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A STUDY ON CORRELATION BETWEEN ACANTHOSIS NIGRICANS (AN) AND POLYCYSTIC OVARY SYNDROME (PCOS) IN INDIAN ADOLESCENT GIRLS

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ABSTRACT

Acanthosis nigricans (AN) is a readily recognizable dermatological manifestation of an underlying metabolic defect like insulin resistance (IR) or obesity which is closely associated with polycystic ovarian syndrome (PCOS). The aim of the study was to compare the clinical and biochemical parameters of Indian adolescent girls with PCOS with and without AN. 58 adolescent girls in the age group of 14-19 years with the complaints of oligomenorrhoea (≤ six menses per year) with clinical evidences of hyperandrogenism (hirsutism and/ or acne) were studied. In each case clinical parameters like body mass index (BMI) (as kg / m ^{2}) from height and weight measurements, abdominal circumference (AC), blood pressure (BP), hirsutism score, presence of acne and acanthosis (AN) were noted. Biochemical tests included the estimation of serum total testosterone (TT) and sex hormone binding globulin (SHBG) levels. Plasma insulin (PPI) and plasma glucose (PPG) levels. The study group was divided into two, based on the presence or absence of acanthosis nigricans. Significant differences were found in the parameters of BMI (p=0.0001), AC (p=0.0001); DBP (p= 0.01); TT (p= 0.002); FAI (p=0.002) between the two groups. The model signifies positive impacts of BMI, testosterone level, PP insulin level and negative influence of PP sugar, SHBG levels on AN.. AN in adolescent girl with PCOS is another clinical marker of obesity. This study shows that presence of AN is not an indicator of underlying insulin resistance or glucose intolerance.

KEY WORDS: Acanthosis nigricans (AN), adolescent, adult, body mass index (BMI), polycystic ovary syndrome.

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INTRODUCTION

Acanthosis Nigricans(AN) is a dermatological manifestation characterized by velvety, papillomatous, brownish-black, hyperkeratotic plaques. It is seen on the intertriginous surfaces and neck[1]. It is a manifestation of an underlying metabolic defect like insulin resistance (IR) or obesity [2].AN is also found in women with polycystic ovarian syndrome (PCOS) because of its association with insulin resistance (IR) and hyperandrogenism (HA) [3]. It has been reported that between 5 and 33% of patients with PCOS have AN [4, 5].Presence of AN appears to be more of a sign of IR or medication reaction than distinct disease itself. Other pathological conditions rarely associated with AN are insulinoma and malignant diseases, especially adenocarcinoma of the stomach.Acanthosis is more common in obese PCOS patients. Hyperkeratosis and papillomatosis are the histological characteristics of AN. AN is a frequent occurrence in HA and diabetes mellitus [6]. In 1976, Kahn and colleagues [7] found an association of HA and insulin resistance with AN.There are very few studies which have reported the clinical, hormonal and metabolic parameters in PCOS with AN. In the present study various clinical and biochemical parameters (hormonal and metabolic) of adolescent Indian women having PCOS with and without AN are reported.

