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Case Report

Hyperandrogenism-insulin resistance-acanthosis nigricans syndrome with PCOS and Hashimoto's thyroiditis: case report

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ABSTRACT

Female hyperandrogenism is a frequent motive of consultation. It is revealed by hirsutism, acne or seborrhea, and disorders in menstruation cycle combined or not with virilisation signs. Several etiologies are incriminated but the hyperandrogenism-insulin resistance-acanthosis nigricans syndrome is rare. A 21-year female, having had a three-year-old secondary amenorrhea, known case of hypothyroidism since 4 years on medication. The exam revealed a patient, hypertensive with blood pressure at 170/110 mmHg with a Body Mass Index (BMI) at 40.08 (Obese Class-3, as per WHO 2004) and a waist measurement of 106cm, a severe hirsutism assessed to be 27 according to Ferriman and Gallwey scale, acanthosis nigricans behind the neck and elbows. The assessment carried out revealed testosteronemia at 1.07 ng/mL, which is more than twice the upper normal of the laboratory. Imaging studies revealed enlarged right adrenal gland, hepatomegaly with fatty infiltration of grade-1 also bilateral polycystic ovaries. The retained diagnosis is HAIR-AN syndrome with polycystic ovaries, hypertension, type-II diabetes mellitus, hypothyroidism since last 4-years and dyslipidemia and was provided with metformin 500 mg thrice daily, spironolactone 25 mg twice daily, atorvastatin 20 mg once daily, telmisartan 20 mg once daily with continuation of eltroxin 50 Mcg for hypothyroidism. To our knowledge this is the first case report of HAIR-AN syndrome in 21 year old female associated with Hashimoto's thyroiditis, dyslipidaemia, hypertension and type-2-diabetes and this case also highlights about early diagnosis and management of HAIR-AN Syndrome with PCOS and Hashimoto's thyroiditis which could help prevent long-term sequalae such as cardiovascular disease and endometrial cancer and with the advent of knowledge and availability of health resources we can prevent long-term adverse effects (threefold) on health of women. This woman should be observed for these ailments in later life.

Keywords: HAIR-AN syndrome, Polycystic ovary syndrome, Insulin resistance, Type-II diabetes mellitus, Hashimoto's thyroiditis, Dyslipidaemia

INTRODUCTION

Female hyperandrogenism is frequent motive of consultation in endocrinology, in dermatology, or in gynecology. It is revealed by hirsutism, acne or seborrhea, and disorders in menstruation cycle combined or not to virisilisation signs that are androgenic alopecia, harsh voice, hyperhidrosis, clitoromegaly, and/or big lips. Hirsutism being the most common symptom, is found in approximately 5% of women in procreation age.[1] The etiologies of the hyperandrogenism are dominated by polymicrocystic ovaries (71-86%); congenital hyperplasia of adrenal (3-10%); the tumoral ovarian and adrenalian causes (0.3%); and idiopathic hirsutism (10%).[2,3] The hyperandrogenism-insulin resistance-acanthosis nigricans syndrome (HAIR-AN syndrome) is also incriminated.[4,5]

We here describe a typical case of a 21 year old female presenting with HAIR-AN syndrome with PCOS associated with Hashimoto's thyroiditis since 4 years on medication.

To our knowledge this is the first case report of the HAIR-AN syndrome with PCOS in 21 year old female associated with Hashimoto's thyroiditis, dyslipidaemia, hypertension and type-2-diabetes.

CASE REPORT

A 21-year-old female came to our out-patient department complaining of having had her first menstruation at the age of 18 years, with history of hirsutism with secondary amenorrhea, with no abdominal pain and no pelvic heaviness. She is a known case of hypothyroidism since 4 years and is on medication (eltroxin 50 Mcg) for the same. The exam revealed patient in good general condition, Blood pressure at 170/110 mmHg with a Body Mass Index (BMI) at 40.08 (Obese Class-3, as per WHO 2004) and a waist measurement of 106 cm, a severe hirsutism assessed to be 27 according to Ferriman and Gallwey scale (Figure 1), and an acanthosis nigricans behind the neck (Figure 2, 3), in the elbows (Figure 4), obese, breast development stage-IV, pubic hair stage-IV, external genitalia healthy, while there is no galactorrhea, or melanodermia.

