ORIGINAL ARTICLE

A cross sectional study for the evaluation of hyperandrogenaemia in acne vulgaris

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ABSTRACT

Background: Acne is one of the most prevalent skin conditions and affects more than 85% of teenagers. Hyperandrogenaemia can lead to severe acne.

Objective: To assess the clinical and hormonal parameters of hyperandrogenism, ovarian morphology for PCOS by ultrasonography and to correlate the severity of acne with androgen levels.

Material and method: This cross-sectional observational study included 40 female patients with acne vulgaris and control group consisted of 40 consenting age matched females, without acne vulgaris and/or hyperandrogenism. Physical examination was done to identify the clinical features of hyperandrogenemia. The fasting blood samples were obtained between 2nd to 5th day of menstrual cycle for the assessment of free and total testosterone, DHEAS, androstenedione, fasting blood glucose, insulin 17-OHP, LH/FSH ratio, prolactin, fT3, fT4, TSH, albumin and SHBG. All the patients were subjected to ultrasonographical examination between 2nd -5th day of the menstrual cycle to rule out polycystic ovaries.

Result: DHEAS, prolactin and androstenedione were significantly increased in cases as compared with the control. Hormonal parameters such as DHEAS, prolactin and androstenedione were significantly associated with severity of acne. Amongst different clinical parameters of hyperandrogenism viz. androgenic alopecia, acanthosis nigricans, high BMI & presence of polycystic ovaries on ultrasound, were significantly associated with severity of acne.

Conclusion: Hormonal evaluation and USG abdomen and pelvis should be included in management of patients presenting with severe acne along with other signs of hyperandrogenism.

KEY WORDS: Acne, hyperandrogenemia, polycystic ovarian syndrome (PCOS)

INTRODUCTION

Acne vulgaris is characterized by seborrhoea. Sebocytes and follicular keratinocytes have exaggerated response to androgens, thereby leading to hyperplasia of glands and increased sebum production, which characterize acne.[1,2] Circulating androgen and acne have a well established association. There are studies which shows positive correlation between acne severity and testosterone, DHEAS (Dehydro epiandrostenedione sulphate), AS(Androstenedione), prolactin, LH/FSH ratio, 17-OHP(17-Hydroxy progesterone) levels.[4,5,6] Walton et al [7] found a significant positive correlation between acne severity, the number of inflammatory lesions, and concentrations of circulatory DHEAS and free T as well as negative correlation with levels of SHBG(Sex hormone binding globulin). Borgia et al[8] in their study on androgens in acne reported a weak negative correlation between acne severity and

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SHBG and a positive correlation between acne severity and DHEAS, AS, prolactin, LH/FSH ratio, 17-OHP levels. There is paucity of studies from India regarding the role of hormones in acne vulgaris, and its correlation with clinical severity and underlying causes of hyperandrogenism. Therefore, it is important to evaluate the patient of acne vulgaris for the markers of androgenicity.

MATERIAL AND METHODS

The study group comprised 40 female patients with acne vulgaris and control group consisted of 40 consenting age matched females without acne vulgaris and/or hyperandrogenism.

Inclusion Criteria

1. Female patients of acne vulgaris of age group of 12 to 45 years.

Exclusion Criteria

1. Patients who have taken oral contraceptives in the previous 6 months, oral antibiotics in the previous 4 weeks or oral retinoids within the previous 3 months.
2. Patients on drugs which are likely to interfere with androgen metabolism (e.g. cimetidine, spironolactone, cyproterone acetate, danazol, stanazol, nandrolene) and drugs producing acneiform eruptions (e.g. glucocorticoids, lithium, isoniazid, phenytoin, halogenated compounds).
3. Pregnant patients and subjects less than three months post-partum.
4. Patients who have attained pre-mature menopause below the age of 45 years.

Procedure

After obtaining ethical approval from Institutional Ethical Committee, a cross sectional study was conducted during a period of 2 years extending from 2011 to 2013 at Department of Dermatology, Venereology & Leprosy, Department of Endocrinology & Department of Biochemistry PGIMER, Dr RML Hospital New Delhi, India. Written informed consent from the patients was taken before inclusion in the study. Detailed history including menstrual history and physical examination of the patients was recorded. The duration, history of evolution and progression of acne with special reference to any aggravating or inciting factors, was also documented. History of any concomitant illness was also obtained. General physical examination of each patient was done. A systemic examination was done to rule out any systemic illness. A detailed cutaneous examination was carried out which included assessment of signs of endocrinopathy i.e. acne, acanthosis nigricans, striae, clitoromegaly, temporal hair recession, hirsutism, palmar erythema, spider angioma and obesity. Global acne grading system was used to grade the acne severity.[9] Modified National Institute of Health criteria[10] were used for diagnosis of polycystic ovarian syndrome (PCOS). The clinical assessment of hirsutism was done using modified Ferriman-Gallwey scoring system.[11] The biochemical investigations and hormonal evaluation were conducted after overnight fasting between 3rd to 5th day of the menstrual cycle in the midfollicular phase in patients with regular menstrual cycles or on any other day in patients who have not menstruated in the past one and half months, for the assessment of the following hormone levels and biochemical parameters: Free testosterone (FT) and total testosterone (T), SHBG, serum DHEAS, 17-OHP, AS, LH/FSH ratio, Prolactin, Free triiodothyroxine (fT3), free tetraiodothyroxine (fT4), thyroid stimulating

