Review Article

Facial melanoses: Indian perspective

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ABSTRACT

Facial melanoses (FM) are a common presentation in Indian patients, causing cosmetic disfigurement with considerable psychological impact. Some of the well defined causes of FM include melasma, Riehl's melanosis, Lichen planus pigmentosus, erythema dyschromicum perstans (EDP), erythrosis, and poikiloderma of Civatte. But there is considerable overlap in features amongst the clinical entities. Etiology in most of the causes is unknown, but some factors such as UV radiation in melasma, exposure to chemicals in EDP, exposure to allergens in Riehl's melanosis are implicated. Diagnosis is generally based on clinical features. The treatment of FM includes removal of aggravating factors, vigorous photoprotection, and some form of active pigment reduction either with topical agents or physical modes of treatment. Topical agents include hydroquinone (HQ), which is the most commonly used agent, often in combination with retinoic acid, corticosteroids, azelaic acid, kojic acid, and glycolic acid. Chemical peels are important modalities of physical therapy, other forms include lasers and dermabrasion.

Key words: Corticosteroids, erythema dyschromicum perstans, facial melanosis, hydroquinone, lichen planus pigmentosus, melasma, Riehl's melanosis, retinoids

Facial melanoses (FM), a common presentation of Indian patients, are complex diagnostic (and even greater therapeutic) problems consisting of few somewhat well defined clinical entities, several of which have overlapping features and some of which have defied classification [Table 1].

Most FM are commoner in darker races with both light and photosensitizing chemicals (occupational/ in cosmetics) playing an important role. Based on the location of melanin (as identified by color of lesion, accentuation of color under Wood's light and histopathology, though the correlation between Wood's lamp findings and histopathology is less than satisfactory) three types of hypermelanosis are identified:

- ***Brown hypermelanosis:*** Wherein excess melanin is in basal and suprabasal (rarely throughout epidermis including the horny) layers and the pigmentation is accentuated under Wood's lamp. The increased epidermal melanin can be a:
  - *Melanotic hypermelanosis*: due to increased melanin production by normal number of melanocytes.
  - *Melanocytic hypermelanosis*: due to increased number of melanocytes.
- ***Blue hypermelanosis (ceruloderma)***: Wherein excess melanin is in dermis and the pigmentation is

Table 1: Causes of facial melanoses

Melasma
Erythema dyschromicum perstans (EDP)
Lichen planus pigmentosus (LPP)
Riehl's melanosis (RM)
Erythromelanosis peribuccale pigmentaire of Brocq (EPP)
Poikiloderma of Civatte
Erythromelanosis follicularis of face and neck
Nevus of Ota
Miscellaneous causes

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not accentuated under Wood's lamp. Ceruloderma is due to:

- *Increased transfer of melanin from epidermis to dermis* (pigmentary incontinence): melanin granules accumulate within melanophages or may be free in the extracellular matrix of the dermis.
- *Production of melanin*: by ectopic dermal melanocytes.
- *Binding of melanin*: to exogenous pigments deposited in the dermis.

- ***Mixed hypermelanosis***: due to increased epidermal and dermal melanin.

MANIFESTATIONS

MELASMA (CHLOASMA)

Melasma is derived from Greek word melas (black) while chloasma is derived from the word chloazein (green), and since the pigmentation is brown-black, melasma is the preferred term.[1]

Epidemiology

Melasma is commoner in constitutionally darker skin types being most common in people with light brown skins, especially in people of East and South East Asian and Hispanic origin who live in areas with intense solar ultraviolet radiation (UVR).[1] It is commoner in women than in men (9:1) and is rare before puberty, occurring most commonly in women of reproductive age.

Etiology

The exact etiology of melasma is not known but several factors have been implicated. UVR (UVA and UVB) and visible light cause peroxidation of lipids in cellular membranes, leading to generation of free radicals, which stimulate melanogenesis. Elevated levels of estrogens and progesterone (as occurring in pregnancy) are important. Melasma also develops with estrogen- and progesterone-containing pills used for prostatic cancer.[2] However, progesterone may be more important, as melasma develops in postmenopausal woman who are given progesterone and not when given estrogen supplementation. Estrogens probably stimulate melanogenesis through estrogen receptors present on melanocytes.[1] Other hormones may also be important. Melasma is several times commoner in patients with thyroid disease than in controls and MSH may be important as melasma frequently begins as well as worsens during pregnancy as also after profound emotional stress.

Genetic factors are indicated because more than 30% of patients have a family history of melasma and melasma has been reported in identical twins without affecting other siblings.[3] Constituents of cosmetics have been frequently incriminated since the commonest site of affliction is face of women. Drugs (phenytoin, griseofulvin, and NSAIDs) can cause melasma-like pigmentation.

Pathogenesis

The number of melanocytes in the lesions may be normal[2] or increased.[3] Melanosomes both within melanocytes and keratinocytes are increased in size probably due to increased expression of α-MSH in keratinocytes and overexpression of stem cell factor in fibroblasts and its receptor C-kit in melanocytes of involved skin.[4,5]

Clinical features

Melasma is characterized by symmetrical hyperpigmented macules [Figure 1], which may be blotchy, irregular, arcuate, or polycyclic and rarely have a linear or a starburst distribution. Depending on the location of melanin (*vide supra)*, melasma is classified into:[6]

- ***Epidermal type***: in which the pigment is brown and margins of the lesions are well defined and geographical
- ***Dermal type***: in which the pigment is grey-brown and the margins of the lesions are poorly defined.
- ***Mixed or epidermo-dermal type***: in which melanin is present both in epidermis and dermis.
- ***Indeterminate type:*** in which it is difficult to classify melasma, even with Wood's light as melasma in dark skinned individuals.[7]

The face is most commonly affected though rarely pigmentation may extend on to V of the neck or may be confined to the forearms. On the face, three patterns of melasma are recognized:

- ***Centrofacial:*** the most frequent (63%) pattern, with pigmentation on cheeks, forehead, upper lip, nose, and chin.
- ***Malar:*** constituting 21%, with pigmentation present only on cheeks and nose.
- ***Mandibular:*** the least common (16%), with pigmentation on ramus of the mandible.

Course

Depending on the natural history of the lesions, melasma may also be classified into:

- ***Transient type:*** which disappears within a year of withdrawal of hormonal stimulus.

- ***Persistent type***: which persists for more than a year after withdrawal of hormonal stimulus and is maintained by UVR and other factors.

ERYTHEMA DYSCHROMICUM PERSTANS (EDP)

Syn: Ashy dermatosis of Ramirez, erythema chronicum figuratum melanodermicum.[8]

Although Ramirez first described what is today labelled EDP, it is Sulzberger who is credited with coining the term EDP.[8]

Epidemiology

Though EDP has been reported from many countries including India,[9] it is most common in Latin America and Asia. It occurs in both sexes, but causes greater concern in women. Though it can affect any age group, characteristically lesions start in the 1st-2nd decade of life.

Etiology

The etiology of EDP is unknown, but anecdotal reports have incriminated exposure to ammonium nitrite, radiographic contrast media and chlorothalonil, intestinal whipworm infestation, cobalt allergy and HIV infection. In Mexican Mestizo patients, HLA-DR4 is associated with a genetic susceptibility to develop EDP. The relation of EDP to lichen planus (LP) is uncertain, both have several clinical, histological, and immunohistochemical similarities and often coexist[10] making some authors consider EDP a variant of LP.[11] The pigmentation in EDP is due to presence of melanin in the melanosome complexes in dermis (frequent) and in epidermis (sometimes).

