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Original Article

Clinical Features, Investigative Profile and Association with Metabolic Syndrome in Facial Acanthosis Nigricans: A Case–Control Study in Indian Patients

T. Narayana Rao[1], K. V. T. Gopal[1], Kavya Chennamsetty[2], Sai Teja Reddy Velapati[1], K. Ananditha[1], Pallavi Sai Adapa[1]

[1]Department of Dermatology, Venereology and Leprosy, Maharajah's Institute of Medical Sciences, Vizianagaram, [2]Department of Dermatology, Leelavathi Skin and Laser Center, Guntur, Andhra Pradesh, India.

***Corresponding author:**
K. V. T. Gopal,
Department of Dermatology, Venereology and Leprosy, Maharajah's Institute of Medical Sciences, Vizianagaram, Andhra Pradesh, India.

kvtgopal77@gmail.com

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ABSTRACT

Objectives: The present study was undertaken to study the clinical profile and laboratory abnormalities in patients with facial acanthosis nigricans (FANs). The significance of FAN as a marker of insulin resistance (IR), metabolic syndrome (MS) and its components was determined by comparing with controls without FAN.

Materials and Methods: Fifty clinically diagnosed cases of FAN of all ages and both sexes were enrolled. Age- and sex-matched obese patients without FAN were included as controls. Waist circumference, blood pressure and body mass index were measured. Venous samples were taken from all patients and controls for measuring fasting glucose level, fasting insulin levels and fasting lipid profile. Statistical analysis was done using the Chi-square test and unpaired *t*-test.

Results: The prevalence of hypertension, dysglycaemia, hyperlipidaemia, elevated Homeostatic Model Assessment for IR (HOMA-IR) and MS was significantly higher in cases of FAN than controls ($P < 0.05$). The mean levels of fasting blood sugar, HOMA-IR, hypertension, high-density lipoprotein and serum triglycerides were significantly higher in patients of FAN than controls ($P < 0.05$). The odds ratio for FAN cases developing MS was determined to be 5.31.

Conclusion: FAN may be considered as a significant clinical marker of IR with increased risk for MS and its component when compared to controls. All patients with FAN should be considered for a thorough biochemical workup to rule out MS. In all detected cases, it is prudent to initiate prompt remedial measures including lifestyle changes and pharmacotherapy to prevent long-term morbidity and mortality.

Keywords: Facial acanthosis nigricans, Insulin resistance, Metabolic syndrome, Obesity, Dyslipidaemia

INTRODUCTION

Acanthosis nigricans (ANs) are defined as thickened, hyperpigmented, velvety plaques usually distributed symmetrically in the intertriginous areas such as neck, axillae and groins. It is a widely known marker of obesity, insulin resistance (IR) and metabolic syndrome (MS).[1,2] Facial acanthosis nigricans (FANs) is characterised by hyperpigmentation developing over the temples, malar area and the forehead with ill-defined margins and different degrees of textural changes.[3,4]

In obesity-associated ANs, the pivotal role of hyperinsulinemia and IR in the pathophysiology of MS is well established.[5,6] Studies describing FAN and its significance as cutaneous indicator

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for IR are scarce in literature.[7,8] The present study was undertaken to analyse the clinical features and laboratory profile in patients with FAN. The significance of FAN as a clinical marker of IR, MS and its components was also ascertained by comparing with age- and sex-matched obese individuals without FAN.

MATERIALS AND METHODS

The present observational case–control study was carried out at a suburban medical college hospital over 18 months from July 2016 to December 2017 after being approved by the Institutional Ethics Committee. The study participants were selected by convenience sampling and all patients who gave consent during the recruitment period were enrolled in the study.

Fifty obese patients with a clinical and dermoscopic diagnosis of FAN of age >18 years of both sexes who presented with brown-to-black macular pigmentation of face with poorly defined margins and varying degrees of textural changes were included in the study. Fifty age- and sex-matched obese patients attending the outpatient department (OPD) with conditions other than FAN were included as controls. Pregnant and postpartum females within 1 year of delivery, patients presenting with facial pigmentary conditions not suggestive of FAN such as melasma, pigmented contact dermatitis, lichen planus pigmentosus, post-inflammatory hyperpigmentation and drug induced pigmentation were excluded from the study.