MATERIALS AND METHODS

The comparative cross sectional observational study was done in KPC Medical College which is a tertiary care hospital, from February 2015 to March 2016. Permission was obtained from the ethics committee of the institute and all studied women agreed to the investigation protocol.58 adolescence women (age 14-19 years) with PCOS were studied. These women had detailed clinical and hormonal evaluations for the diagnosis of PCOS according to the Rotterdam 2003 criteria [8] with at least two of the following features: (i) oligo-ovulation or chronic anovulation, (ii) clinical and/or biochemical hyperandrogenism, and (iii) ultrasound appearance of polycystic ovaries. Secondary causes of hyperandrogenism, as per the Rotterdam criteria, were excluded by appropriate clinical and laboratory tests. Women with history of steroid or oral contraceptive drug intake in the preceding 3 months as well as previously diagnosed diabetes were also excluded from the study. Oligo-ovulation and / or anovulation was characterized by oligomenorrhea (intermenstrual intervals of ≥35 days) and amenorrhea (intervals >3 months). Clinical hyperandrogenism was defined as the presence of alopecia, or hirsutism (modified Ferriman-Gallwey score of ≥ 6) and /or acne. Biochemical hyperandrogenism was considered if total testosterone level was more than 0.82 ng/ml (normal laboratory range 0.06-0.82ng/ml) or calculated free androgen index was more than 2.06 [9]. Polycystic ovary on ultrasound (Transabdominal) was defined as the presence of at least one ovary 10 cc or more in volume.A standard questionnaire was used to document length of menstrual cycles; personal, medical, and family history of diabetes; hypertension; obesity; and ischemic heart disease. Signs of androgen excess (hirsutism, acne, and alopecia), insulin resistance and presence of acanthosis were noted in the physical examination. Anthropometric measurements included abdominal circumference in centimeter as per internationally accepted guidelines (using a 1cm wide measuring tape). Body mass index (BMI) (kg/m^2) was calculated in each case from height and weight measurements. Height was recorded to the nearest 0.5cm. Weight (kg) was taken on a platform type (bathroom scale) machine, the accuracy of which was checked each time before weighing. Blood pressure was measured using a mercury sphygmomanometer, both systolic (SBP) and diastolic (DBP) BP was measured in mm of Hg.Fasting plasma glucose (FG) and Fasting plasma insulin (FI) levels were estimated after 12- hour overnight fasting for all subjects. Plasma glucose was measured by Glucose oxidase peroxidase method (Roche Diagnostics Gmbh, Mannheim, Germany) and was expressed in mg % and plasma insulin level in mcu / ml. Glucose-insulin ratio (G:I) and homeostasis model assessment (HOMA) was calculated from FG and FI level. The method for assessing HOMA is FG (mg %) x FI (mcu/ml) /405. Serum total testosterone level (TT) was measured by using Electrochemiluminescence Immunoassay, Roche Lot. No. 181371- 01(Roche Diagnostics Gmbh, Mannheim,Germany) in ng/ml. Sex hormone binding globulin (SHBG) level was also measured (nmol/l) on the second or third day of progesterone induced bleeding. Free androgen index (FAI) was measured by the method (TT×100×3.47) / SHBG.Trans-abdominal ultrasound was performed to study the morphology of ovaries. Ovarian volume measurements were carried out by measuring three perpendicular dimensions (volume for a prolate ellipsoid = 0.5 × length × width × thickness). Follicle number was estimated both in longitudinal and antero-posterior cross-sections of the ovaries. Secondary causes of hyperandrogenism like 21-hydroxylase deficiency, Cushing'ssyndrome,hypothyroidism,hyperprolactinemia, and androgen-secreting tumors were excluded by appropriate clinical and/or laboratory tests.

STATISTICAL ANALYSIS

Assuming a confidence limit of 95%, the calculated confidence interval was 10%. For comparison of various clinical and biochemical parameters all parameters were tested for normality pre-test (using KS). The continuous variables were compared with T test and Chi-square test with Yates correction was also done as and when needed. To assess the degree of causality, logistic regression was done, (pseudo R^2=0.3447), (Prob > chi^2 = 0.0000) predicting a good fit model, p -value <0.05 was considered as significant.

RESULTS

Table 1 shows the clinical parameters of the two groups of patients studied**.** Out of the 58 studied girls, 18 were found to have Acanthosis Nigricans (Group A) (31.03%) and 40 girls did not have AN (Group B). There were significant differences in mean BMI (p=0.0001), AC (0.0001), SBP (p=0.03), DBP (p=0.01) and Waist-hip ratio (WHR) (p=0.0001).Table 2 shows the biochemical parameters of the two groups of patients. There is significant differences in serum testosterone level (p=0.002), FAI (p=0.002) and number of cases having

post prandial insulin level more than or equal to 150mcu/ml (p=0.09) whereas it has little significant correlation with SHBG level and number of cases having post prandial glucose level more than or equal to 140mgdl.By bivariate analysis it was found that AN had positive correlations with abdominal circumference, BMI, systolic and diastolic BP, serum testosterone level, FAI and number of cases having PP insulin level more than or equal to 150mcu/ml , AN had highest correlation with abdominal circumference, followed by BMI and serum testosterone level.