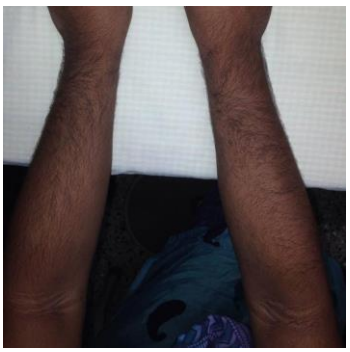

Figure 1: Showing severe hirsutism and also note acanthosis nigricans at both the elbows.

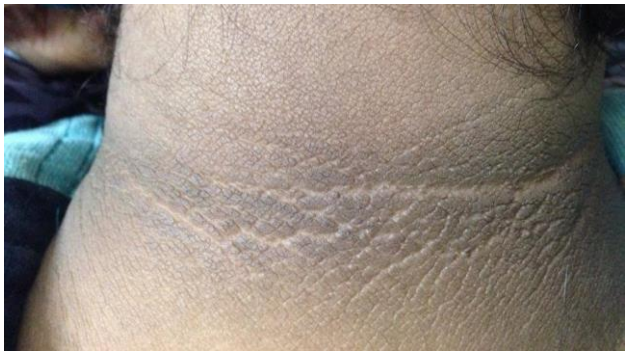

Figure 2: Showing acanthosis nigricans on the neck.

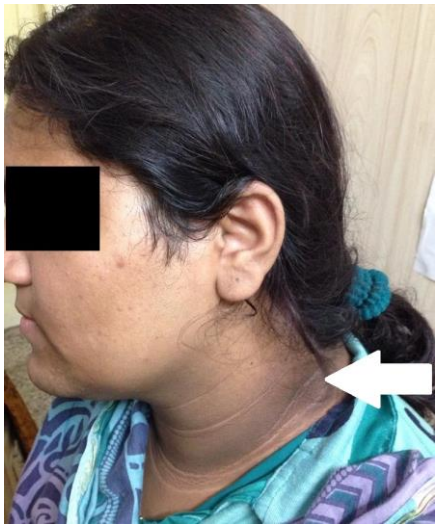

Figure 3: Arrow showing gross acanthosis nigricans at the neck.

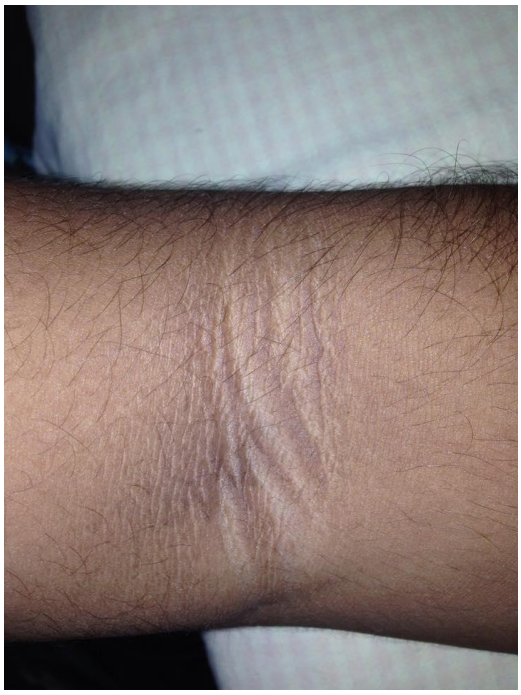

Figure 4: Showing acanthosis nigricans at right elbow.