Clinical features

EDP presents as numerous asymptomatic, gradually enlarging and coalescing, persistent, macules of variable sizes. Initially having an erythematous hue and an elevated dusky border (not always noted), lesions eventually become pigmented. Initially localised, lesions eventually cover extensive areas of face, trunk, and limbs.

Pathology

Under light microscopy (LM), there is vacuolar basal cell degeneration (BCD) with pigment incontinence (PI) and dermal melanophages and perivascular sleeve of lymphohistiocytic infiltrate at the active border while in the central pigmented area, there is increased epidermal pigmentation, PI, melanophages, and perivascular lymphohistiocytic infiltration. Ultrastructural studies have demonstrated melanosome complex-containing vacuoles within the cytoplasm of the basal and suprabasal keratinocytes with direct immunofluorescence show IgM cytoid bodies.

LICHEN PLANUS PIGMENTOSUS

Etiology and pathogenesis

Though the exact etiology of lichen planus pigmentosus (LPP) is not known, cosmetics including fragrances, hair dyes, and mustard oil have been incriminated.[11]

Clinical features

LPP is characterized by generally asymptomatic (sometimes itchy), diffuse (less frequently reticular, blotchy, or perifollicular) hyperpigmented dark-brown to slate-grey to black macules [Figure 2] present mostly over exposed areas and flexures. The lesions lack the erythematous border of EDP. The clinical association of this entity with lesions of classical LP in about a third of patients and demonstration of colloid bodies on histopathology prompted Bhutani *et al.*,[12] to consider LPP a macular variant of LP and very similar to EDP. Though the mucous membranes are characteristically spared, some patients may have LP-like lesions.

RIEHL'S MELANOSIS

Syn: Pigmented cosmetic/ contact dermatitis

Etiology

Riehl's Melanosis (RM) is probably a pigmented contact dermatitis (CD) to antigens present in cosmetics and textiles with anecdotal reports of air borne CD to musk ambrette and other plants.[13,14] Cosmetic allergens, include red and yellow pigments, chromium hydroxide, aniline and azo dyes, bactericidal agents (carbanilides, ricinoleic acids), hair dyes, red kumkum,[15] and fragrances. Textile allergens include optical whiteners, dyes, textile finishes, mercury compounds, formaldehyde, and rubber components. Sometimes occupational allergens like coal tar, pitch, asphalt, mineral oil, and chromates have been incriminated.[16]

Pathogenesis

Repeated contact with low levels of allergens (present in cosmetics and textiles) produces a type IV cytolytic reaction characterized by vacuolar BCD and PI rather

than a frank eczematous reaction.[17] UV exposure may contribute in some, since pigmentation is often photo-localized and some of the chemicals implicated not only stimulate melanogenesis but are known photosensitizers.

Epidemiology

Incidence of RM is not known and though most reports are from Japan, cases have been reported from Europe, South America, India, and South Africa. In general, it is most pronounced in darkly pigmented races. Women appear to have a greater predilection, with majority of patients being young-middle aged women.

Clinical features

RM is characterized by diffuse/patchy/ rarely reticular pigmentation, often with satellite perifollicular pigmented macules and scaly follicular hyperkeratosis. Pigmentation is brown (almost black on the forehead and temples of dark skinned patients). It is sometimes preceded by mild erythema (often imperceptible in dark skinned) and pruritus. Sites of involvement depend on the allergen responsible – lesions due to cosmetics begin on forehead and temples spreading to involve rest of the face, even the chest, neck, scalp, hands, and forearms, while those due to textiles more often involve anterior aspect of thighs and axillae (sparing the vault).[18] Patients may show positive patch test to cosmetics or their ingredients.[19]

Pathology

LM of early lesions shows BCD, PI, and perivascular or band-like dermal infiltration, while older lesions show upper dermal melanophages.

ERYTHROSE PERIBUCCALE PIGMENTAIRE DE BROCQ [EPP]

Epidemiology

Middle aged women are most frequently affected.[20]

Etiology

Photodynamic substances in cosmetics are probably responsible. A similar hyperpigmentation has been reported in patients with subsiding perioral dermatitis due to topical steroids.[21]

Clinical features

EPP is characterized by diffuse brown-red pigmentation present symmetrically around the mouth, with sparing the vermillion border. It may extend to the forehead, temples, and angles of the jaw. The erythema may fluctuate but pigmentation is persistent unless the cause is eliminated when it may fade very gradually.

POIKILODERMA OF CIVATTE

Epidemiology

Though rarely reported, milder disease is probably not uncommon. It occurs predominantly in middle-aged women.[22]

Etiology

Photodynamic substances in cosmetics may be important.

Clinical features

It is characterized by the presence of reddish-brown reticulate pigmentation, telangiectasia and atrophy in irregular, symmetrical patches on the convexities of cheeks and the sides of the neck, sparing the area under the chin.

ERYTHROMELANOSIS FOLLICULARIS OF FACE AND NECK [EF]

Epidemiology and etiology

Mainly reported in Japanese, EF is also not uncommon in Whites. Though mainly affecting young and middle-aged men, it is also seen in adult females. Its cause is unknown.[23-25]

Clinical features

EF manifests as gradually progressive reddish-brown pigmentation and telangiectasis surmounted with pale, tiny follicular papules from which vellus (not terminal) hairs are lost [Figure 3]. The pigmentation involves periauricular areas sometimes, extending to the side of neck.

Pathology

The lesions are characterized by enlargement of sebaceous glands and hair follicles with the latter containing lamellar horny masses. The overlying flattened epidermis contains excess melanin and there is an inconspicuous lymphocytic infiltrate around dilated vessels.

NEVUS OF OTA

Syn: Oculodermal melanocytosis

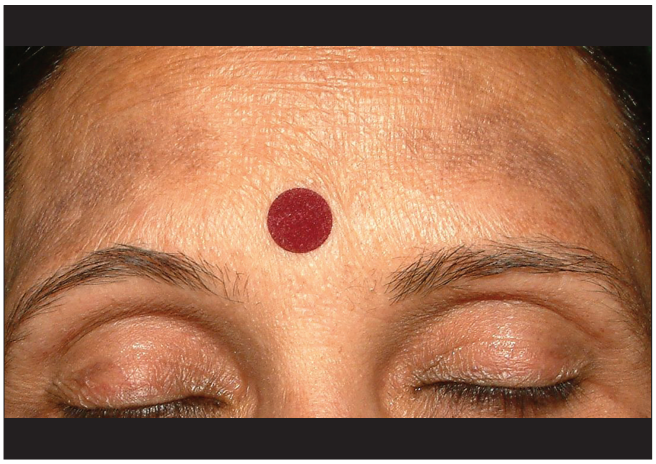

Figure 1: Melasma: hyperpigmented, irregular, brown macules on the forehead

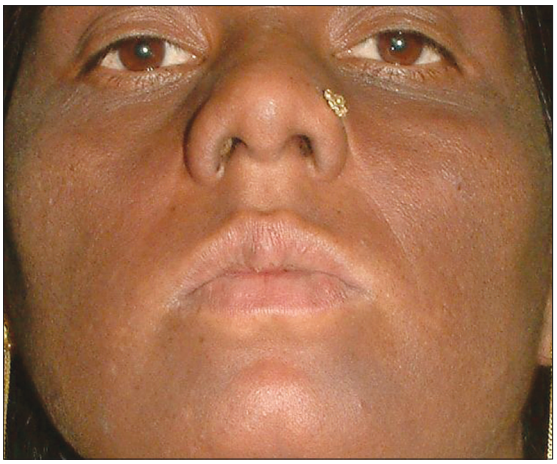

Figure 2: Lichen Planus Pigmentosus: asymptomatic, diffuse hyperpigmented slate-grey to black macules on the face

