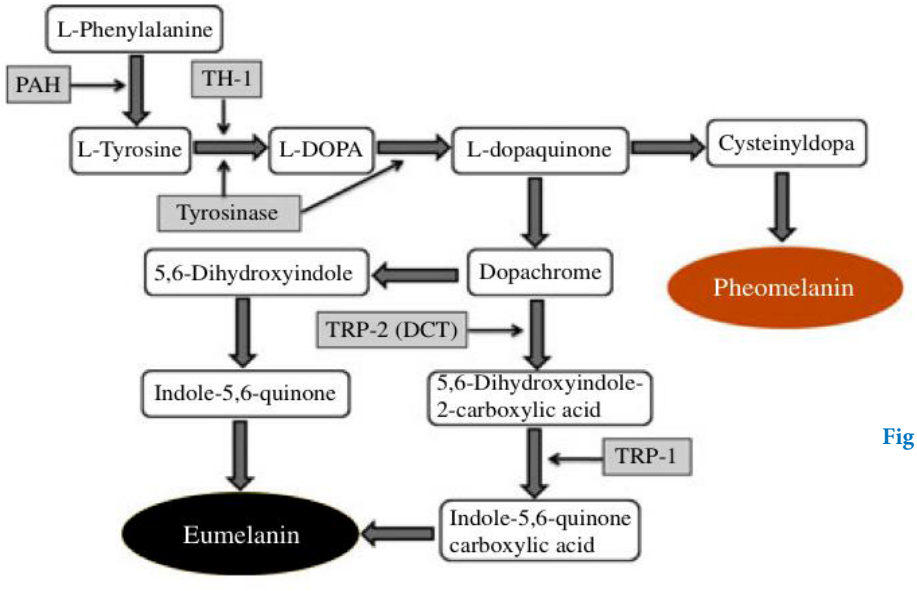

Fig 1. Melanin synthetic pathway[5]

Melasma

The term "facial hyperpigmentation" or "melasma" is obtained from the Greek word "melas", meaning "black". It also refers to "chloasma gravidarum" or "the pregnancy mask". Its onset starts commonly during the 2nd half of gestation, and it exists in 40-75% of all pregnancies. It occurs usually in dark hair, brown eyes, and dark-epidermis women. The main variations of melasma prevalence in various studies were accredited to the proven fact that explaining the pigmentary alterations are more visible in individuals with fair skin.[14]

Melasma commonly influences the principal photo-exposed skin regions, particularly the facial and neck areas. The commonly involved sites include the cheeks, chin, forehead, nose, upper lip, and temples; while the rarely involved sites may distress the sternal region and extensor arms. However; this condition considers as a benign disorder that usually with aesthetic implications only, but it can influence the self-esteem and self-image, with negative effects on an individual's life quality.[15]

Clinical features of melasma

Melasma is localized at sun-exposed regions, where symmetrical light or dark brownish confluent macules or punctate are present, most sharply delimited, particularly on the cheeks, forehead, chin, and upper lip. There are three kinds of melasma lesions; centrofacial type (implicates cheeks, forehead, nose, chin, and upper lip), mandibular type (over the mandibular ramus), and symmetrical malar type (localized to nose and cheeks).[8,12,16] In male individuals, the malar type is the commonest, while the centrofacial is the common type revealed in females. Wood's lamp may clinically divide the pigmentation depth; in the epidermal type may be shown highlighting multiple pigments in (50%) of cases, compared to dermal type (5%), were not.[17] While the mixed type in (45%) of all cases just a partial pigmentation highlighting is found. Clinically, the dermal type becomes mildly visible bluish because of the Tyndall effect. The disease severity may be objectified with Melanin Index (MI) estimated by specific tools, Melanin Area and Severity Index (MASI) determining the regions and densities of involvements, with patient self-evaluations.[18,19]

Extra-facial melasma includes many features such as irregular, hyperchromic, symmetrical discolorations at the neck, cervical, sternal areas, arms, forearms, and eventually at the back. It affects the upper limbs predominantly among old adults, menopausal women, and those receiving hormonal replacement therapy.[20]

Diagnosis of Melasma

1. Melasma examination under normal light

The skin of melasma lesion is inspected by natural solar radiations, the macular lesions have irregular, quite sharply demarcated borders with a "stuck on" appearance The hypermelanosis type can be epidermal (brownish), a dermal (bluish-gray), or a mixed (brownish-gray).[7,21]

2. Wood's lamp examination

This procedure used to evaluate the melasma clinical status, depending upon Wood's light (320-400 nm) and four types of melasma can be recorded:-

A. The epidermal type: has increased melanin in suprabasal, basal, and stratum corneum layers. The pigmentary lesions are emphasized with Wood's light.