After taking informed consent, general demographic data were noted. A detailed history was taken regarding occupation, age of onset and duration of FAN, associated symptoms and family history of AN including FAN. Menstrual and reproductive history was noted in females. A general examination was performed and height, weight and waist circumference (WC) were noted. Body mass index (BMI) was calculated by weight in kilograms divided by height in metres squared. We considered normal BMI as 18.0–22.9 kg/m^2, overweight as 23.0–24.9 kg/m^2, obesity as >25 kg/m^2 and morbid obesity as >30 kg/m^2.[9] Blood pressure was measured using manual mercury sphygmomanometer. Detailed dermatological examination was performed taking note of the colour, textural changes, parts of the face involved and presence of AN on other parts of the body. In all cases, dermoscopy was performed using DermLite DL3 dermoscope. Skin biopsy for histopathological examination was done in consenting patients who agreed to undergo the procedure.

Venous samples were taken from all patients and controls after an overnight fast of at least 8 h for measuring haemoglobin, fasting glucose level, fasting insulin levels and fasting lipid profile. Homeostatic Model Assessment for IR (HOMA-IR) as a guide to IR was calculated as = Fasting glucose (mmol) × Fasting insulin (uU/mL)/22.5. Classification was done as normal <2, borderline 2–2.2, moderate 2.2–3 and severe >3. According to the consensus statement provided by Misra *et al*., three out of the following five factors are needed for the identification of MS: Abdominal obesity (>40 inches [101 cm] in males and >34.5 inches [87.63 cm] in females), fasting blood glucose ≥100 mg/dL, blood pressure ≥130/85 mmHg, triglycerides ≥150 mg/dL and high-density lipoprotein (HDL) (<40 mg/dL in males and <50 mg/dL in females).[9] Laboratory values which were more than the above-mentioned cutoff values were considered as abnormal.

The primary objective of the study was to determine the association of FAN with established MS syndrome. Secondary objective was to study the clinical, dermoscopic features of FAN and compare the prevalence of IR, components of MS in patients with and without FAN. Quantitative data collected from all patients were tabulated and analysed using the Statistical Package for the Social Sciences (SPSS) trial version 25. Microsoft Office Excel sheet was used to find means and standard deviations. Statistical analysis was done using a Chi-square test and unpaired *t*-test to compare mean values of quantitative variables and $P < 0.05$ was considered as statistically significant.

RESULTS

In the present study, 36 (72%) males and 14 (28%) females with FAN and 35 (70%) males and 15 (30%) female controls were enrolled ($P = 0.825$). Duration of pigmentation ranged from 8 weeks to 12 years with a mean duration of 3.5 years. The pattern of facial pigmentation differed among the female and male population. In females, mild thickening without velvety texture was seen over the perinasal area in 7 patients (50%), followed by the periorbital area in 5 (35.71%), transnasal in 4 (28.57%) and perioral area in 3 (21.42%) patients.

In contrast, males showed predominant involvement of forehead with horizontal band like pigmentation extending to the temporal region in 17 cases (47.22%) and involvement of zygomatic areas in 16 cases (44.44%) [Figure 1a and b]. Pigmentation over perinasal area in 7 (19.44%), earlobe crease in 4 (11.11%) and periorbital area, transnasal area in 2 cases (5.55%) each was observed. Only one male patient presented with diffuse pigmentation all over the face with mild thickening and roughness of skin [Figure 2a]. Fourteen out of the 36 male patients (38.88%) showed velvety texture. AN of other body sites such as neck, axilla and groins was noted in 37 patients [Figure 2b]. Common dermoscopy findings seen in all cases included crista cutis, sulcus cutis arranged linearly along with hyperpigmented dots and perifollicular hyperpigmentation [Figure 3].

Figure 1: (a) Horizontal band like pigmentation over the forehead with thickened skin and velvety texture and (b) blackish pigmentation over the temporal region with mild thickening of skin.

Figure 2: (a) Diffuse pigmentation all over the face and neck with mild thickening and roughness of skin and (b) diffuse pigmentation and thickening of skin over the axilla extending onto the surrounding areas.

Histopathological examination performed in 18 cases showed hyperkeratosis and intense melanisation of the basal layer in all cases whereas papillomatosis and presence of upper dermal melanophages was noted in nine cases each.