hormone (TSH), Fasting insulin, Fasting blood glucose. Ultrasonography of all the patients was performed between days 2-7 of menstrual cycle in regularly menstruating women while oligo/amenorrhoeic women were scanned at random or between days 3 and 5 after a progestin-induced withdrawal bleeding. The follicle numbers, maximum diameter of each follicle, echogenicity of ovarian stroma was also noted.

STATISTICAL ANALYSIS

The mean value of each hormone in each cause of acne was compared to the appropriate controls using the student's t-test. Clinical features were correlated with each other using chisquare test. P value <0.05 was considered statistically significant. Analysis was done on SPSS version 15.0 (Statistical package for social sciences, Microsoft Inc, Chicago IL, USA).

OBSERVATION AND RESULT

Forty patients and 40 controls were included in the study. Table 2 illustrates the severity of acne based upon The Global Acne Grading System. None of the patient had very severe acne (Score >39). The mean score of acne observed in our study was 22.7. From table 3 it is clear that, as severity of acne increases the occurrence of other clinical features of hyperandrogenemia increases. Table 4 reveals that the difference between the means of DHEAS, prolactin and androstenedione of cases was found to be statistically significant when compared with the control group by t-test ($p < 0.05$). The mean levels as well as the range of hormones studied in the instant study on acne vulgaris are also depicted in the table. From table 5 it is evident that raised DHEAS, Androstenedione and raised SHBG level are associated with increase in severity of acne. From the above table 6 it is apparent that raised prolactin level and raised fasting insulin level are associated with increase in severity of acne.

Table 1 Demographic parameters of cases

Demographic Parameter	Mean ± SD values
Age	24.3 ± 5.7 years
Age of onset of acne	20 ± 4.6 years
Duration of acne	4.7 ± 2.9 years
Age of menarche	13.3 ± 1.13 year

Table 2 Severity of acne

Severity of Acne	Number of Patients	Percentage (%)
Mild (1-18)	10	25
Moderate (19-30)	26	65
Severe (31-38)	4	10
Very severe (>39)	0	0
Total	**40**	**100**

Table 3 Relationship between severity of acne and clinical features of hyperandrogenaemia

Grades of Acne	Mild (1-18) N= 10	Moderate (19-30) N=26	Severe (31-38) N = 4
Hirsutism	10%	38.4%	50%
Menstrual irregularities	10%	30.8%	100%
Androgenic alopecia	0%	23.07%	75%
Raised BMI (Overweight & Obesity)	10%	34.6%	75%
Seborrheic dermatitis	10%	30.8%	75%
Acanthosis nigricans	0%	30.8%	75%
Striae	0%	23.1%	75%
PCOS	10%	26.9	100%

DISCUSSION

Pathogenesis of acne includes altered follicular hyperkeratinization of the pilosebaceous unit, P.

acnes follicular colonization, increased sebum production and release of inflammatory mediators. Sebum production is stimulated by androgens and is the key in development of acne vulgaris.[17,18] Increase in the availability of potent androgens at the pilosebaceous unit can occur either by alterations in androgen metabolism in the skin resulting in increased local formation of metabolites or by high circulating androgens resulting from increased ovarian or adrenal production.[19] Hyperandrogenism is a condition