B. The dermal type: does not show enhancement with the Wood's light. Melanophages exist in the deep and superficial dermis.

C. The mixed type: the dermal and epidermal pigment type that shows no or slight enhancement with the Wood's light.

D. Wood's light unapparent is seen in dark individuals.

As the Wood's lamp was utilized to determine the melanin pigment situation either in the dermis or epidermis (i.e. dermal versus epidermal melasma), the histopathological and confocal microscopy reports revealed that it is usually a mixture from the two types in the same patient even they have only epidermal type by Wood's light.[8,9,17,22]

3. Hormonal assay

The hormonal level assessments can be guaranteed because of the activity of hormones imbalance in melasma disease. FSH, LH, MSH, progesterone, thyroid, and prolactin hormones level must be estimated, just if indicated.[23,24]

4. Microscopic histopathology

Melasma may be clinically diagnosed; however, the histological report may be also helpful. The histological findings are the same in both males and females. Furthermore, the histopathological features of melasma in males are still unclearly defined. These features include flattening in the rete ridge, solar elastosis, and mild infiltrations of the inflammatory cells.[25] The amount of melanin is raised in the dermis or epidermis or even in both. In the epidermis, it presents in the keratinocyte cells of suprabasal and basal layers. The number of melanocyte cells is not increased but these cells are larger in size with more dendrites, greater melanosomal size, and; therefore, more activity will be produced. Dermal melanin amount increased in the middle and superficial dermis in macrophage cells, usually in aggregation at areas nearby the small dilated blood vessels. The epidermal melanization with the existence of melanophages at papillary dermis may be

revealed in Fontana-Masson and Haematoxylin-Eosin staining.[26] There is no proof of degeneration in the basal layer was recorded. Significantly elevated expressions for Stem Cell Factor (SCF) allover fibroblasts in the dermis with its C-kit receptors at the epidermal basal layer were present in diseased skin in comparison with non-diseased.[27]

Several special stains are present that facilitate the light microscopic visualization of melanocytes and their products including; silver stain, dopa reaction, and Fontana-Masson. Histologically, two types of pigmentation had been characterized, dermal and epidermal.[11]

Epidermal melasma appeared to be the most predominant type proceeded by mixed type. While melasma has classically been classified as epidermal- or dermal-based on the presence or absence of Wood's light enhancement, respectively, most cases show both epidermal and dermal melanin. Dermal melanophages are a normal finding in sun-exposed skin.[17,22]

Increased melanophages may also recognize in several melasma individuals by reflectance confocal microscopy (RCM) examination. Interestingly, RCM examinations revealed that the topographic distribution of the melanophages is very diverse from one lesional area to another and also within the same lesional area. These findings supposed that histological classifications (dermal, epidermal, and mixed) regarding the depth of the pigment utilizing a single specimen of skin biopsy can be very risky. A reliable classification could be dependent upon the dermal/epidermal melan in ratio present over the entire involved skin area. Until nowadays, it is not clear, if the origin of dermal pigments comes from the epidermal layer. Besides, it is unclarified if dermal pigments may be resolved spontaneously when they are not supplemented from epidermis. In darkly pigmented individuals (e.g. those with indeterminate melasma), a skin biopsy is occasionally performed before treatment is initiated.[6,28-32]

5. **Electron microscopy**

It shows high amounts of melanin within all layers of the epidermis and also within the dermis, according to the melasma histological type. Also, the numbers of melanocyte cells included the high numbers of melanosomes compared to melanocyte cells of the normal skin is high. It may reveal the increased melanosomes were associated with findings of many organelles in the melanocyte cells from the diseased lesions. The melasma lesions included more Golgi apparatus, mitochondria, rough endoplasmic retinaculum, dendrites, ribosomes, and supposing more production ability of those cells.[33,34]