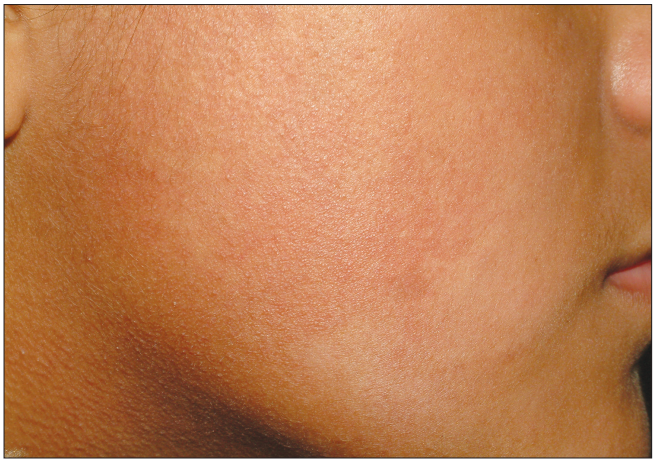

Figure 3: Erythromelanosis follicularis: reddish-brown pigmentation and telangiectasis surmounted with pale, tiny follicular papules involving periauricular area

Epidemiology

Nevus of Ota (NOO) is more common in Japanese, in women (9 times) with onset either in the perinatal period (50%) or around puberty (30%).[26]

Etiology

Due to racial differences, genetic factors are thought to be important but familial cases are rare.

Pathogenesis

NOO represents aborted embryonic migration of melanocytes from neural crest to epidermis. Late pubertal onset is explained by pigmentation of the amelanotic nevoid cells present at birth by adolescent spurt of sex hormones.

Clinical features

NOO is characterized by speckled or mottled coalescing blue-grey pigmentation of the area supplied by ophthalmic and maxillary divisions of trigeminal nerve. It is usually unilateral (90%). In addition to skin, pigmentation of NOO may involve oral mucosa and the eye (conjunctiva, sclera, retrobulbar fat, cornea, and retina) in which two levels of pigmentation - brown of conjunctiva and blue of sclera (often not overlapping) are clearly discernable. Based on the extent, NOO is classified into:

- ***Type I (mild):***
  - IA: Mild orbital type: On upper and lower eyelids, periocular and temple region.
  - IB: Mild zygomatic type: On the infrapalpebral fold, nasolabial fold and zygomatic region.
  - IC: Mild forehead type: On forehead only.
  - ID: On ala nasi only.
- ***Type II*** (***moderate)***: On upper and lower eyelids, periocular, zygomatic, cheek, and temple regions.
- ***Type III (severe):*** On scalp, forehead, eyebrow, and nose.
- ***Type IV*** (***bilateral type):*** Bilateral

Variants

Hori nevus,[27] or acquired bilateral nevus of Ota like macules (ABNOM) is probably a distinct variant seen in Koreans and Japanese. Unlike NOO, it has a late onset in adulthood, spares the mucosae, and is clinically characterized by bilaterally symmetrical speckled or confluent brownish-blue or slate-grey pigmentation over the malar regions, temples, root of the nose, alae nasi, the eyelids, and forehead. In cases of ABNOM confined only to the malar area or forehead, diagnosis is difficult because it mimics the centrofacial type of melasma. Without careful examination of alae nasi, forehead, and eyelids, brown ABNOM looks just like

melasma, though histologically, fusiform-elongated dendritic melanocytes and melanophages are scattered among collagen bundles. The differentiation is essential because both are treated differently- melasma with topical agents while ABNOM with lasers.

Course

Though NOO persists, is only rarely complicated by melanoma and is anecdotally associated with ipsilateral glaucoma.

PERIORBITAL MELANOSIS

Periorbital melanosis (POM) (or dark circles) is an ill-defined entity of great cosmetic concern.[28]

Etiology

Factors incriminated in etiology of POM include dermal melanin deposition, post inflammatory hyperpigmentation (atopic or contact allergic dermatitis), shadowing from lax skin, and infraorbital swelling have been incriminated. Familial periorbital hyperpigmentation is determined by an autosomal dominant gene[29] and in one study POM was found to be an extension of pigmentary demarcation lines over the face (PDL-F).[30] Pigmentary demarcation lines (PDL), also known as Futcher's lines or Voigt's lines, are abrupt transition lines from areas of deeper pigmentation to areas with less pigmentation. These are most often observed in darker races and are considered to be normal variants of pigmentation

Clinical features

POM is characterized by variegated brown to almost black discoloration around the eyes.

ADDISON'S DISEASE

Another cause of FM is Addisonian pigmentation.[31,32]

Etiology

Addisonian pigmentation typically occurs in primary adrenal insufficiency due to autoimmune adrenalitis, tuberculosis or other granulomatous diseases, metastatic malignant disease, sarcoidosis, amylodosis, and congenital adrenal hypoplasia.

Pathogenesis

Excessive production of ß-MSH and ACTH by the pituitary due to low circulating levels of adrenocortical steroids

Pathology

It is epidermal melanotic hyperpigmentation.

Clinical features

The pigmentation is most pronounced on the light exposed areas, flexures (e.g., axillae and fossae), palmar and plantar creases, areas subjected to repeated friction, the normally pigmented sites (e.g., nipples and genitalia) and mucous membranes (buccal, conjunctival, and vaginal) less distinctive pattern of hyperpigmentation may sometimes be observed. Pigmentation is minimal, if Addison's disease develops rapidly.

EXOGENOUS OCHRONOSIS

Exogenous ochronosis (EO), a rare complication of hydroquinine (HQ), develops after prolonged use of high concentrations in dark-skinned patients and rapidly after use of even 2% in white-skinned.[33] It presents with diffuse pigmentation,[34] which under high magnification especially when using polarized light, is characterized by tiny, less than 1-mm sooty blue macules in a reticulate pattern.[35] Lesions are present in the HQ-treated photo-exposed areas *viz* cheeks, forehead and temporal and periorbital skin with less frequent involvement of nasal, peribuccal, and chin areas. Biopsy shows banana-shaped yellow-brown granules in and around collagen bundles along with giant cells and melanophage rich granulomas. Improvement occurs only very slowly (if at all) on withdrawal of HQ.

POST CHIKUNGUNYA PIGMENTATION

Epidemiology

Since 2005, there is an ongoing outbreak of chikungunya in India.[36]

Etiology

Chikungunya is caused by alpha virus and is transmitted by *Aedes aegypti* and *Aedes albopictus.*

Pathogenesis

The exact cause of cutaneous manifestations in chikungunya fever is not known. Biopsy from hyperpigmented lesions shows an intact basal layer with diffuse hypermelanosis of the entire epidermis, suggesting an increased intraepidermal melanin dispersion/retention triggered by the virus.