The mean age, BMI and WC of FAN cases and controls were comparable with $P > 0.05$ [Table 1]. The prevalence of various parameters fulfilling the criteria for diagnosis of MS among cases and controls is shown in Table 2. The prevalence of hypertension with blood pressure more than 130/85 mm of Hg (along with known cases of hypertension on medication) was seen in 26 cases (52%) and 6 controls (12%) ($P = 0.001$). The mean systolic and diastolic blood pressure recorded were 131.8, 93 mmHg in cases and 120.3, 83.82 mmHg in controls, respectively ($P = 0.0001$). Elevated fasting blood glucose levels above 100 mg/dL were detected in 24 cases (48%) and 10 controls (20%) with a mean fasting blood glucose of 112.1 mg/dL in cases and 83.12 mg/dL in controls ($P = 0.001$).

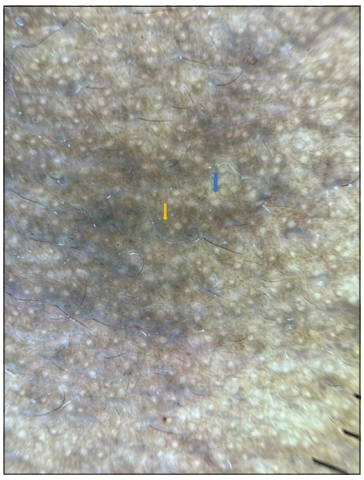

Figure 3: Crista cutis (yellow arrow), sulcus cutis (blue arrow), along with perifollicular hyperpigmentation seen on dermoscopy (×10 magnification).

HOMA IR index above 3 was detected in 44 cases (88%) and 23 controls (46%) ($P = 0.045$) with a mean HOMA IR of 8.21 in cases and 5.16 in controls ($P = 0.003$). Reduced HDL levels were found in 26 cases (52%) and 6 controls (12%) with mean HDL levels of 34.3 mg/dL in cases and 41.59 mg/dL in controls ($P = 0.001$). Elevated serum triglyceride levels of >150 mg/dL were noted in 23 patients (46%) and 12 controls (24%) ($P = 0.031$) with a mean serum triglyceride level of 162.4 mg/dL and 124.52 mg/dL in cases and controls, respectively ($P = 0.001$). Overall, the prevalence of established MS was seen in 21 patients (42%) and 6 controls (12%) ($P = 0.009$). The odds ratio for FAN cases developing MS was determined to be 5.31 [Table 3].

DISCUSSION

FAN is being increasingly recognised as one of the common causes for cosmetic disfigurement of the face.[10,11] The previous studies have shown that FAN has similar clinical and histopathological features as that of AN of neck and axillae – mainly hyperpigmentation, thickening with or without velvety appearance and acanthosis, papillomatosis together with epidermal and dermal melanosis.[12,13] In the present study, male preponderance was seen with male: female ratio of 2.57:1 which correlated closely with the male: female ratio of 2.9:1 reported by Verma *et al*.[14]

The common patterns of pigmentation in males in our study were horizontal band like pigmentation over forehead seen in 17 cases (47.22%), zygomatic areas in 16 cases (44.44%) and perinasal area in 7 cases (19.44%) which were in accordance with the findings of Shah *et al*.[8] However, higher prevalence

Table 1: Comparison of means of parameters of metabolic syndrome in cases and controls.

	Age	BMI	WC	Fasting glucose	HOMA IR	SBP	DBP	HDL	TG
Cases (with FAN) (*n*=50)	39.02	30.6	105.3	112.1	8.21	131.8	98.48	34.3	162.4
Controls (without FAN) (*n*=50)	36.58	29.4	101.1	98.12	5.16	120.3	83.82	41.59	124.52
P-value	0.069	0.869	0.873	0.001	0.003	0.0001		0.001	0.001

BMI: Body Mass Index, WC: Waist Circumference, HOMA IR: Homeostatic Model Assessment For Insulin Resistance, SBP: Systolic Blood Pressure, DBP: Diastolic Blood Pressure, HDL: High-Density Lipoprotein, FAN: Facial Acanthosis Nigrican, TG: Triglycerides