6. **Immunohistochemistry**

It may show high expression for stem cell factor in the dermal layer and for c-kit in epidermal layer with high expression for vascular endothelial growth factor, which can be the main factor achieved in the changed blood vessels occurs in melasma.[27,35-37]

7. **Dermoscopy** may play a principal role in melasma diagnosis and in demonstrating the melanin pigment deposition level. The main findings include pigmented dots, globules, more prominent vascularity, and telangiectasia. Also, the accentuation for the pseudo-reticular pigmentary network and Owl's eye structures exist. In addition, dermoscopy can be used in the assessment of melasma severity.[38,39]

Epidemiology of melasma

Although melasma may influence individuals from any race, it is usually common among darker skin phototypes and the commonest in persons with Fitzpatrick IV-VI skin types.[4]

In a random study including self-recording for melasma among Hispanic female individuals, it reported that the incidence about 8.8% but the previous incidence was 4%. A survey among Arab Americans who lived in the USA mentioned that the fifth commonest skin disease was melasma with 14.5% from a surveyed population,[12] while another study screened 200 persons with melasma found men demonstrated 20.5%.[20] Another published article reported the results of three studies that estimating the incidence of melasma among adult males of Latino laborers with 36.0%, 7.4%, and 14%.[11] The average age in affected males was 33.5 years and the duration was about 3.5 years; however, it may be present also among older males and for more periods.[9] It may cause embarrassment in men due to its awful-looking; and a general community stigma that classified it as a disorder or disease when affects pregnant women. It was recorded that its prevalence up to 75% among pregnant women, but it exists rarely before puberty and; therefore, it most commonly starts in the reproductive years of life.[40]

Melasma has recognizable psychological influences and significant emotions on affected individuals. The effect on the life quality of individuals with melasma may be standardized by the Melasma Quality of Life Scale (MELASQOL) or/and by the Dermatology Life Quality Index (DLQI); the individuals who have high DLQI scores signify poor Quality of Life (QOL).[18]

Etiology of melasma

The exact causes of melasma have not been defined,

but numerous factors are possible to be suspected including genetics, pregnancy, cosmetic use, sun exposure, antiepileptic medications, oral contraceptives, and thyroid dysfunction.[41] Among these factors, the following are the most important:-

1. Risk Factors

The precise melasma cause is still undetermined; even numerous factors may be involved in this lesion's pathogenesis. These factors are implicated as etiologic or genetic predispositions and influences, in approximately 40% of melasma individuals there is one relative at least affected with this lesion.[4] Other factors influencing the onset or/and triggering its onset including hormonal alterations during gestation or hormonal therapy, exposure to UV radiations, phototoxic drugs, cosmetics, chemicals, steroids, antiseizure therapy, and darker skin colorations.[32,42,43] Psychotropics and anxiety traits may be strongly related to melasma development; so that melasma is regarded as "the stress mask". All the previously mentioned factors are suggested to cause an increment in both melanocytosis and melanogenesis, the primary histological disturbances revealed in melasma. Furthermore, although its pathogenesis is unknown yet, the above factors are considered to trigger the disease in a population with genetic predispositions. Study of those factors may urge physicians to get better improvement for preventative measures, management of melasma individuals, expectation treatment result, and disease recurrence.[20]

The lesion onset is usually proved by deteriorated stratum corneum layer integrity with the overdue barrier recovery period, while a high amount of different inflammatory cells that exist in the lesional region are the common findings distinguished during melasma development in Asian population skin.[10]

2. Endocrine factors

The levels of hormones either because of hormonal therapy or during pregnancy periods are regarded to be one of those most influencing factors or even the most remarkable factor on the onset and melasma development. During pregnancy, endocrine, immunologic, vascular, and metabolic alterations increase the susceptibility of pregnant women to obvious alterations in the skin with its related appendages.[44] Progesterone, estrogen, and alpha-MSH which are commonly elevated during pregnancy time and especially at third trimester, are supposed to stimulate the melasma onset by for example through estrogen tentative pathway III that causing increase tyrosinase enzyme and melanosome transfer (Fig 2). Even with the multiple and various cases that found, no high levels for the mentioned hormones proved. However, several researchers believed that hormonal changes with increased Luteinizing Hormone (LH) and decreased estrogen levels, as a result of ovarian dysfunctions, can underlie the pathogenesis process in some conditions of the idiopathic melasma.[16,22,24]

