INTRODUCTION

Acanthosis Nigricans (AN) typically affects armpits, groin and neck, is a readily recognizable dermatological manifestation characterized by velvety, papillomatous, brownish-black plaques1. Hyperkeratosis and papillomatosis are histological characteristics of AN. It is a manifestation of an underlying metabolic defect like insulin resistance (IR) or obesity (BMI) 1, 2. Kahn et al noted AN is a frequent occurrence in hyperandrogenism and IR3.

Polycystic ovary syndrome (PCOS) is a common hormonal condition in women of all ages starting from adolescent period with reproductive, metabolic, and psychological sequelae4. Affecting 8 to 13% of all women of reproductive age and 21% in high risk groups, polycystic ovary syndrome (PCOS) is the most prevalent reproductive disorder causing significant health consequences for women impairing quality of life and increasing morbidity5. Under diagnosis or delayed diagnosis frequently happens in women with PCOS. The complexity of the disorder, and the impact on quality of life, requires timely diagnosis, screening for complications and management strategies4.

PCOS according to the Rotterdam 2003 criteria is a condition of reproductive age group females with at least two of the following features: 1) oligo-ovulation or anovulation, 2) clinical and/or biochemical hyperandrogegism, and 3) ultrasound appearance of polycystic ovaries6. Ovulatory dysfunction is assessed after 1-year post-menarche. The Rotterdam Criteria are now internationally accepted, with different phenotypes recognized with varying clinical presentations of PCOS cases like oligo-anovulation (OA), hyperandrogenism (HA), polycystic ovary morphology (PCOM) and varied risk profiles. In Rotterdam revised criteria of 2018 phenotypes of PCOS are classified as A (OA+HA+PCOM), B (OA+HA), C (HA+PCOM), D (OA+PCOM) 7.

PCOS in adolescent girls is a Common occurence8. These girls are more prone for development of metabolic syndrome in their future life with unopposed action of excessive estrogen, androgen and insulin.

AN might be present in patients with polycystic ovary syndrome (PCOS) due to their association with insultin resistance (IR), hyperinsulinemia, and hyperandrogenism (HA)8. But AN is not considered in the diagnostic criteria of PCOS3. Hyperandrogenism in PCOS may not always have unwanted hair growth 9. AN is more common in obese PCOS patients10. Presence of AN appears to be more of a sign of IR. Other pathological conditions rarely associated with AN are insult coma and malignant diseases, especially adenocarcinoma of stomach11.

Need for the study

There are very few studies which have reported the clinical, hormonal and metabolic parameters in adolescent girls of PCOS with AN. In the present study various clinical and biochemical parameters (hormonal and metabolic) of Indian adolescent girls having PCOS with and without AN are compared with an aim to know the significance of the presence of AN.

MATERIALS AND METHODS

This comparative analytical study was done in College of Medicine& JNM Hospital,WBUHS, Kalyani,Nadia and Sambhunath Pandit Hospital. Both are tertiary care hospital with a study period from November 2020 to April 2021. All studied girls and their at least one accompanied parent agreed to the clinical evaluation and investigation protocol.

59 adolescents' girls (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. These girls had detailed clinical and hormones and USG evaluations for the diagnosis of PCOS according to the Rotterdam 2003 criteria with at least two of the following features: 1) oligo-ovulation or anovulation, 2) clinical and/or biochemical hyperandrogegism, and 3) ultrasound appearance of polycystic ovaries.

Secondary causes of hyperandrogegism, as per Rotterdam criteria, were excluded by appropriate clinical and laboratory tests.

Exclusion criteria

a) Adolescent girls within 1 year of menarche.

b) Patients with history of steroid or oral contraceptive drug intake in the preceding 3 months

c) Diabetes Melitus-type 1 & 2.

