International Journal of Reproduction, Contraception, Obstetrics and Gynecology
Khan B et al. Int J Reprod Contracept Obstet Gynecol. 2022 Mar;11(3):765-769
www.ijrcog.org
pISSN 2320-1770 | eISSN 2320-1789

DOI: https://dx.doi.org/10.18203/2320-1770.ijrcog20220553

Original Research Article

Acanthosis nigricans in adolescents with polycystic ovary syndrome

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Received: 01 February 2022
Revised: 16 February 2022
Accepted: 17 February 2022

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ABSTRACT

Background: In this study we compared the clinical and biochemical variables of adolescent females with PCOS (polycystic ovarian syndrome) and its association with or without acanthosis nigricans (AN).
Methods: Adolescent girls (14-19 years) with oligomenorrhoea and hyperandrogenism were studied. Clinical parameters like blood pressure (BP), body mass index (BMI), abdominal circumference (AC), presence or absence of acne and AN and hirsutism score were noted. Biochemical tests included serum total testosterone (TT), sex hormone binding globulin (SHBG) levels and free androgen index (FAI). Postprandial plasma insulin (PPI) and glucose (PPG) levels were measured to assess insulin resistance and glucose tolerance respectively.
Results: Significant differences were observed in BMI, AC, DBP, TT and FAI between the two groups. The difference in the prevalence rate of abnormal glucose tolerance and insulin resistance between the two groups was insignificant. Logistic regression modelling with AN as the response variable of interest and BMI, AC, SBP, DBP, testosterone level, PP insulin and PPG levels as its predictors yields BMI, testosterone, PP sugar, PPI, SHBG as main determinants. The model signifies positive impacts of BMI and testosterone level, while negative influence of PP sugar, PPI level and SHBG levels on AN. This analysis was an evidence for a strong relation between BMI and AN.
Conclusions: AN in adolescent girl with PCOS is another clinical marker of obesity but not an indicator of underlying insulin resistance or glucose intolerance. Further studies are needed to detect how many of them ultimately develop insulin resistance or diabetes in future.

Keywords: Acanthosis nigricans, Adolescent, Body mass index, Modified Ferriman-Gallwey, Polycystic ovary syndrome, Risk factors

INTRODUCTION

AN is an easily visible, cosmetic paraneoplastic dermatologic condition characterized by brownish-black, velvety thickening, papillomatous, hyperkeratotic plaques. It is typically observed on the intertriginous areas of the skin, commonly in pigmented population.[1,2] AN was first reported in the International atlas for rare skin diseases about 130 years ago and the term was proposed by Paul Gerson Unna, Hamberg, Germany.[3] AN is a manifestation of several underlying metabolic defect like insulin resistance (IR), obesity, PCOS and hyperandrogenism (HA).[3-6] Studies show that between 5 to 33% of patients with PCOS have AN.[6,7] AN is also rarely associated with other pathological conditions like insulinoma and malignant diseases, especially adenocarcinoma of the stomach.[8]

AN is more common in obese PCOS patients.[9] The histological characteristics of AN are mainly hyperkeratosis and papillomatosis changes of the skin. As early as in 1976, Kahn et al reported an association of HA and insulin resistance with AN.[10] Since then AN is often detected in HA and diabetes mellitus patients.[11-13]

There are scanty studies which have reported the clinical, hormonal and metabolic parameters in PCOS with AN. In the present paper we studied various clinical and biochemical variables (including hormonal and metabolic parameters) of adolescent girls having PCOS with and without AN.

METHODS

The present comparative cross-sectional observational research was conducted at the KPC medical college, Kolkata, India, which was a tertiary care hospital, for a duration of 24 months (April 2017 to March 2019). Clearance was obtained from the human ethical committee of the institute and all females candidates were duly informed about the investigation procedure.

The data were collected at the time of encounter from 59 adolescence girls between the age of 14-19 years, with PCOS. A complete demographic data including their age, socio-economic status, habitat along with family history of DM in first degree relative was noted. As per the Rotterdam 2003 criteria, these girls were subjected to detailed clinical and biochemical evaluations for the diagnosis of PCOS, with at least two of the following characteristics: chronic anovulation or oligo-ovulation; hyperandrogenism (clinical and/or biochemical) and (polycystic ovaries appearance under transabdominal ultrasound.[14] As per the Rotterdam criteria, secondary causes of hyperandrogenism were excluded by relevant clinical and biochemical laboratory tests. Women with reported history of previously diagnosed diabetes, steroid or oral contraceptives consumption in the prior to 3 months of the study were also eliminated from the study.