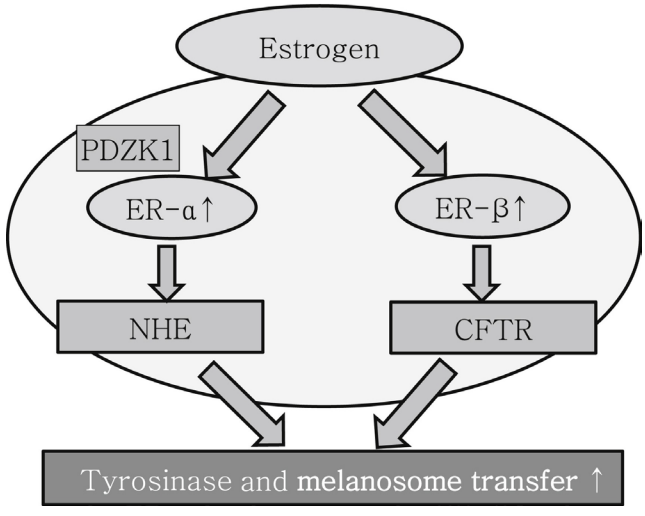

Fig 2. Tentative pathway III of the estrogen[25]

In addition to pregnancy, women taken contraceptive pills with progesterone or women at the post-menopausal period taken progesterone as hormonal therapy, the extra-facial melasma was usually common among them, therefore; the progesterone regarded as a principal factor in this disease. Impressively, the hyperpigmentation resulted from sequential or combined contraceptive pills are incompletely regressing after ceasing, contrary to melanoderma of pregnant women. Researchers; however, have mentioned that estrogen receptors and progesterone receptors expression at melasma-affected regions need more investigations and clarifications, these researches can cause better development for the topical anti-estrogen therapy of melasma.[7,19,45]

The thyroid autoimmune characteristic is also regarded as another important element in the melasma onset because a significant number of Hashimoto's diseased women get melasma and also those women who get the disease during pregnancy, will or even already have thyroid autoimmunity.[28]

Finally, other factors have been involved having the main role in melasma development, like melanocytic nevi and lentigines. Although, the presence of these factors is not very closely connected to the disease onset and its development, like the previously mentioned factors; on the other hand, melasma is usually revealed in women,

some articles have been done on men with melasma. In those articles, the most remarkable factors indicated for melasma development are regarded to be the usage of cosmetics, sunlight exposure, familial hyperpigmentation, hepatic disorders, and infections.[9,11,21,46-48] Even there are a few studies that suggest the circulating LH is crucially increased in melasma men, while testosterone is remarkably decreased in the very same category, information that assumes that melasma can implicate precise testicular resistance.[4]

3. Genetic factors

The skin phototypes III, IV, and V with the female gender regarded as the most recognized genetics, other inheritable characters, probably multi-genetic. One of the most important international researches in this scope was carried out in dermatological centers of 9 countries (USA, Germany, France, Mexico, Netherlands, Singapore, Italy, Hong Kong, and South Korea) and exhibited that 48% from 324 melasmic females had a positive familial history of this disease. Also in about 97% of total cases, another family member from the first degree of relativity is affected.[48] Epidemiological information in this consideration may seriously differ in other countries individuals: the prevalence of positive familial history recorded in literature are 70.3% in male individuals and 56% in female individuals in Brazil,[40] 54.7% in Iran,[23] 33% in India.[49] Although scattered and occasionally not implicating large patient's sample, these articles that reveal important variations even between individuals living in the same environmental situations, suppose that the susceptibility to melasma lesion is polygenic and might be also affected by the epigenetic modulations of melanogenesis. A study reported that expression of 16 microRNA (miRNA) could differ between the melanocyte cells managed with (forskolin and solar-stimulated UV radiation) from untreated melanocyte cells; one of those miRNAs, known as miR-145, was remarkably down-regulated and also capable of affecting the expression of some main pigmentary genes (Tyr, Trp1, Rab27a, Sox9, Mitf, Myo5a, Fscn1).[50,51]