Clinical features

Though the most common cutaneous manifestation of chikungunya is an erythematous maculopapular rash. An asymptomatic, brownish-black pigmentation, predominantly involving the centrofacial area, in form of freckle-like macules or slate-colored pigmentation is not uncommon. This may persist for about three-six months after the infection. Other patterns of pigmentation observed include melasma-like pigmentation over the face, periorbital melanosis, and a flagellate pattern of pigmentation on the face and extremities.

ACANTHOSIS NIGRICANS

Acanthosis nigricans is characterized by hyperpigmented, velvety plaques of body folds may also involve the face as well. Symptomatic treatments include topical retinoids and keratolytics.[37]

APPROACH TO A PATIENT WITH FM

DIAGNOSIS

Some of the well-defined causes of FM include melasma, RM, LPP, EDP, and EPP and poikiloderma of Civatte. However, it is not possible to slot all patients into these clinical entities due to overlap in features. In case of any unexplained hyperpigmentation, evaluation of adrenal function is essential.

TREATMENT

FM causes cosmetic disfigurement with significant emotional impact.[38-41] Its treatment includes removal of provoking factors, vigorous photoprotection, and some form of active pigment reduction either with topical agents or physical modes of treatment. There is no universally effective specific therapy — existing agents have varying degrees of efficacy and relapses are frequent.[38]

Photoprotection

Photoprotection is essential, because photodarkening can occur with just a couple of hours of sun exposure.[1]

Life style modification

This entails avoiding peak hours of sunlight (in tropics, between 11 AM - 4 PM), using shady side for activities and making use of sunshades like parasols and broad rimmed hats.

Sunscreens

Opaque sunscreens containing zinc oxide, 10% (and SPF of 30) have dual benefit of camouflaging FM and preventing photo-induced darkening. Addition of benzophenones has added benefit.

Avoidance of provoking factors

Avoiding triggers is necessary in melasma, RM, and other causes of FM

Lightening agents

Topical agents need to be used for several months before effect becomes apparent[39] and are much more effective when pigment is epidermal.

Hydroquinone

Hydroquinone (HQ), used alone or in combination, is the gold standard for the treatment of melasma and other FM, particularly of epidermal type. HQ inhibits tyrosinase (decreasing conversion of DOPA to melanin) and so reduces formation and melanization of melanosomes. It also promotes degradation of melanosomes and destruction of melanocytes.[40] The efficacy of HQ in FM depends on several factors. Epidermal pigmentation responds better than dermal. Higher concentrations give better results (4% being more effective than 2% and 6-10% prepared extemporaneously being effective even in resistant cases) with a hydroalcoholic solution being most effective. Used in concentration of 2−5%, the response in melasma becomes evident after 5−7 weeks and therapy needs to be continued for at least 3−12 months.[41] HQ has been combined with retinoic acid (RA) and fluocinolone acetonide (triple combination) or with 10% glycolic acid (GA) to improve its efficacy. Adverse reactions of HQ are “dose” and “duration of use” dependant. Acute reactions like asymptomatic transient erythema and dose dependent irritation are not uncommon but allergic CD and nail discoloration are infrequent. A confetti-like depigmentation may develop with concentrations higher than 2% as also with monobenzylether of HQ, which should never be used in melasma. A rare complication of HQ is exogenous ochronosis (*vide supra)*. Use of HQ is banned in cosmetics in Japan, Europe, and USA, because of safety issues.[42] Being an oxidizing agent, HQ changes from white to brown and this needs to be discarded as it is ineffective.[43]

Azelaic acid

Azelaic acid (AA) is antiproliferative and cytotoxic to melanocytes. It is a weak competitive inhibitor

of tyrosinase.[44] It also reduces production of free radicals. AA has been used for treatment of melasma and postinflammatory hyperpigmentation (PIH). In melasma, AA 20% is as effective as 4% and superior to 2% HQ, but without its side effects.[45] To hasten and improve response, AA has been combined with 0.05% RA or 15−20% GA.[46] However, combining with clobetasol propionate does not enhance its effect.[47] AA is generally well tolerated. Pruritus, mild erythema, and burning may develop but improve even on continuation of treatment. Phototoxic and allergic reactions are rare.

Kojic acid

Kojic acid (KA) inhibits production of free tyrosinase and is a potent antioxidant.[48] When used alone, KA, 1−4%, is only modestly efficacious. However, KA has a place as a combination therapy in management of FM, if the patient has difficulty tolerating other first-line therapies. A combination of KA, 2% and HQ, 2% is superior to combination of GA 10% and HQ 2%[49] and a combination of GA, 5% and KA, 4% was as effective in melasma as a combination of GA 5% and HQ 4% at 12 weeks.[50] KA may cause CD and erythema.

Retinoids

All topically available retinoids *viz.,* retinoic acid RA, isotretinoin, adaplene and tazarotene have been used to treat melasma, either as monotherapy or combined with HQ, topical steroids and a host of other agents. Retinoids reduce hyperpigmentation by promoting loss of melanin through increased epidermal turnover, reducing transfer of melanosomes from melanocytes to keratinocytes by decreasing contact time and reducing melanogenesis by inhibiting tyrosinase transcription.[51] Used as monotherapy, 0.1% RA is more effective than 0.05% and 0.025%, but is also more irritating.[52] With isotretinoin the response is equivocal but in Indian patients, adapalene is as efficacious as RA but with significantly less irritation.[53] Though RA takes longer than HQ to act (clinically significant lightening evident only after 24 weeks), the response when combined with HQ (5%), and lactic acid (7%) or ascorbic acid (10%) is not only better but faster as well. Irritation is the commonest side effect and may even cause hyperpigmentation, particularly in dark-skinned. It is more frequent with higher concentration of RA and less with adaplene. Photosensitivity is also not uncommon.

Topical steroids

Mechanism of skin-lightening with topical corticosteroids is ill-understood, but they inhibit synthesis of mediators like prostaglandin and leukotriene and this may partly explain their effect on melanogenesis. Though potent/superpotent steroids do reduce pigmentation of melasma,[54] monotherapy is best avoided due to frequent adverse effects. Steroids of different potencies have been combined (for synergistic effects and reducing irritation due to other products) with HQ (2−10%) and RA (0.025−0.1%) in treatment of melasma.[55] Disadvantages of topical steroids include rosacea-like dermatosis, atrophy, telangiectasia and hypertrichosis.

Glycolic acid

Glycolic acid (GA) acts in hyperpigmentation probably due to its effect on epidermal remodelling and accelerated desquamation, resulting in quick pigment dispersion. It also directly inhibits tyrosinase.[56] A combination of 10% GA and 4% HQ has been shown to have good clinical efficacy in treating melasma in Hispanic patients. Irritation is common and resolves with temporary withdrawal combined with application of moisturizers.[57]

Lesser used agents

Although experimental evidence suggests efficacy of a number of natural and synthetic agents in FM, dependable, controlled clinical trials are lacking. Most of these agents have been used in combinations and marketed as over-the-counter preparations.