Table 4 Mean hormone levels in cases and controls

Hormones	Controls (n=40) mean ± S.D.	mean ± S.D.
Free Testosterone (Range in ng/L)	1.72±0.94 (0.25 – 4.27)	1.9±1.4 (p>0.44) (0.3-8.7)
Total Testosterone (Range in nmol/L)	1.08 ± 0.51 (0.2 – 2.8)	1.09 ±0.54 (p>0.97) (0.24 – 2.4)
DHEAS (Range in µg/ml)	1.21 ± 0.57 (0.48 – 3.0)	1.7 ± 0.89 (p<0.006) (0.28 – 3.6)
17-OHP (Range in ng/ml)	0.38 ± 1.2 (0.3 – 1.2)	0.49 ±0.25 (p>0.103) (0.2– 1.2)
LH/FSH	0.95 ± 0.4 (0.95 – 0.4)	1.5±0.71(p>0.05) (0.14 – 2.6)
Prolactin (Range in ng/ml)	11.08 ± 4.5 (4.6 – 19.6)	14.14 ± 4.09 (p<0.002) (4.9 – 21.32)
Free T3 (Range in pg/ml)	3.025 ± 0.75 (2 – 5.3)	3.2± 0.58 (p>0.121) (1.1 – 4.6)
Free T4 (Range in ng/dl)	1.29 ± 0.38 (0.77 – 2.2)	1.19± 0.30 (p>0.2) (0.85 – 2.6)
TSH (Range in mIU/ml)	2.7 ± 0.18 (0.6 – 5.6)	2.98 ± 1.35 (p>0.39) (0.7 – 5.6)
Androstenedione (Range in pmol/L)	0.99 ± 0.45 (0.12 – 2.7)	1.36 ± 0.61 (p<0.014) (5.4 – 2.7)
Fasting blood glucose (Range in mg/dl)	84.98 ± 8.52 (72 – 104)	86.8± 9.39 (p>0.53) (72– 116)
Fasting insulin (Range in µIU/ml)	6.8 ±3.4 (1.0-15.0)	7.91±3.32 (p>0.14) (0.5-18)
SHBG (Range in nmol/L)	72.51 ±29.9 (18.92-109.4)	69.38±34.52 (p>0.61) (8.9-117)
S. Albumin (Range in g/dl)	4.12 ±0.5 (3.4-5.51)	3.8±0.36 (p>0.77) (3.6-4.8)

Table 5 Relationship between severity of acne and increased androgens

Grades of Acne	Mild (1-18) N= 10	Moderate (19-30) N=26	Severe (31-38) N = 4
Raised Free Testosterone level	0%	0%	25%
Raised Free Testosterone level	0%	0%	0%
Raised DHEAS Level	0%	11.05%	100%
Raised Androstenedione level	0%	3.8%	25%
Raised SHBG	0%	3.8%	25%

Table 6 Relationship between severity of acne and other hormones and proteins

Grades of Acne	Mild (1-18) N= 10	Moderate (19-30) N=26	Severe (31-38) N = 4
Raised 17-OHP Level	0%	0%	0%
Raised LH/ FSH Ratio	0%	23.1%	25%
Raised Prolactin level	10%	19.2%	50%
Raised Free T3 level	0%	3.8%	0%
Raised Free T4 level	0%	3.8%	0%
Raised TSH level	10%	3.8%	25%
Raised Fasting Insulin level	0%	23.1%	50%
Raised Serum albumin level	0%	0%	0%

characterized by excessive production and/or secretion of androgens. The causes include polycystic ovarian syndrome (PCOS), idiopathic hirsutism, non-classical adrenal hyperplasia, congenital adrenal hyperplasia, hypothyroidism, hyperprolactinemia, androgen secreting tumours and Cushing's syndrome. Thiboutot et al[20] has mentioned that serum levels of androgens play a role in the development of acne by acting directly on sebaceous glands, by stimulating tissue enzyme activity or both.[20] Other contributing factors for acne include genetic influence, stress. Among androgens DHEAS level were elevated in 11.5% patients of moderate acne, 100% cases of severe acne. The DHEAS levels and its association with acne was statistically significant ($p<0.006$). DHEAS is almost wholly and AS is partly secreted from the adrenal cortex and can be peripherally converted to T and DHEAS. Thus, it is possible that there may be a state of adrenal hypersecretion in patients with severe and recalcitrant acne. Similarly, Hatwal et al[16] in their study found that DHEAS was significantly elevated in the patients as compared to controls. Walton et al[7] in their study found a significant positive correlation between acne severity and DHEAS levels. Cibula et al[15] in their study found that DHEAS was elevated in 30% patients and it correlated positively with acne severity which is similar to findings in our study. The AS levels and its association with acne was significantly different from the controls ($p<0.014$) and this statistically significant difference was found only in the sub-group of severe cases. In a study by Cibula et al[15] AS was elevated in 79% of the patients and they found a significant positive correlation between acne severity and AS levels. Among androgens, we found that the free T levels and its association with acne was not significantly different from the controls in all the mild and moderate patients having normal free T, and 1 (25 %) patient with severe acne having raised levels. Walton et al[7] in their study found a significant positive correlation between acne severity and free testosterone levels. In our study all the patients had normal levels of total testosterone and there was no significant association between cases and controls. Similarly, Walton et al[7] in their study did not find a significant positive correlation between acne severity and total testosterone levels. But Cibula et al[15] in their study found that T was elevated in 24% patients and it correlated positively with acne severity. We did not find a significant correlation between acne severity and SHBG. Measurement of SHBG is important because low levels imply a relative increase in free testosterone even in the presence of normal total T levels. Hence, the tissue may suffer from the effects of raised circulating metabolically active T level. Walton et al[7] in their study found a significant negative correlation with SHBG and acne severity. Borgia et al[8] in their study found that SHBG values were significantly lower in subjects with moderate acne than those with minor and mild acne. Among other hormone and protein, Prolactin levels were elevated in 20% patients in the present study and statistically significant association was observed in moderate and severe groups with severity of acne. The prolactin levels and its association with acne was significantly different from the controls ($p<0.002$). Similarly, Borgia et al[8] in their study found serum prolactin was elevated in 19.38% patients but it was not significantly associated with the severity of acne. LH/FSH ratio were raised in 17.5% of patient in our study group but correla-