4. Sun exposure

The most principal and obvious environmental stimulating factor for melasma is sunlight exposure. Among the various constituents of sunlight, UV radiation (A and B) has the main role; since they may induce or increase melanogenesis, migration directly, and melanocyte proliferations, but even indirectly, through triggering the formation of endothelin 1, interleukin 1 (IL-1), ACTH, and α-MSH by keratinocyte cells.[52-54]

The major role for the visible and the infrared radiation in the melanogenesis process is less remarkable, but not negligible; an association between occupational great exposure to the heat or the intense artificial lighting and exacerbation of melasma or/and low react to management was recorded by several researchers.[4] The indirect proof for the effect of the visible light revealed that the sunscreen compounds causing absorption for ultraviolet irradiations, and also the visible light reinforces the depigmentation effect for hydroquinone further than the sunscreen that blocks UV radiation only.[32,55]

The UV light is regarded as another important agent or factor that has a specified and proven role by multiple previous studies and also case reports.[12,13,39] The UV light is not regarded to be capable to develop melasma without any hormonal changes or genetic predispositions, but it is supposed to be essential in stimulating the lesion when the background presents. Apart from the genetic predispositions, autoimmunity and systemic disorders are highly associated with the development and appearance of the lesion. Systemic disorders like Addison's disease could almost always be doubtful and required exclusion in the clinically relative cases.[22,28]

5. Drugs

Melasma-like pigmentation has been noticed in individuals taking antiepileptic drugs like phenytoin or mephenytoin. Chlorpromazine and related phenothiazines may induce pigmentations at sun-exposed parts of skin especially those who received high doses for long periods. Other drugs include anti-tumor agents like cyclophosphamide, bleomycin, and adriamycin.[4,7,56,57]

In order to induce skin hyperpigmentation, sometimes even more than a single mechanism is involved. The tetracycline especially minocycline, tricyclic antidepressants particularly imipramine and desipramine, antimalarials, cytotoxic drugs, phenothiazines mostly chlorpromazine, amiodarone, anticonvulsants, sulfonylureas, and clofazimine are all could be listed as the drugs stimulating hyperpigmentation. Clofazimine stimulated pigmentations is a brown color, clarified in sun-exposed regions, sometimes unrecognizable from melasma. In most cases, those lesions are accompanied by nail involvement. The fixed drug eruption considers as a clinical distinctive kind of drug-stimulated hyperpigmentation presented by recurrent plaques in the same situations. It more frequently implicates genitalia, acral areas, and the lips. Many medications may develop this disease, but the greatly remarkable are sulfonamides, ibuprofen, and barbiturates.[8,10,39,41,58,59]

6. Cosmetic

These include a wide variety of perfumes, soaps, creams, powders, shampoos, that contain psoralen, tar derivatives, or hexachlorophene substance which are photodynamic that may cause facial pigmentation.[45]

However, the pigmented cosmetic dermatitis consider as a variant of the pigmented contact dermatitis because the cosmetic ingredients are the primary allergens where the face is predominantly involved. Clinically, the patchy or diffuse brown hyperpigmentation presents over forehead and/or cheeks or the entire face making it hardly differentiate from melasma.[60]

7. Idiopathic

Most cases among males and at least one-third of all cases among females are idiopathic.[18]

Melasma in pregnancy, post-menopausal women, and oral contraceptives role

During pregnancy, particularly in the third trimester, females have elevated levels of pituitary, ovarian and placental hormones, which exhibit a trigger for melanogenesis that can describe the relations between pregnancy and melasma.[23] High levels of progesterone, estrogens, and MSH also cause an increment in the transcription of dopachrome and tyrosinase tautomerase that can be implicated in developing pigmentations in this specific period.[61] Those findings suggest that melasma lesions in pregnant women are more possible to be related to the circulated female hormone than the MSH peptides. In fact, the high levels of progesterone, which occurs during pregnancy; and the estrogen formation, which takes place from the 8th till the 31st week of gestation mirrors the perfect progressive patterns of hyperpigmentation. In melasma, the major role of female hormone onset is proposed by its increased incidence in women getting exogenous progesterone or/and estrogen and its association with the menstrual period.[4,11]

