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Original Research Article

Clinico-investigation on epidemiological study in 119 Indian cases of melasma

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ABSTRACT

Background: Melasma, a multifactorial disease, constitutes the most common facial melanosis in Indian population.
Methods: 119 cases of melasma aged 18 years or above were enrolled. Detailed history, examination and laboratory investigations were done.
Results: 20 (16.8%) were males and 99 (83.2%) females. Mean age was 35.25 years. Disease duration was more than 1 year in 102 (85.7%), 6 months to 1 year in 10 (8.4%) and less than 6 months in 7 (5.9%). 22 (18.49%) had occupation-related increased duration of sun-exposure 19 (86.3%) or heat-exposure 3 (13.6%). 79 (66.4%) had skin type IV, 26 (21.8%) type III, 14 (11.8%) type V. Centrofacial was commonest distribution pattern in 87 (73.1%), malar in 30 (25.2%), mandibular in 2 (1.7%). Mean duration of daily sun-exposure was 53.36 minutes (male-124.75, female-38.94). Mean Melasma Area and Severity Index (MASI) score was 11.602. There was significant association between MASI and skin type ($p<0.001$). Other etiological factors were: Oral Contraceptive Pills (OCPs) use in 17 (17.17%), melasma during pregnancy in 39 (39.4%), family history of melasma in 24 (20.2%), hair dye use in 66 (55.5%), cosmetics use in 19 (16%), mustard oil use in 31 (26.1%), mustard oil along with other oil(s)' use in 39 (32.8%). Laboratory investigations revealed anemia in 60 (50.42%), dyslipidemia in 73 (61.34%), abnormal thyroid function test in 26 (21.85%), serum vitamin B12 deficiency in 35 (29.4%) and vitamin D deficiency in 94 (79%).
Conclusions: Higher skin phototypes should be cautious about general measures and associated risk factors (hair dye/oils, cosmetics). Increased daily sun-exposure, OCPs use, pregnancy, thyroid disorders are risk factors. Housewives and indoor occupations should be advised physical sunscreens for protection against infra-red radiation. Anemia, dyslipidemia, thyroid dysfunction, vitamin D and B12 levels can be assessed although their exact role in perpetuating/precipitating melasma needs further studies

Keywords: Melasma, Epidemiology, Pigmentary disorder

INTRODUCTION

Melasma constitutes one of the most common facial melanosis in Indian population.[1] It is more frequent in women and Fitzpatrick skin types IV- VI.[2] The exact pathogenesis is not known. However multiple factors are associated with melasma, which include pregnancy, sun exposure, hormone therapy, OCPs, cosmetics, certain drugs, racial and genetic predisposition.

Validated questionnaires in several populations have shown that even mild melasma can cause significant emotional and psychological distress. Patients with lower

levels of education or underlying psychiatric disorders may be at greater risk of emotional impairment.[3]

Several etiological factors are implicated in its pathogenesis. These vary according to ethinicity, sex, skin phototype, genetic predisposition and intensity and duration of sun exposure. We attempted to study some of the etiological factors in patients of melasma hailing from northern part of India.

METHODS

119 cases of melasma aged 18 years or above attending outpatient clinic of department of dermatology at a tertiary care hospital from 2015 to 2017 were included as cases. Approval for the study was obtained from the institutional ethical review board. Other facial melanoses were excluded. Detailed clinical history and examination was taken as per self-made proforma to note demographic details, relevant history, cutaneous examination and relevant laboratory investigations. Examination was done in uniform light conditions and comfortable sitting position. Standard hand lens with magnification power 4X and 6 LED bulbs was used to examine lesions. MASI score[4] was calculated for all patients. Patients were evaluated and classified as epidermal, dermal and mixed type based on clinical examination. In all consenting cases, 5 ml venous blood sample was drawn under aseptic conditions from cubital vein. It was tested for hemoglobin, lipid profile, antinuclear antibody (ANA), thyroid function tests (TFT), serum vitamin B12 and 25(OH) vitamin D levels. Anaemia was defined as per WHO as <12 gm/dl for women and <13gm/dl for men.[5] Lipid profile was defined as deranged if total cholesterol ≥200 mg/dl, triglycerides (TG) ≥150 mg/dl, high density lipoprotein (HDL) <40 and low density lipoprotein (LDL) ≥100 mg/dl as per standard values of our hospital biochemistry laboratory. ANA was either positive or negative. The normal ranges for serum Thyroid stimulating hormone (TSH), vitamin B12 and 25(OH) vitamin D were 0.34 to 5.6 µIU/ml, 180-914 pg/ml and 30-70 ng/ml respectively as per standard values of our hospital biochemistry laboratory.