tion with acne severity was not statistically significant. Similarly, Borgia et al[8] found LH/FSH ratio was increased in 29.4% patients and LH/FSH ratio was not statistically significant when compared with severity of acne. In the present study all the cases of acne had normal levels of 17-OHP. The association between severity of acne and 17 OHP levels was not found to be statistically significant ($p>0.103$). Similarly, Borgia et al[8] in their study found elevated 17-OHP values in 19.38% patients without significant correlation between acne severity and 17 OHP levels. There was no significant association of free T3, T4 and TSH with acne severity ($p>0.121$), ($p>0.21$), ($p>0.39$) respectively. In our study, fasting blood insulin levels and its association with acne was not significantly different from the controls with a p value of ($p>0.14$). Aizawa and Niimura[21] examined female patients of acne and found no significant difference in insulin levels between acne and control groups which agrees with our findings. Kaymak et al[22] concluded that insulin levels do not have a role in pathogenesis of acne in younger patients. There was no significant association between acne severity and serum albumin levels ($p>0.77$). In our study we found that 30% patients showed polycystic ovaries on ultrasound and we observed a statistically significant association of polycystic ovaries with severity of acne ($p<0.003$). Similarly, Borgia et al[8] in their study reported polycystic ovaries in 46.15% patients on ultrasound. Jebralli et al[14] in their study found that presence of polycystic ovaries was correlated positively with severity of acne which agrees with our findings. Among clinical parameters, in present study, hirsutism was noted in 32.5% patients, and we did not find an association between acne and hirsutism ($p>0.05$). Similarly, Borgia et al[8] in their study found hirsutism in 19.38% without significant association between acne severity and hirsutism. A statistically significant association between severity of acne and androgenic alopecia was observed in our study ($p<0.01$). In a similar study by Adityan and Thappa[12] noted female androgenic alopecia in 11.4% patients. We found acanthosis nigricans in 27.5% patients in our study population and the relationship between severity of acne and acanthosis nigricans was significant ($p<0.015$). Adityan and Thappa[12] in their study found that acanthosis nigricans was present in 52.9% of the patients. We found a statistically significant correlation between the severity of acne and BMI in our study ($p<0.035$). Similarly, Tsai et al[13] in their study found that, mean BMI of acne subjects was significantly higher than the mean BMI of non-acne group. Hence patients who have higher BMI have increased probability of developing acne. In current study, we assessed several of the clinical and laboratory parameters of androgenicity and USG abdomen pelvis. We demonstrated statistically positive correlation between acne severity and clinical parameter viz androgenic alopecia, acanthosis nigricans, raised BMI. Among laboratory and USG evaluation DHEAS, prolactin a presence of polycystic ovaries on ultrasound were significantly associated with severity of acne. Other clinical parameters of hyperandrogenism are hirsutism, seborrheic dermatitis, striae and menstrual irregularity. Observing these clinical signs of hyperandrogenicity is very imperative, as it indicates the need for further evaluation and starting patient on adjuvant hormonal therapy along with conventional line of treatment.

CONCLUSION

All the patients presenting with acne should be subjected to detailed history including menstrual history and physical examination specially to look for clinical signs of hyperandrogenemia. All the patients with severe acne and patients having one or more clinical symptoms or signs of hyperandrogenism should undergo complete hormonal evaluation and ultrasound of abdomen and pelvis to detect the underlying endocrinological abnormality, so that the appropriate therapy could be initiated.

Limitations: Larger sample size is required to validate our findings.

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