Niacinamide

Niacinamide, an important component of the over the counter 'fairness creams' reduces pigmentation by reversibly preventing transfer of melanosomes from melanocytes to the keratinocytes without affecting the tyrosinase activity.[58] In clinical studies, niacinamide decreases hyperpigmentation compared with vehicle alone after 4 weeks of use.[59] Its efficacy is doubled by low-frequency sonophoresis, which enhances percutaneous absorption.[60]

Mequinol

Mequinol is a derivative of HQ. It acts as a competitive inhibitor reducing formation of melanin precursors. Though efficacious, controlled clinical trials are needed to establish its place in management of FM. In melasma, a 2% lotion used in combination with

0.01% RA (to enhance penetration), has been found superior to 3% HQ.[61] This combination resulted in complete clearance in 4 of the 5 patients with melasma at 12-weeks with all patients maintaining the improvement at 16-weeks.[62] In France, it is used in concentration of 8−10% in treatment of melasma and PIH. Side effects include irritation (reduced by using a sunscreen[63]), halo hypopigmentation and depigmentation both locally and at distant sites.

Arbutin and deoxyarbutin

Arbutin is a natural occurring derivative of HQ and deoxyarbutin is a dehydroxylated derivative of arbutin. Arbutin is hydrolysed in the skin by the flora to HQ and produces skin-lightening by direct, dose dependent inhibition of tyrosinase.[64] Although good controlled clinical trials are lacking, initial *in vitro* and *in vivo* experiments have demonstrated its safety and efficacy in hypermelanotic disorders.[65]

Ascorbic acid

Ascorbic acid (AsA) has antioxidant properties and reduces melanogenesis by inhibiting conversion of dopaquinone to DOPA. It also absorbs UVR, preventing free-radical production. Because of its instability in aqueous solution, esters like magnesium ascorbyl-2-phosphate (MAP) with similar properties are used.[66] AsA can be used alone or in combination therapy. Though 5% AsA is less effective than 4%HQ in melasma, but it has a better safety profile.[67] MAP was found to significantly reduce pigmentation in 19 of 34 patients with melasma and senile freckles but only in 3 of 25 patients with normal skin.[68] A 25% L-ascorbic acid formulated with a penetration enhancer, was found to significantly improve melasma.[69]

Liquorice derivatives

Liquorice is root of the perennial herb *Glycyrrhiza glabra*. Glabridin and other oil-soluble derivatives of liquorice inhibit tyrosinase *in vitro*.[70] Liquiritin, another derivative, reduces skin pigmentation, but without inhibiting tyrosinase. A 20% liquiritin cream was found effective at 4 weeks in treatment of melasma.[71]

Miscellaneous agents

N-acetyl-4-S-cysteaminylphenol (NCAP) acts as an alternative substrate for tyrosinase, inhibiting its activity. In a retrospective analysis of 12 patients with melasma who used 4% NCAP, 66% showed marked improvement with the lightening being evident as early as after 2−4 weeks.[72] It is more stable and less irritant than HQ. Alpha-tocopheryl ferulate absorbs UVR and significantly retards melanogenesis, possibly by inhibiting tyrosine hydroxylase in an indirect manner. Flavonoids including catechin (from green tea leaves), ellagic acid (from green tea, strawberies, eucalyptus *etc.*), and aloesin (from aloe tree), are naturally occurring polyphenols, with antioxidant and hypopigmentary properties. Their role in FM is still being investigated. Other agents known to affect melanin pigmentation and sometimes used in formulations are N-acetyl glucosamine, thiotic acid (alpha-lipoic acid), gentisic acid, soybean extract, and paper mulberry extract.

Combination treatment

Topical agents act on different stages of melanogenesis, therefore when combined give better therapeutic results. Agents are also combined to reduce untoward effects *e.g.*, topical steroids reduce irritation due to both HQ and retinoids and retinoids themselves counter steroid-induced atrophy. Some agents are used as "stabilizers" and hypomelanotic agents are often combined with sunscreens. HQ is the most commonly used agent, often being combined with GA, AA, KA, RA, or corticosteroids. The most extensively studied and widely used combination with HQ is with RA and corticosteroids-the "triple combination". First proposed by Kligman and Willis,[73] the original combination contained 5% HQ, 0.1% tretinoin, and 0.1% dexamethasone and was found effective in melasma, ephelides, and PIH. Due to the irritation, the combination has been modified to reduce HQ to 2−4% and tretinoin to 0.025−0.05% and the steroid has been variously changed to fluocinolone acetonide or others. Due to its efficacy in clinical situations it is extensively used as first line therapy for melasma and other FM. Only when the triple combination is unavailable or when patients do not tolerate it, should other modalities be used.

Physical therapies

Chemical peels

Chemical peels have been used to treat FM either as stand alone treatment or combined with other modalities. Epidermal melasma responds best and patients who continue topical therapy after the peel, maintain improvement better than those who do not.[74] Medium depth peels should be performed with great caution, especially in dark skinned patients and deep peels are not recommended for Indian skin because of high risk of prolonged or permanent pigmentary

changes.[75] Side effects of chemical peels include erythema, stinging, exfoliation and post inflammatory hypo and hyperpigmentation.

Used in concentration of 50−70%, a 91% reduction in MASI is seen with three peels of GA at monthly intervals.[76] The addition of 20% GA peels every 3 weeks marginally improves the response of moderate to severe melasma to combination of 10% GA and 2%HQ.[77] Addition of KA improves the response to GA peels.[78] Salicylic acid (SA), 20−30% peels used at 2-weekly intervals also results in moderate-significant improvement in 88% of patients with FM (including melasma). Similarly, RA, 1−5% peels at 2−3 days intervals has shown both clinical and histological evidence of improvement in melasma in patients with skin types I−IV.[79]

Laser therapy

Treatment of Nevus of Ota with lasers is extremely gratifying. QS Nd:YAG laser (wavelength 1064 nm) is the most widely used laser in darker skin types because longer wavelengths and a large spot size allows deeper penetration. Six to eight treatments at intervals of 2−6 months are necessary, with lightening seen even in between sessions. Temporary postinflammatory hyper and hypo pigmentation is frequent in Indian skin but can be minimized with good pre and postoperative care. Purpura and pin point bleeding occur at higher fluences or if smaller spot size is used.[80]

In contrast, though anecdotally several lasers have been reported to be effective in patients with other causes of FH, they should not be the first line therapy (unpredictable response, frequent relapses despite initial improvement, risk of postinflammatory hyper and hypopigmentation). Lasers may, however, be used in selected resistant cases, after proper counselling and preferably after a test patch. A combination of pulsed CO_2 laser (to remove epidermal pigment) and alexandrite laser (to remove dermal pigment) gives a better reduction in MASI than with either used alone.[81] Q-switched alexandrite laser has also been effectively used in other causes of FM in combination with 15−25% TCA and Jessner's solution, with 67% of these patients maintaining the good-excellent response at 24 months.[82] Similarly Erbium: YAG laser (2.94μ m; at 5.1 to 7.6J/cm^2) has been found effective women with melasma unresponsive to topical therapy and chemopeeling.[83] Q-switched ruby laser is ineffective in melasma.