Statistical evaluation

Data was entered in Microsoft Excel and SPSS version 18 was used for analysis. Observations were presented as mean±standard deviation, absolute numbers and percentages. Chi square test and t test of significance were applied wherever applicable. For all statistical tests, a $p<0.05$ was taken as significant.

RESULTS

A total of 119 cases were evaluated in this study. 20 cases were males (16.8%) and 99 were females (83.2%). Demographic data and disease characteristics are shown in (Tables 1 and 2).

Table 1: Demographic data and other relevant information.

		Overall	Males	Females
Age (years)		35.25±7.184 (range: 18 - 60)	30.50±7.851 (range 18-48)	36.21±6.683 (range 23-60)
Age at onset (years)				
Range	**Frequency (%)**	30.67±7.372 (range 15–53)	27.40±8.178 (range 17-45)	31.33±7.060 (range 15-53)
15-24	26 (21.8)			
25-34	55 (46.2)			
35-44	33 (27.7)			
≥45	5 (4.2)			
Daily sun-exposure (minutes)		53.36±87.76 (range 5-480)	124.75±151.939 (range 5-480)	38.94±59.553 (range 5-420)
MASI score				
Range	**Frequency (%)**	11.602±7.015 (range 0.6-30.6)	10.655±6.031 (range 0.6-24.9)	11.793±7.209 (range 1.2–30.6)
<6	30 (25.2)			
6≤11	35 (29.4)			
11≤16	27 (22.7)			
16≤21	12 (10.1)			
21≤26	9 (7.6)			
≥26	6 (5)			

78 (65.5%) patients were housewives in our study. 22 (18.49%) patients had occupation-related increased duration of sun-exposure (19 cases) or heat exposure (3 cases). The patients with increased sun-exposure included occupations such as security guard (1.7%), salespersons (1.7%), vendor (0.8%), shopkeeper (5.9%), businessmen (2.5%), teacher (3.4%) and factory/industry worker (5.9%). History of using skin-lightening cream was noted in 50 (42.1%) cases. Out of total 99 female patients, 17 (17.17%) used OCPs in the past or currently. Mean duration of OCPs use was 10.12±11.752 months (range 1-36). The duration was ≤6 months in 10(8.4%) cases, 7 to ≤12 months in 3(2.5%) and >12 months in 4 (3.4%)

cases. 39 (39.4%) cases gave history of onset of melasma during pregnancy. None of the cases in our study used anti-epileptic drugs. 14(11.8%) had thyroid disease. All the cases were females. Out of 99 female cases, history of thyroid disease was positive in 14.14%. Overall, 24 (20.2%) cases had history of melasma in first and second-degree family members. Among females, positive family history was present in 21.2% while in males in 15%. 66 (55.5%) cases used hair dye. 19(16%) patients gave history of use of cosmetics. Out of 119 cases, 114 (95.8%) gave history of use of hair oil. 31(26.1%) cases used mustard oil and mustard oil along with other oils in 39 (32.8%) cases. This was followed by coconut oil in 14 (11.8%), combination of oils other than mustard oil seen in 11 (9.2%) cases, amla in 10 (8.4%) and other perfumed oils in 8(6.7%) cases. 63(52.9%) cases had received treatment in the past in the form of triple combination cream, other topical creams or chemical peels. Mean duration of previous treatment was 12.44±24.680 months (range 0-168). In case of males, it was 3.11±1.431 months whereas in females it was 14±26.560.

Centrofacial pattern was the commonest distribution pattern followed by malar and mandibular. Majority had skin type IV followed by type III, V (Table 2).

Table 2: Disease characteristics.

	N (%)
Disease duration	
<6 months	7 (5.9)
6 months-1 year	10 (8.4)
>1 year	102 (85.7)
Skin type	
III	26 (21.8)
IV	79 (66.4)
V	14 (11.8)
Pattern	87 (73.1)
Centrofacial	
Malar	30 (25.2)
Mandibular	2 (1.7)
Areas involved	
Cheeks	118 (99.2)
Forehead	88 (73.95)
Chin	12 (10.1)
Types	
Epidermal	90 (75.6)
Mixed	26 (21.8)
Dermal	3 (2.5)
Other findings	
Erythema	29 (24.4)
Telengectasias	72 (60.5)
Atrophy	1 (0.8)

Table 3: Results of investigations.