Table 2: Prevalence of variables of metabolic syndrome in cases and controls.*

	BMI (>25kg/m^2) (%)	Increased waist circumference (%)	Increased Fasting glucose (%)	HOMA IR (>3) (%)	Hypertension (%)	Increased HDL levels (%)	Increased triglyceride levels (%)	Metabolic syndrome (%)
Cases (with FAN) (*n*=50)	50 (100)	37 (74)	24 (48)	44 (88)	26 (52)	26 (52)	28 (56)	21 (42)
Controls (without FAN) (*n*=50)	50 (100)	30 (60)	10 (20)	23 (46)	6 (12)	6 (12)	12 (24)	6 (12)
P-value	1	0.507	0.037	0.045	0.001	0.001	0.031	0.009

BMI: Body mass index, HOMA IR: Homeostatic model assessment for insulin resistance, HDL: High-density lipoprotein, FAN: Facial acanthosis nigrican, *As per the consensus statement for diagnosis of obesity, abdominal obesity and metabolic syndrome proposed by Misra *et al*.[9]

Table 3: Calculation of OR of FAN cases developing MS.

	With MS (%)	Without MS (%)
Cases (with FAN) (*n*=50)	21 (42)	29 (48)
Controls (without FAN) (*n*=50)	6 (12)	44 (88)

OR: 5.31, OR: Odds ratio, MS: Metabolic syndrome, FAN: Facial acanthosis nigrican

of pigmentation over forehead and temples (69.10%) and zygomatic area (57.72%) was reported by Panda *et al*.[7] The difference in the distribution between males and females in our study could be attributed to increased sun exposure, frequent rubbing of forehead and temples with a cloth to wipe off sweat, indicating that friction may accentuate FAN as supported by Verma *et al*.[14] AN of other areas such as neck, axilla and groin was noted in 74% of our study population that correlated with the findings of Shah *et al.* (92.50%) and Verma *et al.* (86.27%).[8,14]

In the present study, the prevalence of established MS and its components – hypertension, dysglycaemia, hyperlipidaemia and elevated HOMA-IR >3 was significantly higher in cases of FAN compared to the controls ($P < 0.05$). Mean fasting blood sugar and mean HOMA-IR index in cases of FAN were 112.1 mg/dL and 8.21 compared to 98.12 and 5.16 in controls, respectively ($P = 0.001$ and 0.003, respectively). The means of other parameters for diagnosis of MS including hypertension, HDL and serum triglycerides were also significantly higher in patients of FAN than the control population with $P = 0.0001$, 0.001 and 0.001, respectively. The odds ratio for FAN cases developing MS was determined to be 5.31, suggesting that cases with FAN were nearly 5 times more likely to acquire MS than controls. Higher prevalence of various parameters of MS in FAN has been reported in previous clinicoinvestigative studies.[7,8] These observations along with the findings of our study clearly establish that individuals with FAN are at an increased risk of IR, MS and its individual components when compared to obese individuals without FAN.[15,16]

Histological changes responsible for the clinical manifestations of FAN including velvety texture are increased thickness of epidermis and increased melanin in all layers of epidermis.[17,18] Elevated level of growth hormone plays a cardinal role in the pathogenesis of FAN by stimulating and increasing the activity of fibroblasts and keratinocytes. Pigment epithelium-derived factor (PEDF) also has a pathogenic role in FAN based on the strong correlation between circulating PEDF and fasting insulin and HOMA IR.[19] In a milieu of increased IR, increased PEDF which is abundant in stage I melanosomes increases pigment granules. This explains the observation of weight loss and lifestyle modifications being more vital than depigmenting creams and procedural treatments in the management of FAN.[20]

Limitation

Histopathological confirmation could not be obtained in all patients. Grading of the severity of FAN and its correlation with metabolic derangements could not be performed. In the future, studies with larger sample size would help in validating the correlation of FAN with IR and MS.

CONCLUSION

Our study demonstrated a clear statistical significance of FAN as a clinical marker of IR with increased risk for MS and its components when compared to obese individuals without FAN. All patients with FAN should be considered for thorough biochemical workup to rule out MS. In all detected cases, it is prudent to initiate prompt remedial measures including lifestyle changes and pharmacotherapy to prevent long-term morbidity and mortality.

Ethical approval

The research/study approved by the Institutional Review Board at Maharajah's Institute of Medical Sciences, Nelllimarla, Andhra Pradesh, number 107/02/16, dated 21st June 2016.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Nil.

Conflicts of interest

There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

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