The feature oligo-ovulation and/or anovulation was indicated by oligomenorrhea (intermenstrual intervals of ≥35 days) and amenorrhea (intervals >3 months). The presence of acne, hirsutism (modified Ferriman-Gallwey mFG score of ≥6) or androgenic alopecia were taken as clinical criterion of hyperandrogenism. Total testosterone level more than 0.82 ng/ml (normal laboratory range 0.06-0.82 ng/ml) or calculated free androgen index more than 2.06 was considered as biochemical hyperandrogenism.[14] The detection of not less than one ovary 10 cc or more in volume during transabdominal ultrasound was considered as polycystic ovary.

A questionnaire-based survey was conducted to document the personal and family history of diabetes, obesity, hypertension and/or ischemic heart disease along with the length of menstrual cycles. Symptoms of hyperandrogenism (hirsutism, persistent acne and/or oily skin, and androgenic alopecia), existence of acanthosis and insulin resistance were noted during the physical examination. The anthropometric measurements encompassed abdominal and hip circumference (cm) using measuring tape. BMI (kg/m^2) was calculated from height (±0.5 cm) and weight (±0.5 kg) measurements. Waist and hip ratio (WHR) was measured using measuring tape. Weight was measured on a digital platform weighing scale. Both SBP and DBP were measured using a mercury sphygmomanometer (mm of Hg) as per standard procedure.

Fasting plasma glucose (FG) (expressed in mg%) and FI levels (in mcu/ml) were measured after overnight fasting (~12 hour) for all candidates. Glucose oxidase peroxidase method (Roche Diagnostics Gmbh, Mannheim, Germany) was used to measure the plasma glucose. Glucose-insulin ratio (G:I) along with homeostasis model assessment (HOMA) was calculated from FG and FI level, using the formula,

$$\text{HOMA}=\frac{FG\ (mg\%)\times FI(mcu/ml)}{405}.$$

Electrochemiluminescence immunoassay, Roche Lot. No. 181371-01 (Roche Diagnostics Gmbh, Mannheim, Germany) was used to measure serum TT (in ng/ml). SHBG level was measured (nmol/l) on the second or third day of progesterone induced withdrawal bleeding. FAI was measured using the formula,

$$\text{FAI}=\frac{TT\times 100\times 3.47}{SHBG}.$$

Trans-abdominal ultrasound was performed to study the morphology and volume of the ovary. Ovarian volume measurements were made as per standard protocol by measuring three perpendicular dimensions (volume for a prolate ellipsoid=0.5×length×width×thickness of ovary). The presence of total number of follicles in each ovary was calculated both in cross-sections (longitudinal and antero-posterior) of the ovaries. Secondary causes of androgen excess like hypothyroidism, Cushing's syndrome, 21-hydroxylase deficiency, androgen-secreting tumors and hyperprolactinemia were eliminated by suitable clinical and/or biochemical tests.

Statistical analysis

Presuming a confidence limit (CL) of 95%, the calculated confidence interval (CI) was 10%. All variables were evaluated for normality pre-test (using KS) for the comparison of all clinical and biochemical parameters detected. The continuous variables were compared with t test and Chi square test with Yates correction as and when needed. Logistic regression was done, (pseudo R^2=0.3447), (Prob>Chi^2=0.0000) predicting a good fit model ($p<0.05$) was done to assess the degree of causality.

RESULTS

In the present study, significant differences were found in the parameters of BMI (p=0.0001); AC (p=0.0001); WHR (p=0.0001); SBP (p=0.03); DBP (p= 0.01); TT (p=0.002); FAI (p=0.002) between the two groups (Table 1 and 2).

Table 1: Clinical parameters in the two groups of AN present and absent in adolescent girls (Data are mean (standard deviation) or number %).

Variables	AN absent (n=19)	AN present (n=40)	P value
	N (%)	N (%)	
BMI (kg/m^2)	22.8 (2.4)	28.1(4.4)	0.0001
AC (cm)	72.3 (5.3)	85.6 (8.8)	0.0001
WHR (cm)	0.76 (0.03)	0.84 (0.05)	0.0001
SBP (mm of Hg)	117.7 (11.03)	125.0 (14.5)	0.03
DBP (mm of Hg)	72.9 (7.5)	78.3 (8.1)	0.01

BMI, body mass index; AC, abdominal circumference; WHR, waist-hip ratio; SBP, systolic blood pressure; DBP, diastolic blood pressure.

Table 2: Hormonal and metabolic parameters of AN present and absent in adolescent girls.

Variables	AN absent (n=19)	AN present (n=40)	P value
TT (ng/ml)	0.39 (0.13)	0.62 (0.43)	0.002
SHBG (nmol/l)	35.8 (28.1)	31.8 (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 mg/ml (%)	4 (21.0)	8 (20.0)	0.92

TT, total testosterone; SHBG, sex hormone binding globulin; FAI, free adrogen index; PPI, post prandial insulin; PPG, post prandial glucose.

Table 3: Demographic characteristics of patients received for study of AN.