Disease condition	N (%)
Anemia	60 (50.42)
Dyslipidemia	73 (61.34)
Abnormal TFT	26 (21.85)
Positive ANA	1 (0.8)
Serum vitamin B12 deficiency	35 (29.4)
Vitamin D deficiency	94 (79)

We found a statistically significant association by chi square test between MASI score and skin type (ANOVA, $p<0.001$). There was no significant association of daily sun exposure with MASI. 60 patients (50.42%) had anemia. All were women. Out of 99 female patients, 60.6% had anemia. Thyroid stimulating hormone (TSH) was >5.6 µIU/ml (hypothyroidism) in 25 (21%) cases whereas it was <0.34 µIU/ml (hyperthyroidism) in 1 (0.8%) case (Table 3).

DISCUSSION

Female preponderance was seen in our study (4.95:1) as in the studies by Jagannath et al., Achar et al. (4:1) and by Sarkar et al. (3.88:1).[6,7,8] Majority of studies report female preponderance in child-bearing age, suggesting contributory role of hormones (estrogen, progesterone) in pathogenesis of melasma. 16.8% were men in our study. In the two studies by Sarkar et al., men comprised 25.83% and 20.5% cases.[8,9] However, in a study by Vazquez et al., on Latino patients, men comprised only 10%.[10] Melasma is frequently observed in Indian men as they have greater sun-exposure due to their outdoor work

culture. Moreover, certain occupations can expose men to chemical fumes, pollution, heat, which might act as triggers of melasma in men.[11]

Mean age for onset of melasma in our study (30.67±7.372 years) is in concordance with the studies by Jagannathan et al. (31.22 years), Achar et al. (29.99 years) and by Hexsel et al. (29.8±8.8 years).[6,7,12] In Jagannathan et al. study, mean age of onset for males and females were similar as in our study.[6] Age at onset for most patients fell within the range (25-34) years followed by (35-44). In our study, both mean age and mean age of onset, support the hormonal relationship in the pathogenesis of melasma. Majority developed melasma in second to fourth decades of life (reproductive age). Male patients showed an early age of onset than female patients in our study. Several incriminating factors have been identified for melasma, which include sunlight and cosmetics application, hormones and drugs. We hypothesize that outdoor occupation related sun-exposure in Indian men and exposure to mustard oil (known to be a common photosensitizer) used by a large number of men in our study could have a role in the causation of melasma at an earlier age.

Our study did not show any association between age of onset ranges and skin type. This association was shown in the study by Hexsel et al. where they found that skin types II, III had earlier onset of melasma, in comparison to darker skin types.[12]

Achar et al. found that majority of patients in his study presented after a mean duration of 3.59 years of onset.[7] Hexsel et al. found the mean duration to be 10.3±8.4 years.[12] KrupaShankar et al. found disease duration to be >1 year in 89% cases.[13] These results are in concordance to our findings. Majority of the studies looking at duration have seen that melasma was present for >1 year, which point towards the chronicity of melasma and its resistance to treatment.

Only 15.97% had occupations with increased sun-exposure and 2.52% with heat exposure. However, Tamega et al. reported a higher prevalence of melasma (48.5%) of occupations related with increased sun-exposure.[14] There is a paucity of studies commenting on association of occupational photo exposure. Since, we did not encounter a higher prevalence of melasma in occupations with increased sun exposure, we may hypothesize that UV exposure could be one of the many triggering factors in melasma, however it remains a multifactorial chronic disease with several pathomechanisms. Apart from the role of ultraviolet radiation and visible light in pathogenesis, infrared radiation has also been seen to play some role. However, its potential in development and maintenance of melasma remains unclear.

Majority in our study had skin type IV followed by type III, V. This was consistent with the findings by Jagannathan et al. where most patients were of Fitzpatrick skin types III, IV.[6] In a study by Tamega et al. on Brazilian women, prevalence of melasma was found more in intermediate skin types III, IV, V.[14] Cakmak et al. in his study on Turkish women, found majority of skin type III (51.1%) followed by IV and II.[15] Review of literature regarding the prevalence of melasma in various skin types suggest increased prevalence in Latin and Asian people, in contrast to decreased frequency of melasma in Caucasians and Africans. Incidence of melasma decreases in extreme phototypes (I,VI) suggesting some stability or homogeneity in ultraviolet reaction regarding their pigmentary system.[16]

In our study, centrofacial was the most common distribution pattern followed by malar and mandibular. Achar et al. and KrupaShankar et al. also found centrofacial to be the most common pattern followed by malar.[7,13] However, Jagannathan et al. and Manjunath et al. in their studies found malar to be the most common pattern.[6,17]

We observed that cheeks were mostly involved (99.2%), then forehead (73.9%) and chin (10.1%). Similarly, in a multicentric study by KrupaShankar et al., cheeks were seen to be most commonly involved (94%) followed by forehead (26%) and chin (5%).[13] Hexsel et al. in his study on Brazilian patients also found malar areas to be the most common location (90.1%) followed by frontal area.[12] Unprotected UV exposure seems to be the strongest environmental trigger,[16] which could be evidenced by predominance of centrofacial and malar distribution in most of the studies.