Dermabrasion

Patients with resistant melasma especially with a prominent dermal component have been successfully treated with local or full-face dermabrasion upto upper or mid dermis using a 16-mm diameter coarse grit diamond fraise with 97% of the patients maintaining the improvement for a mean of 5 years. Less than 1% patients developed hypertrophic scars or permanent hypopigmentation.[84]

Special situations

It is best to defer treatment of melasma of pregnancy primarily because frequently disappears after delivery. Even if treated, it is resistant to treatment, due to persistent hormonal trigger. During pregnancy it is best just to advocate frequent application of a broad spectrum sun screen.

CONCLUSION

Management of FM is challenging requiring withdrawal of the 'trigger', vigorous use of sunscreens, an array of depigmenting agents of which HQ is considered gold standard. Although *in vivo* and *in vitro* studies have shown the efficacy of several other agents, their place in the management of FM is still not defined.

For melasma, the consensus is that first line therapy

Table 2: Drugs for which there is adequate evidence of efficacy in melasma

Therapy	LOE**	QOE††
Topical		
2% HQ*	II-ii	C
4% HQ*	I	B
0.1% RA†	I	B
0.05% RA†	I	C
0.5% isotretinoin	II-ii	C
4% HQ* + 0.05% RA†+ 0.01% fluocinolone acetonide	I	A
4% HQ* + 5% GA‡	II-ii	B
4% KA§ + 5% GA‡	II-ii	B
4% HQ* + 10% GA‡	I	B
20% AA¦¦	I	B
Vitamin C iontophoresis	II-i	C
Adapalene	II-ii	B
Chemical peels		
10-50% GA‡	II-ii/III	C
10% GA‡ + 2% HQ* + 20%-70% GA‡	II-ii	C
20%-30% GA‡+ 4% HQ*	II-i	B
70% GA‡	II-i	B
Jessner's solution	II-i	C

*Hydroquinone, †Retinoic acid, ‡Glycolic acid, §Kojic acid, ¦¦Azelaic Acid, **Level of evidence, ††Quality of evidence

should consist of effective topical therapies, mainly fixed triple combinations [Table 2]. Where patients have either sensitivity to the ingredients or a triple combination therapy is unavailable other compounds with dual ingredients (HQ plus GA) or single agents (4% HQ, 0.1% RA, or 20% azelaic acid) may be considered as an alternative. In patients for whom therapy has failed, options for second-line therapy include peels either alone or in combination with topical therapy. Most patients will require therapy to maintain remission status and a combination of topical therapies should be considered. Lasers should rarely be used in the treatment of melasma and, if applied, skin type should be taken into account.

There are currently no guidelines for the management of other FM and given their heterogeneous nature and the variations of assessing treatment modalities, it is difficult to make effective comparisons between outcomes.

REFERENCES

1. Bandyopadhyay D. Topical treatment of melasma. Indian J Dermatol 2009;54:303-9.
2. Grimes PE, Yamada N, Bhawan J. Light microscopic, immunohistochemical and ultrastructural alteration in patients with melasma. Amer J Dermatopathol 2005;27:96-101.
3. Kang WH, Yoon KH, Lee ES, Kim J, Lee KB, Yim H, *et al*. Melasma: Histopathological characteristics in 56 Korean patients. Br J Dermatol 2002;146:228-37.
4. Imokawa G. Paracrine interactions of melanocytes in pigmentary disorders. In: Nordlund JJ, Boissy RE, Hearing VJ, King RA, Oetting WS, Ortonne JP, editors. The pigmentary system. 2nd ed. Malden, MA: Blackwell Publishing; 2006. p. 421-44.
5. Kang HY, Hwang JS, Lee JY, Ahn JH, Kim JY, Lee ES, *et al*. The dermal stem cell factor and c-kit are overexpressed in melasma. Br J Dermatol 2006;154:1094-9.
6. Katsambas A, Antoniou C. Melasma: Classification and treatment. J Eur Acad Dermatol Venereol 1995;4:217-23.
7. Hann SK, Im S, Chung WS, Kim do Y. Pigmentary disorders in South East. Dermatol Clin 2007;25:431-8, 10.
8. Novick NL, Phelps R. Erythema dyschromicum perstans. Int J Dermatol 1985;24:630-3.
9. Kanwar AJ, Bharija SC, Belhaj MS. Erythema dyschromicum perstans. Indian J Dermatol Venereol Leprol 1987;53:237-8.
10. Berger RS, Hayes TJ, Dixon SL. Erythema dyschromicum perstans and lichen planus: Are they related? J Am Acad Dermatol 1989;21:438-42.
11. Bhutani LK, Bedi TR, Pandhi RK, Nayak NC. Lichen planus pigmentosus. Dermatologica 1974;149:43-50.
12. Aggarwal RR, Garg RK, Sehgal RK. Riehl's melanosis. Indian J Dermatol Venereol Leprol 1975;41:131-3.
13. Pires MC, Manoel Silva dos Reis V, Mitelmann R, Moreira F. Pigmented contact dermatitis due to Plathymenia foliosa dust. Contact Dermatitis 1999;40:339.
14. Nath AK, Thappa DM. Kumkum-induced dermatitis: An analysis of 46 cases. Clin Exp Dermatol 2007;32:385-7.
15. Forester HR, Schwartz L. Industrial dermatitis and melanosis due to photosensitization. Arch Derm Syphilol 1939;39:55-68.
16. Nakayama H. Pigmented Contact Dermatitis and Chemical Depigmentation. In: Rycroft R, Menne T, Frosch P, Lepoittevin J, eds. Textbook of Contact Dermatitis. 3rd ed. New York, NY: Springer; 2001. p. 319-33.
17. Shenoi SD, Rao R. Pigmented contact dermatitis. Indian J Dermatol Venereol Leprol 2007;73:285-7.
18. Nakayama H, Harada R, Toda M. Pigmented contact dermatitis. Int J Dermatol 1976;15:673-5.
19. Tritsch H, Greither A. Erythrosis pigmentata faciei. Arch Derm Syphilol 1955;199:221-7.
20. Belisario JC. Report on a case of erythrose peribuccale de Brocq. Australas J Dermatol 1954;2:153.
21. Allen BR, Hunter JA. Abnormal facial pigmentation associated with the prolonged use of topical corticosteroids. Scott Med J 1975;20:277.
22. Pierini LE, Bosq P. Maladie de Civatte. Ann Dermatol Syphilol 1938;9:381-420.
23. Watt TL, Kaiser JS. Erythromelanosis follicularis faciei et colli. A case report. J Am Acad Dermatol 1981;5:533-4.
24. Anderson BL. Erythromelanosis follicularis faciei *et* colli. Case reports. Br J Dermatol 1980;102:323-5.
25. Sardana K, Relhan V, Garg V, Khurana N. An observational analysis of erythromelanosis follicularis faciei et colli. Clin Exp Dermatol 2008;33:333-6.
26. Tanino H. Nevus fuscoceruleus ophthalmomaxillaris of Ota. Jpn J Dermatol 1939;46:435-51.
27. Hori Y, Kawashima M, Oohara K, Kukita A. Acquired, bilateral naevus of Ota-like macules. J Am Acad Dermatol 1984;10: 961-4.
28. Lowe NJ, Wieder JM, Shorr N, Boxrud C, Saucer D, Chalet M. Infraorbital pigmented skin. Preliminary observations of laser therapy. Dermatol Surg 1995;21:767-70.
29. Goodman RM, Belcher RW. Periorbital hyperpigmentation. An overlooked genetic disorder of pigmentation. Arch Dermatol 1969;100:169-74.
30. Malakar S, Lahiri K, Banerjee U, Mondal S, Sarangi S. Periorbital melanosis is an extension of pigmentary demarcation line-F on face. Indian J Dermatol Venereol Leprol 2007;73:323-5.
31. Braverman IM. Skin signs of systemic disease. Philadelphia: WB Saunders; 1981.
32. Lang PG. Adrenal Disroders. In: Callen JP, editor. Cutaneous aspects of internal disease. London: Year Book Medical Publishers; 1981. p. 451-62.
33. Barrientos N, Ortiz-Frutos J, Gómez E, Iglesias L. Allergic contact dermatitis from a bleaching cream. Am J Contact Dermat 2001;12:33-4.
34. Levin CY, Maibach H. Exogenous ochronosis. An update on clinical features, causative agents and treatment options. Am J Clin Dermatol 2001;2:213-7.
35. Fallabella R. Pigmentary disorders in Latin America. Dermatol Clin 2007;25:419-30, 10.
36. Inamadar AC, Palit A, Sampagavi VV, Raghunath S, Deshmukh NS. Cutaneous manifestations of Chikungunya fever. Observations made during a recent outbreak in South India. Int J Dermatol 2008;47:154-9.
37. Schwartz RA. Acanthosis nigricans. J Am Acad Dermatol 1994;31:1-19; quiz 20-2.
38. Rigopoulos D, Gregoriou S, Katsambas A. Hyperpigmentation and melasma. J Cosmet Dermatol 2007;6:195-202.
39. Prignano F, Ortonne JP, Buggiani G, Lotti T. Therapeutic approaches to melasma. Dermatol Clin 2007;25:337-42, 8.
40. Jimbow K, Obata H, Pathak MA, Fitzpatrick TB. Mechanism of depigmentation by hydroquinone. J Invest Dermatol 1974;62:436-49.
41. Pérez-Bernal A, Muñoz-Pérez MA, Camacho F. Management of facial hyperpigmentation. Am J Clin Dermatol 2000;1:261-8.
42. Draelos ZD. Skin lightening preparations and the hydroquinone controversy. Dermatol Ther 2007;20:308-13.
43. Draelos ZD. Cosmetic therapy. In: Wolverton SE, editor. Comprehensive Dermatologic Drug Therapy. 2nd ed. Philadelphia: Saunders; 2007. p. 761-74.
44. Nguyen QH, Bui TP. Azelaic acid: Pharmacokinetic and