S. No.	Demographic characteristics	Frequency		Percentage (%)	
		AN absent (n=19)	AN present (n=40)	AN absent (n=19)	AN present (n=40)
1.	Age of study patients				
	14	2	5	11	13
	15	2	2	11	5
	16	4	9	21	23
	17	3	12	16	30
	18	4	7	21	18
	19	4	7	21	13
2.	Socio-economic status				
	Low income	4	11	21	28
	Medium income	7	14	37	35
	High income	8	15	42	38
3.	Habitat				
	Rural	14	7	74	18
	Urban	5	35	26	88
4.	Family history of DM in first degree relative				
	PCOS with AN	12	29	63	73
	PCOS without AN	7	11	37	28

There was no significant difference in the prevalence rate of abnormal glucose tolerance (p=0.92) and insulin resistance between the two groups (p=0.09). Logistic regression modelling with AN as the response variable of interest and BMI, AC, SBP, DBP, testosterone level, PP insulin and PP glucose levels as its predictors yields BMI, testosterone, PP sugar, PP insulin, SHBG as the statistically main determinants. The model signified positive impacts of BMI, testosterone level and negative influence of PP sugar, PP insulin level and SHBG levels on AN. The overall model was statistically significant with a p value of less than 0.000. This analysis was also evidence for a strong relation between BMI and AN.

Demographic data revealed that both higher (39%) and middle (36%) income group had higher frequency of AN

as compared to low (25%) income group (Table 3). Also urban (64%) adolescents showed higher frequency of AN-PCOS association as compared to rural population. Similarly, a family history of DM was observed in the first degree relatives was present in 69% adolescent patients with AN and in 31% of the patients without AN.

DISCUSSION

PCOS is one of the most common gynecological endocrinal disorders of today's time affecting about 4 to 8% reproductive-aged women across the world and have been suspected to be associated with AN.[14,15] However adequate studies to strongly showed such correlation have not been performed or discussed. In the present study, 68% of adolescent girls with PCOS were observed to have AN in contrast to 33% reported in adult patients with PCOS by Khan et al.[14]

As the sedentary lifestyle was rising, obesity in adolescence was increasingly becoming an increasing health priority as it often tracked into adulthood, resulting in enormous medical and social problems.[3] Our studies showed significantly higher mean BMI (28.1 kg/m^2) in AN present group in comparison to AN absent group (22.8 kg/m^2). Other studies also showed that obese patients with more than 30 kg/m^2 BMI were more prone to develop AN.[16] The study further showed that among obese PCOS patients, 58% with high BMI value (of more than 30 kg/m^2) had AN as compared to 19% patients who did not have AN.[16] Similar to our study, strong correlation between AN and obesity had recently been reported in children as well.[17] Similar to our study, low SHBG level was observed to be associated with AN by other researchers as well.[18] WHR which indicated central obesity was high in both AN absent and present groups. However it was significantly higher in AN positive group. Similar observations in adult females were observed by other researchers as well.[16] A detailed study comparing obese and nonobese PCOS showed that the percentage of AN in obese PCOS is significantly higher (91%) as compared to nonobese PCOS (36%).[19] Obesity had been shown as an independent predictor of conversion to impaired glucose tolerance or type 2 DM in patients with PCOS.[19]

Lifestyle enhancements and work patten in recent times have resulted in less physical activities, increased consumption of sugary and fatty food and alcohol in adolescents resulting in increased obesity and associated disorders.[20] Weight loss, lifestyle modifications in combination with oral contraceptive pill and insulin santitizers like metformin have been considered as first-line treatment.[21]

Unlike our observation (69%) Shivaprakash et al observed a family history of DM in 100% of the first degree relatives of all patients.[16] AN in adolescent girl with PCOS was another clinical marker of obesity. This study showed that presence of AN was not an indicator of underlying insulin resistance or glucose intolerance.

Limitations

The major limitation of the study was that the data included in the manuscript encompasses on one selected private hospital in Eastern India which attracted more middle and higher income patients from urban setting. Thus, the demographic data may be biased. More similar studies under different demographic settings needed to be done taking into account possible variabilities.

CONCLUSION

In conclusion, this study reveals that the presence of AN in adolescent girls with PCOS, is an important indicator of central obesity and consequent metabolic disorders. In a low resource clinical setting, presence of AN in patients, should direct the clinician to suspect underlying metabolic and hormonal problems in PCOS so that we can detect early and adapt suitable precautionary steps for future metabolic complications in adolescents. This study shows that presence of AN is not an indicator of underlying insulin resistance or glucose intolerance. Prospective follow up studies are needed to detect how many of them ultimately develop insulin resistance or diabetes in future. Detection of AN may thus be taken to encourage lifestyle changes in the patients.

ACKNOWLEDGMENTS

The authors wish to thank S. M. Bhattacharjee for helping out with the statistical analysis and inferences.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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Cite this article as: Khan B, Basu R. Acanthosis nigricans in adolescents with polycystic ovary syndrome. Int J Reprod Contracept Obstet Gynecol 2022;11:765-9.