Mean MASI score was 11.602±7.015 in our study. However, in Cakmak SK et al. study, mean MASI score was 4±2.1.[15] The two clinico-epidemiological studies from India did not include MASI scores in their analyses.[7,13] In our study, we found a statistically significant association between MASI score and skin type. Higher MASI was associated with higher skin phototypes.

No significant association was seen between disease duration ranges and MASI in our study or between daily sun-exposure and MASI. Hexsel et al., in his study, found skin types II, III to have an onset of melasma earlier than patients with phototypes IV, V, VI.[12] Guinot et al. also showed a correlation between age of onset and MASI score.[19]

Mean duration of daily sun-exposure was 53.36±87.755 minutes. In a study by KrupaShankar et al., mean duration of sun-exposure was 35.9±25.7 hours/week.[13] Achar et al. reported 55.12% patients and Jagannathan et al. reported 22% with a history of melasma exacerbation during sun-exposure.[7,6] Mean daily sun-exposure was higher for males on account of outdoor occupations in males. We found no significant statistical association between daily sun-exposure ranges and MASI score.

In our study, 14.3% of the female patients used OCPs in the past or currently. In the studies by Jagannathan et al. 13.8% and Achar et al. 18.4% of female patients were using OCPs.[6,7] KrupaShankar et al. observed OCPs usage in 8.6% of female patients.[13]

39.4% cases in our study gave history of onset of melasma during pregnancy. In a study by Jagannathan et al., 28.7% female patients reported that their disease started during pregnancy and 18.7% reported exacerbation during pregnancy.[6] KrupaShankar et al. observed that 61% of women who had pregnancies, developed melasma.[13] They concluded that pregnancy might be a precipitating factor in melasma. Tamega et al. had reported pregnancy to be a triggering factor in 36.4% cases.[14]

In our study, 11.8% cases had thyroid disease. Similar finding was observed by Jagannathan et al. (10%).[6] Achar et al. found hypothyroidism in 6.4% cases.[7] Higher values were found in studies by Lufti et al. (58.3%) and Tamega et al. (25.3%).[20,14] It has been suggested that strong immunoreactivity to alpha-MSH on melasma skin is one of the factors in the pathogenesis. It has been observed that melanocortin system interacts with hypothalamic-pituitary-thyroid axis.[16,21]

Positive family history was in 20.2% cases in our study. This value is lower than found in other studies by Achar et al (33.33%), KrupaShankar et al (31.11%) and by Jagannathan et al (38%).[7,13,6] However, Cakmak et al reported family history in 17.8% patients.[15]

We did not find a significant association between age of onset and positive family history. This is in contrast to the finding in Hexsel et al who reported significant association of early onset of melasma in patients with positive family history.[12] We also did not find any association of family history with MASI score ranges.

55.5% cases used hair dye. Certain hair dyes contain photosensitizers like para-phenylene diamine, which can cause photosensitivity, pigmented contact dermatitis and can mimic melasma. These dyes can also act as triggers or aggravating factors in pathogenesis of melasma. No data is present on the use of hair dye in melasma patients. This suggests contact sensitivity in the occurrence of melasma.

In our study, 16% patients used cosmetics. Jagannathan et al., Achar et al and Krupa shankar et al found 21%, 23.39% and 35% patients with a history of cosmetics' use respectively whereas Tamega et al found its use in only 3.3% cases.[6,7,13,14] Due to the presence of photosensitizing chemicals in cosmetics,[22] they are a risk factor in melasma. However, studies are needed to substantiate the fact.

95.8% gave history of hair oil use, out of which, 26.05% used mustard oil alone and 32.77% used mustard and other oils. In the study by Sarkar et al on Indian men, 43.9% reported use of mustard oil.[9] It is a cultural practice in our country to use hair oil on the scalp as well as on face, like mustard oil and other perfumed oils. Mustard oil is derived from the seeds and belongs to the family *Brassicaceae*.[23] The oil is composed of fatty acids like oleic acid, linoleic acid and erucic acid, which is considered toxic. Mustard oil is a known photosensitizer,[8] also causes contact hypersensitivity as it contains allylthiocyanate.[24] Cases of contact dermatitis caused by synthetic oil of mustard have been reported.[25] In our study, a high percentage of patients used mustard oil. However, its role needs to be explored in subsequent studies.