Oligo-ovulation and /or anovulation was characterised by oligomenorrhoea (intermenstural intervals of >35 days) and amenorrhea (intervals>3 months). Clinical hyperandrogenism was defined as pressnce of alopeecia, or hirsutism (modified Ferriman - Gallwey score of >=6) and /or acne. Biochemical hyperandrogenism was considered if total testosterone level was more than 0.82ng/ml (normal laboratory range 0.06-0.82 ng/ml) or calculated free androgen index was more than 2.06. Polycystic ovary on ultrasound (transabdominal) was defined as the presence of at least one ovary 10cc or more in volume.

A standard questionnaire was used to document length of menstrual cycles, personal, medical and family history of diabetes, hypertension, obesity. Signs of androgen excess (hirsutism, acne, and alopecia), were noted in the physical examination. Alopecia was assessed using the Ludwig visual score. Acanthosis is counted only for its presence in the neck, not in terms of severity. Anthropomrtric measurement included abdominal circumference in centimetre as per internationally accepted guidelines (using a 1 cm wide measuring tape). Body mass index (BMI) (Kg /m2) was calculated in each case from height and weight measurement. Blood pressure was measured using a mercury sphygmomanometer in semi recumbent posture in dominant arm (mostly right arm). Both systolic (SBP) and diastolic (DBP) BP was measured in mm of Hg.

Trans-abdominal ultrasound was performed to study the morphology of ovaries in all subjects (as transvaginal ultrasound is not permitted for unmarried girls in India). Ovarian volume were measured by three perpendicular dimensions (volume of a prolate ellipsoid= 0.523 x length x thickness x height). Volume of more than 10cc taken for study groups.

Post prandial plusma glucose (PPG) and post prandial plusma insulin (PPI) levels were estimated 2 hours after 75 grams of glucose intake for all subjects. Plasma glucose was measured by Glucose oxideseperoxidase method (Roche Diagnostics Gmbh,Mannheim, Germany) and was expressed in mg% and plasma insulin level in mcu/ml. PPI more than 150 mcu / ml were considered as indicative of IR., PPG more than 140 mg / dl was considered as indicative of glucose intolerance.

Serum total testosterone level (TT) was measured by using Electrochemiluminescence immunoassay, 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 calculated by method (TT X 100 X 3.47) / SHBG.

Other causes of secondary hyperandrogegism like 21-hydroxylase deficiency, Cushing's syndrome, hyperthyroidism, hyperprolactinoma and androgen secreting tumours were excluded by appropriate clinical and / or laboratory tests.

RESULTS

Total 59 cases fulfilled all study criterias in the said period of study.The studied adolescents were divided into two groups.

Group A – Without acanthosis nigricans - 19 cases (32.2%).

Group B –With acanthosis nigricans -40 cases (67.7%).

Table 1: Clinical parameters in the two groups.

Datas are plotted as mean (Standard deviation)

Table 1

Parameters	AN absent (n=19)	AN present (n=40)	p value
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**

Table 1			
WHR	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**

There were significant differences in mean BMI (p=0.0001), AC (0.0001), WHR (0.0001), SBP (0.03), DBP (0.01) values between the two groups.

Table 2 : Hormonal and metabolic parameters
Datas are plotted as mean (Standard deviation) / or number (%)

Parameters	**AN absent(n=19)**	**AN present(n=40)**	**P value**
Testosterone(ng/ml)	**0.39(0.13)**	**0.62(0.43)**	**0.002**
SHBG	**35.8(28.1)**	**31.8(25.4)**	**0.60**
FAI	**4.91(2.2)**	**10.1(8.2)**	**0.002**
Number of cases withPPI>=150mcu/ml (%)	**3 (15.8)**	**15(37.5)**	**0.09**
Number of cases with PPG>=140mgm (%)	**4 (21.0)**	**8(20.0)**	**0.92**

Table 2. shows the hormonal and metabolic parameters of the two groups.Testosterone (p=0.002) and FAI (p=0.002) values showed significant difference whereas SHBG (p=0.60), PPI (p=0.09) and PPG (p=0.92) showed no significant differences.