The onset of melasma mostly happens during the 2nd half of pregnancy and it may be present in 40-75% of all pregnancies.[23] On contrary, a study done on 324 women who managed melasma disease in nine different clinics worldwide, recorded the melasma onset in 25% of females after using the OCP, in 27% of females during gestation, and in 41% of females after gestation.[48]

Melasma continues after gestation among less than 10%, though a single study report existence in about 30% of cases after ten years. If the melasma continues postpartum, some females notice a premenstrual hyperpigmentation flare. Regarding that UV exposure triggers up-regulation of melanocyte cells and their activity in the pathogenesis of melasma, susceptible females could be recommended to protect unavoidable heavy sunlight exposures and guarantee preservation with broad-spectrum (UVB and UVA) sunscreens and suitable clothing.[32,54]

As the female sex hormones that exist within OCP show to be principal for melasma development, the same association could be expected in postmenopausal females on Hormone Replacement Therapy (HRT). Indeed, there are some case reports for melasma present in the postmenopausal. Melasma in the forearms appears to be a comparatively common sign particularly in old age individuals and postmenopausal females using estrogen therapy supplementations. As several of those persons had melasma in the face when young that may explain the presence of people with estrogen-sensitive melanocyte cells in forearm skin that show maturation at an older age.[8,9,12,25] Tamoxifen considers a Selective Estrogen Receptor Modulator (SERM) and spends mixed estrogenic with antiestrogenic actions depending upon the tissues and cell types.[57]

Melasma in male

Some articles of melasma developing in men were available; in 1957, the first recorded male melasma case was in a French primary hypogonadism man, presented with low testosterone level and high FSH and LH.[62] Similarly, another study was done on fifteen Indian men who had idiopathic melasma, characterized by a low level of testosterone and high level of LH in comparison with same age controls; the estrogen level was undetected.[20]

In another study, a melasma case after oral therapies with triggers for production of testosterone, a compound containing indole-3-carbinol, androstenedione, dehydroepiandrosterone (DHEA), and Tribulus Terrestres, which is a gonadotropic trigger that elevates LH secretions.[39]

Melasma and the pituitary gland

The melanocortins produced from intermediate lobe of the hypophysis gland, they regarded as a group of peptide hormones important for melanogenesis that activate the formation and release of melanin by melanocyte cells situated at skin and hairs. The melanocortins contain three different kinds of MSH (α-MSH, β-MSH, and γ-MSH) with ACTH; all of them are obtained from a similar precursor, the proopiomelanocortin prohormone (POMC), which secretions are stimulated by the Corticotropin-Releasing Hormone (CRH) created within the hypothalamus.[4,52]

In humans, ACTH and α-MSH are also created regionally in skin (both within keratinocyte and melanocyte cells) and have main roles in pigmentation, probably via autocrine or/and paracrine mechanisms. The CRH

expression with CRH receptors found in the normal human melanocyte, melanoma, and nevus cells. The plasma immunoreactive β-MSH measured for individuals with/without melasma getting progesterone alone or a combination of estrogen-progesterone therapy; the β-MSH level was indifferent from gender and age-matched control group.[7,12,53]

It is essential to recognize melasma that is located mostly on the face and less considerably on neck or forearm, from the generalized hyperpigmentation due to some adrenal or pituitary disorders causing high levels of MSH and POMC-obtained ACTH with subsequent universal skin hyperpigmentation. The individuals influenced by major adrenal insufficiencies, ACTH-depending Cushing's and Nelson's syndromes, diagnosed by increased POMC-obtained ACTH levels.[4,7,22,56]

CONCLUSION

Melasma is a clinical condition caused by multiple factors and etiopathogenetic mechanisms that are required in order to understand more effective management. The discovery of recent pathways and pathogenic mechanisms is essential in collocation the way for recent more effective melasma treatment agents or procedures. The pathogenic melasma mechanisms might be heterogeneous in various ethnic groups among the population. This review approaches toward recognizing the pathogenesis that can provide ideas to solve the therapeutic problems that connect to melasma. Therefore, this article is entirely established on previously performed studies so that no new studies on animal or human subjects were conducted by the author.

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