Table 1
Clinical parameters in the two groups
Data are mean (Standard deviation) or number (%)

Parameters	AN absent (n=18)	AN present (n=40)	p value
BMI (kg/m2)	22.7 (2.4)	28.1(4.2)	**0.0001**
AC (cm)	72.1 (5.1)	85.68(5.2)	**0.0001**
WHR	0.76 (0.03)	0.84 (0.05)	**0.0001**
SBP (mm of Hg)	117.5 (11.03)	125.0 (14.5)	**0.03**
DBP (mm of Hg)	72.6 (7.4)	78.3 (8.1)	**0.01**

Table 2
Hormonal and metabolic parameters

Parameters	AN absent (n=18)	AN present (n=40)	p value
Testosterone (ng/ml)	**0.36 (0.13)**	**0.65 (0.43)**	**0.002**
SHBG (nmol/l)	**35.5 (28.1)**	**31.7 (25.4)**	**0.60**
FAI	**4.91 (2.2)**	**10.1 (8.2)**	**0.002**
Number of cases with PPI > = 150 mcu/ml (%)	**3 (15.8)**	**15 (37.5)**	**0.09**
Number of cases with PPG = > 140 mgm% (%)	**4 (21.0)**	**8 (20.0)**	**0.92**

DISCUSSION

The clinical importance of AN has been claimed to be due to its association with various metabolic and hormonal abnormalities such as obesity, diabetes, PCOS, dyslipidemia, Cushing's syndrome, thyroid dysfunction etc [7,8,9].The clinical importance of AN has been claimed to be due to its association with various metabolic and hormonal abnormalities such as obesity, diabetes, PCOS, dyslipidemia, Cushing's syndrome, thyroid dysfunction etc [7,8,9].The actual prevalence of AN in the population has not been assessed widely in India. A hospital based study done in north India on selected group of diabetic patients and age matched controls had shown a very high prevalence of AN (62% vs. 54%) [10]. But as this was not a community study and as most of the study subjects were obese, these results may not be representative of the population at large.Many studies have shown that fasting insulin level can be considered a good indicator of insulin resistance [11,12,13]. Present study has demonstrated higher mean fasting insulin values among subjects with AN denoting higher insulin resistance among them compared to subjects without AN and are comparable to the results of a similar study conducted in Mumbai, India [14].Menon et al [15] in their study done among south Indian population reported that obesity might be a contributory factor for the high insulin level. They found that though mean insulin level were higher among all BMI categories with AN, it was statistically significant only among the obese group. This suggests that AN is more significantly associated with insulin resistance among the obese population than normal or overweight subjects. Our study also shows that AN in adult woman with PCOS is another clinical marker of obesity. We have found that presence of AN is not always an indicator of insulin resistance, as detected by the fasting G: I ratio rather obesity is a more consistent feature with AN. Panidiset al [16] had stated in their study that insulin resistance is a necessary, but not the only factor leading to the development of AN inpatient with PCOS. Our study has found that AN is strongly correlated with abdominal circumference (highest correlation) followed by BMI and negative correlation with number of girls having post prandial insulin level more than or equal to 150mcu/ml. This suggests that presence of AN should direct the clinician to give advices to patients in reducing abdominal circumference through changes in lifestyle pattern.

CONCLUSION

This study signifies that presence of AN is an important indicator of central obesity and consequent metabolic disorders. In a clinical setting presence of AN should direct the clinician to suspect underlying metabolic problems in PCOS and take appropriate preventive measures for future metabolic problems in them.

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CONFLICT OF INTEREST

Conflict of interest declared none.

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