pharmacodynamic properties and its therapeutic role in hyperpigmentary disorders and acne. Int J Dermatol 1995;34: 75-84.
45. Baliña LM, Graupe K. The treatment of melasma. 20% azelaic acid versus 4% hydroquinone cream. Int J Dermatol 1991;30:893-5.
46. Zaumseil RP, Graupe K. Topical azelaic acid in treatment of melasma-pharmacological and clinical considerations. Melasma- new approaches to therapy. London: Martin Dunitz; 1995. p. 19-41.
47. Sarkar R, Bhalla M, Kanwar AJ. A comparative study of 20% azelaic acid monotherapy vs a sequential therapy in the treatment of melasma in dark-skinned patients. Dermatology 2002;205:249-54.
48. Kahn V. Effect of kojic acid on the oxidation of DL-DOPA, norepinephrine, and dopamine by mushroom tyrosinase. Pigment Cell Res 1995;8:234-40.
49. Lim JT. Treatment of melasma using kojic acid in a gel containing hydroquinone and glycolic acid. Dermatol Surg 1999;25:282-4.
50. Garcia A, Fulton JE Jr. The combination of glycolic acid and hydroquinone or kojic acid for the treatment of melasma and related conditions. Dermatol Surg 1996;22:443-7.
51. Picardo M, Carrera M. New and experimental treatments of cloasma and other hypermelanoses. Dermatol Clin 2007;25:353-62, 9.
52. Kimbrough-Green CK, Griffiths CE, Finkel LJ, Hamilton TA, Bulengo-Ransby SM, Ellis CN, *et al*. Topical retinoid acid (tretinoin) for melasma in black patients: A vehicle-controlled clinical trial. Arch Dermatol 1994;130:727-33.
53. Dogra S, Kanwar AJ, Parsad D. Adapalene in the treatment of melasma: A preliminary report. J Dermatol 2002;29:539-40.
54. Kanwar AJ, Dhar S, Kaur S. Treatment of melasma with potent topical corticosteroids. Dermatology 1994;188:70.
55. Rendon M, Berneburg M, Arellano I, Picardo M. Treatment of melasma. J Am Acad Dermatol 2006;54 (5 Suppl 2):S272-81.
56. Usuki A, Ohashi A, Sato H, Ochiai Y, Ichihashi M, Funasaka Y. The inhibitory effect of glycolic acid and lactic acid on melanin synthesis in melanoma cells. Exp Dermatol 2003;12 Suppl 2:43-50.
57. Guevara IL, Pandya AG. Safety and efficacy of 4% hydroquinone combined with 10% glycolic acid, antioxidants, and sunscreen in the treatment of melasma. Int J Dermatol 2003;42:966-72.
58. Greatens A, Hakozaki T, Koshoffer A, Epstein H, Schwemberger S, Babcock G, *et al*. Effective inhibition of melanosome transfer to keratinocytes by lectins and niacinamide is reversible. Exp Dermatol 2005;14:498-508.
59. Hakozaki T, Minwalla L, Zhuang J, Chhoa M, Matsubara A, Miyamoto K, *et al*. Effect of niacinamide on reducing cutaneous pigmentation and suppression of melanosome transfer. Br J Dermatol 2002;147:20-31.
60. Hakozaki T, Takiwaki H, Miyamoto K, Sato Y, Arase S. Ultrasound enhanced skin-lightening effect of vitamin C and niacinamide. Skin Res Technol 2006;12:105-13.
61. Jarratt M. Mequinol 2%/tretinoin 0.01% solution: An effective and safe alternative to hydroquinone 3% in the treatment of solar lentigines. Cutis 2004;74:319-22.
62. Keeling J, Cardona L, Benitez A, Epstein R, Rendon M. Mequinol 2% tretinoin 0.01% topical solution for treatment of melasma in men: A case series and review of the literature. Cutis 2008;81:179-83.
63. Colby SI, Schwartzel EH, Huber FJ, Highton A, Altman DJ, Epinette WW, *et al*. A promising new treatment for solar lentigines. J Drugs Dermatol 2003;2:147-52.
64. Chawla S, deLong MA, Visscher MO, Wickett RR, Manga P, Boissy RE. Mechanism of tyrosinase inhibition by deoxyArbutin and its second-generation derivatives. Br J Dermatol 2008;159:1267-74.
65. Hamed SH, Sriwiriyanont P, deLong MA, Visscher MO, Wickett RR, Boissy RE. Comparative efficacy and safety of deoxyarbutin, a new tyrosinase-inhibiting agent. J Cosmet Sci 2006;57:291-308.
66. Kobayashi S, Takehana M, Itoh S, Ogata E. Protective effect of magnesium-L-ascorbyl-2 phosphate against skin damage induced by UVB irradiation. Photochem Photobiol 1996;64: 224-8.
67. Espinal-Perez LE, Moncada B, Castanedo-Cazares JP. A double-blind randomized trial of 5% ascorbic acid vs. 4% hydroquinone in melasma. Int J Dermatol 2004;43:604-7.
68. Kameyama K, Sakai C, Kondoh S, Yonemoto K, Nishiyama S, Tagawa M, *et al*. Inhibitory effect of magnesium-L-ascorbyl-2-phosphate on melanogenesis *in vitro* and *in vivo*. J Am Acad Dermatol 1996;34:29-33.
69. Hwang SW, Oh DJ, Lee D, Kim JW, Park SW. Clinical efficacy of 25% l-ascorbic acid (C'ensil) in treatment of melasma. J Cutan Med Surg 2009;13:74-81.
70. Yokota T, Nishio H, Kubota Y, Mizoguchi M. The inhibitory effect of glabridin from licorice extracts on melanogenesis and inflammation. Pigment Cell Res 1998;11:355-61.
71. Amer M, Metwalli M. Topical liquiritin improves melasma. Int J Dermatol 2000;39:299-301.
72. Jimbow K. N-acetyl-4-S-cysteaminylphenol as a new type of depigmenting agent for melasma. Arch Dermatol 1991;127:1528-34.
73. Kligman AM, Willis I. A new formula for depigmenting human skin. Arch Dermatol 1975;111:40-8.
74. Lawrence N, Cox SE, Brody HJ. Treatment of melasma with Jessner's solution versus glycolic acid: A comparison of clinical efficacy and evaluation of the predictive ability of Wood's light examination. J Am Acad Dermatol 1997;36:589-93.
75. Khunger N; IADVL Task Force. Standard guidelines of care for chemical peels. Indian J Dermatol Venereol Leprol 2008;74 Suppl:5-12.
76. Javaheri SM, Handa S, Kaur I, Kumar B. Safety and efficacy of glycolic acid facial peel in Indian women with melasma. Int J Dermatol 2001;40:354-7.
77. Lim JT, Tham SN. Glycolic acid peels in the treatment of melasma among Asian women. Dermatol Surg 1997;23:177-9.
78. Lim JT. Treatment of melasma using kojic acid in a gel containing hydroquinone and glycolic acid. Dermatol Surg 1999;25:282-4.
79. Cucé LC, Bertino MC, Scattone L, Birkenhauer MC. Tretinoin peeling. Dermatol Surg 2001;27:12-4.
80. Jones CE, Nouri K. Laser treatment for pigmented lesions: A review. J Cosmet Dermatol 2006;5:9-13.
81. Angsuwarangsee S, Polnikorn N. Combined ultrapulse CO2 laser and Q-switched alexandrite laser compared with Q-switched alexandrite laser alone for refractory melasma: Split-faced design. Dermatol Surg 2003;29:59-64.
82. Lee GY, Kim HJ, Whang KK. The effect of combination treatment of the recalcitrant pigmentary disorders with pigmented laser and chemical peeling agent. Dermatol Surg 2002;28:1120-3.
83. Manaloto RM, Alster T. Erbium: YAG laser resurfacing for refractory melasma. Dermatol Surg 1999;25:121-3.
84. Kunachak S, Leelaudomlipi P, Wongwaisayawan S. Dermabrasion: A curative treatment for melasma. Aesthetic Plast Surg 2001;25:114-7.