In our study, 52.9% cases had received treatment in the past nearly similar as in the study by KrupaShankar et al. (49%).[13] Among treated and non-treated cases, there was no association with distribution pattern or other clinical features like erythema, telengectasias, atrophy.

Dyslipidemia was present in 61.34% of cases. In a study by Handel et al., 4% patients had dyslipidemia, but it was not found to be significant.[26] Lipid metabolism seems to be the most affected biological process in melasma.[27] Lipid metabolism genes, such as peroxisome proliferator-activated receptor alpha (PPAR), arachidonate 15-lipoxygenase, PPARγ coactivator 1 alpha, type B (ALXO 15B), diacylglycerol o-acyltransferase 2-like 3 were found to be downregulated. And this downregulation is caused by chronic UV exposure.[28]

Recently, the genes involved in the PPAR signaling pathway (ADIPOQ, perilipin 1, FABP4, lipoprotein lipase) were found to be downregulated in melasma patients. Also, the expression of AdipoR1 and AdipoR2 was found lower in lesional skin compared to normal skin.[29] Adiponectin is a hormone released from adipocytes.[30] It is involved in lipid metabolism thus having a role in insulin sensitivity.[31,32] Its transcriptional level is regulated by PPARγ that directly binds to conserved cis-acting regulatory DNA elements. Its serum levels are an indicator of the degree of PPARγ activity.[33] Involvement of PPARγ in the regulation of melanogenesis is recently garnering interest. It has been seen that ciglitazone-induced activation of PPARγ leads to increased melanogenesis.[34] Also, there is growing evidence that there is barrier functional defect in melasma. There is a well-documented relationship between epidermal barrier dysfunction and lipids of stratum corneum. Recent studies show that melasma skin is characterized by impaired stratum corneum integrity and delayed barrier recovery based on the levels of epidermal water loss after tape stripping in melasma skin.[35] Thus, adipose tissue dysfunction, increased PPARγ activity and skin barrier functional defects possibly have a role in the pathogenesis of melasma.[36]

TSH was deranged in 21.85% patients. Abnormal TSH values were found in 25.3% patients in study by Tamega

et al.[14] Cakmak et al. found TSH levels to be significantly higher in the patient group.[15] The mechanism how thyroid hormones affect melasma is not clear. Pigmentary changes occur in thyroid disorders and hyperpigmentation is seen associated with hyperthyroidism.[36] A strong immunoreactivity to alpha-MSH on melasma skin is an important factor in the pathogenesis of melasma.[16] It has been found that the melanocortin system interacts with hypothalamic-pituitary-thyroid axis.[21] An epidermal-dermal unit responds to certain inflammatory stimuli through melanogenesis. Procedures that induce skin inflammation can trigger or aggravate melasma.[16,22] It has been suggested that thyroid hormones induce production of inflammatory cytokines. Higher levels of pro-inflammatory cytokines have been seen in patients with hyperthyroidism.[37]

29.4% patients had low levels of serum vitamin B12. Serum vitamin B12 deficiency is known to cause hyperpigmentation. The mechanism is hypothesized as either vitamin B12 deficiency decreases the level of reduced glutathione, which activates tyrosinase, leading to transfer to melanosomes or there is a defect in melanin transfer between melanocytes and keratinocytes, resulting in pigmentary incontinence.[38,39] However, it is difficult to comment on the association of melasma with low vitamin B12 levels as we did not have a control group in our study.

79% cases had vitamin D deficiency. Due to the avoidance of sunlight as advised to melasma patients and due to use of sunscreens, vitamin D deficiency is seen associated with melasma.[40] Serum vitamin D and B12 levels have not been observed in any study yet.

CONCLUSION

This is the first study to look for risk factors including use of hair dye amongst other contact allergens present in cosmetics and hair oil. Thus, suggesting contact sensitivity in the pathogenesis of melasma. Also, we found a statistically significant association between MASI score and skin type. Higher skin phototypes should be cautious about the general measures and other risk factors including hair oils/dye and other cosmetics, which are associated with melasma. Housewives and indoor occupations should be advised physical sunscreens, containing iron oxide and zinc oxide for protection against infra-red radiation. Anemia, dyslipidemia, thyroid dysfunction, vitamin D and B12 levels can be assessed in patients of melasma although their exact role in precipitating/perpetuating melasma needs further studies.

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