In Statistical analysis, Logistic regression modeling is used and AN as the response variable of interest. All the studied parameters as predictors such as BMI, testosterone, PP sugar, PP insulin, SHBG as the statistically main determinants. By Analysis it was found that there were positive impacts of BMI, testosterone level on AN. PP insulin, PP sugar, SHBG levels have negative influence on AN.

DISCUSSION

We have found highly significant association of increased BMI (p=0.0001) with AN in adolescent girls with PCOS. According to Cassar S et al BMI exacerbated insulin resistance by 15% in women with PCOS and had a greater impact on insulin resistance in PCOS than in controls[12].

Present study has demonstrated higher mean postprandial insulin values although not statistically significant (p=0.09) among subjects with AN. Study done by Menon et al have reported statistically significant insulin resistance only in obese patients having AN[13]. PCOS is associated with impaired glucose tolerance (IGT) in up to 30% and type 2 diabetes in up to 10% of women with PCOS as observed in the study of Legro RS et al[14].

As PPI level is not significantly high (p=0.09) in the AN group of our study, we can infer AN is not always an indicator of insulin resistance. In a study on PCOS patients, Panidis D et al also mentioned that insulin resistance is not the only factor which leads to development of AN[15].

Central obesity plays an important role for

association of AN as revealed in our study result which showed very, very significant p value (p=0.0001) of abdominal circumference in PCOS adolescent girls having AN. Obesity is an important clinical parameter associated with AN- is also found in the study of Araujo L. M. et al[16]. Maitra S.K et al reported that AN is a common finding in obesity syndrome[17]. We have noted statistically very significant higher values of WHR (p=0.0001) in adolescent PCOS girls having AN. To study the Metabolic risk assessment of Indian women with polycystic ovarian syndrome Tripathy P et al found significant predictors for metabolic syndrome within the PCOS cohort are waist circumference >80cm, hypertension (p< 0.001)[18].

In current study both DBP (p=0.01) and SBP (p=0.03) are significantly higher in AN group of PCOS girls. A case–control study of 1,550 women with PCOS by Pinola P reported both systolic and diastolic blood pressure is higher compared with controls, independent of BMI[19].

Biochemical hyperandrogenism as depicted by testosterone level and FAI values are significantly higher (p=0.002) in AN group of our study. Tripathy P et al grouped PCOS women into 4 phenotype divisions as per Rotterdam 2018 criteria. They have noted highest level of androgen in phenotype A (OA+HA+PCOM) which is the commonest group (55.8%), and prevalence of metabolic syndrome is more common in phenotype A and B (OA+HA)[18].

The clinical Importance of AN has been claimed to be due to its association with various hormonal and metabolic abnormalities such as obesity, diabetes, PCOS, dyslipidamia, thyroid dysfunction etc. In a systemic review meta-analysis done by Lim SS et al considered the implications of obesity on reproductive, metabolic, and psychosocial health of PCOS women[20]. To check obesity and its ill effect, lifestyle interventions, including incorporating a healthy diet, increasing physical activity, and implementing behavioral strategies, are the first-line treatment for PCOS[21].

CONCLUSION

Present study signifies that AN in adolescent girl with PCOS is another clinical marker of central obesity. This study shows presence of AN is not always an indicator of glucose intolerance, rather obesity and metabolic syndrome are frequently associated with AN in PCOS adolescent girls. While dealing with PCOS and AN at the tender age of adolescent period, Clinicians should focus on lifestyle adjustments by weight management and physical exercise as the first-line intervention to improve reproductive, metabolic, cardiovascular, and psychosocial outcomes.

Prospective follow up studies are needed to detect how many of them ultimately develop Insulin resistance or diabetes in future. Current study points both the clinician and the public's attention to the importance of a high -quality lifestyle to control obesity and so as to reduce chances of developing metabolic syndrome in adolescent girls with PCOS and AN.

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