Multiple Choice Questions

1. Cerulodema is characterized by?
   a. Excess melanin in dermis, pigmentation not accentuated under Wood's lamp.
   b. Excess melanin in basal and suprabasal layers, pigmentation accentuated under Wood's lamp
   c. Increased epidermal and dermal melanin
   d. Excess melanin in basal and suprabasal layers, pigmentation not accentuated under Wood's lamp

2. Which melanosis is considered to be a pigmented contact dermatitis (CD)?
   a. Erythema dyschromicum perstans
   b. Lichen planus pigmentosus
   c. Riehl's melanosis
   d. Erythromelanosis peribuccale pigmentaire of Brocq

3. Which topical agent is antiproliferative and cytotoxic to melanocytes and a weak competitive inhibitor of tyrosinase?
   a. Kojic acid
   b. Hydroquinone
   c. Retinoids
   d. Azelaic acid

4. Which melanosis is characterized by speckled or mottled coalescing blue-gray pigmentation of the area supplied by ophthalmic and maxillary divisions of trigeminal nerve, usually unilateral?
   a. Hori's nevus
   b. Exogenous ochronosis
   c. Nevus of Ota
   d. Nevus of Ito

5. Which of the following is true for Hori's nevus?
   a. Late onset, sparing of mucosae, bilaterally symmetrical involvement
   b. Early onset, involvement of mucosae, usually unilateral involvement
   c. Early onset, sparing of mucosae, usually unilateral involvement
   d. Late onset, involvement of mucosae, bilaterally symmmetrical involvement

6. The following are the histopathological features of erythema dyschromicum perstans, except
   a. Vacuolar basal cell degeneration (BCD) with pigment incontinence (PI) and dermal melanophages and perivascular sleeve of lymphohistiocytic infiltrate at the active border
   b. Increased epidermal pigmentation, PI, melanophages and perivascular lymphohistiocytic infiltration in the central pigmented area.
   c. Melanosome complex-containing vacuoles within the cytoplasm of the basal and suprabasal keratinocytes with direct immunofluorescence showing IgM cytoid bodies.
   d. Overlying flattened epidermis containing excess melanin and an inconspicuous lymphocytic infiltrate around dilated vessels.

7. Which melanosis is thought to be an extension of pigmentary demarcation lines over the face ?
   a. Melasma
   b. Periorbital melanosis
   c. Poikiloderma of Civatte
   d. Nevus of Ota

8. Which laser has been found to be effective in women with melasma unresponsive to topical therapy and chemopeeling?
   a. QS Nd:YAG laser
   b. Erbium:YAG laser
   c. Q-switched ruby laser
   d. Q-switched alexandrite laser

9. Exogenous ochronosis (EO) is a rare complication of
   a. Hydroquinone (HQ)
   b. Retinoic acid
   c. Azelaic acid
   d. Glycolic acid

10. Addisonian pigmentation is characterized by
   a. Involvement of unexposed areas, extensors
   b. Diffuse /patchy or reticular pigmentation, often with satellite perifollicular pigmented macules and scaly follicular hyperkeratosis
   c. Involvement of light exposed areas, flexures, creases, mucous membranes
   d. Speckled or mottled coalescing blue-gray pigmentation of the area supplied by ophthalmic and maxillary divisions of trigeminal nerve

11. Composition of Kligman's formula is?
   a. HQ 4%, tretinoin 0.05% and 0.01% fluocinolone acetonide
   b. N –acetylcysteine 4.7%, HQ 2%, and triamcinoloneacetonide 0.1%
   c. HQ 2% and tretinoin 0.05-0.1%
   d. HQ 5%, tretinoin 0.1%, and dexamethasone 0.1%

Answers

1. a, 2. c, 3. d, 4. c, 5. a, 6. d, 7. b, 8. b, 9. a, 10. c, 11. d