The assessment carried out revealed blood sugar levels before treatment were fasting blood sugar at 107 mg/dl, post-prandial blood sugar at 190 mg/dl, Oral Glucose Tolerance Test (OGTT) with 75 gm glucose suggestive of type-2-diabetes with hyperinsulinaemia, after treatment Fasting Blood Sugar at 97 mg/dl, Post-prandial Blood Sugar at 130 mg/dl; testosteronemia [Chemiluminescence (CLIA)] at 1.07 ng/mL (0.67 for ovulating) which is more than twice the upper normal of the laboratory, the 17 alpha hydroxy progesterone at 1.3 ng/mL (0.2-1.3 follicular phase, 1.0-4.5 luteal phase, 0.2-0.9 postmenopausal), serum DHEA-S[Chemiluminescence (CLIA) method] at 500 µg/dl (35-430 µg/dl), the serum cortisol (Each) 8:00 AM at 10.52 µg/dl (7-9 AM: 5.0-25.0 µg/dl) 5:00 PM at 7.46 µg/dl (3-5 PM: 2.5-12.5 µg/dl), the prolactinemia at 8.87 ng/mL (3.6-18.9 ng/ml), the thyroid profile T3 at 1.16 ng/mL (0.60-2.00 ng/mL), T4 at 13.8 µg/dl (4.50-12.50 µg/dl), TSH at 3.92 µIU/mL (0.30-5.00 µIU/mL), the glycated hemoglobin (HbA1C) at 7.4%; whereas the lipidic assessment indicated serum cholesterol in normal range at 152 mg/dl, serum triglycerides at borderline 216 mg/dl, low high density lipoprotein at 40 mg/dl, low density lipoprotein at normal 69 mg/dl, high very low density lipoprotein 43 mg/dl; the karyotype was normal (46XX). Further advised ultrasonography of abdomen & pelvis which revealed fatty infiltration of liver Grade-I with Hepatomegaly, enlarged Right adrenal gland measuring 3.1 x 2.9 cm (Figure 5), bilateral polycystic ovaries right 3.7 x 2.5 cm and left 3.8 x 2.4 cm bilateral multiple peripheral follicles noted with e/o multiple interphases (Figure 6). Her current medications include for control tablet metformin (Glyciphage Sr) 500 mg thrice daily 15 minutes before food for type-II diabetes mellitus; tablet spironolactone (Aldactone) 25 mg twice daily for hyperaldosteronism; tablet cyproterone 2 mg with ethinylestradiol (Diane 35) once daily is the principle drug; tablet atorvastatin 20 mg once daily for dyslipidaemia, tablet telmisartan (Telma 20) 20 mg once daily for hypertension, she is also on Eltroxin 50 Mcg for hypothyroidism. Advised change of lifestyle, weight loss, exercise and diabetic diet.

After treatment of about one month duration her fasting blood sugar at 97 mg/dl, post-prandial blood sugar at 130 mg/dl and her blood pressure recorded at 140/90 mmHg.

Investigations showed

Complete blood picture:

Hemoglobin: 13.3 gms% (11.5-16.5 gms%), PCV: 40.8 vol% (36-47 vol%), RBC count: 4 millions/cumms (4.5-5.5 millions/cumms), total WBC count: 12000 cells/cumms (4000-11000 cells/cumms), neutrophils: 70%, lymphocytes: 25%, monocytes: 3%, eosinophils: 2%, basophils: 0%, platelets: adequate, no abnormal cells noted, red cell morphology showed normocytic, normochromic cells, MCV: 102 fl, MCH: 32.2 pg, MCHC: 32.5 g/dl, RDW-CV: 16.3%.

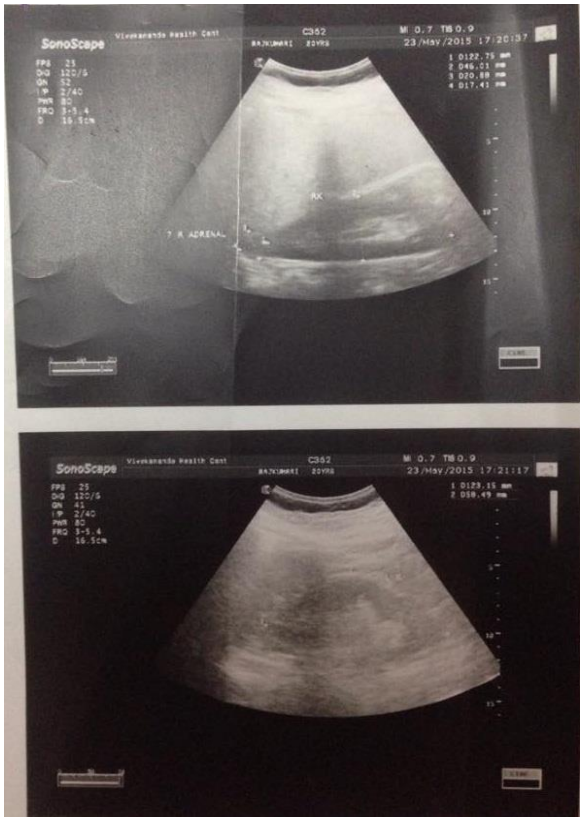

Figure 5: Ultrasonography showing enlarged Right adrenal gland measuring 3.1 x 2.9 cm.

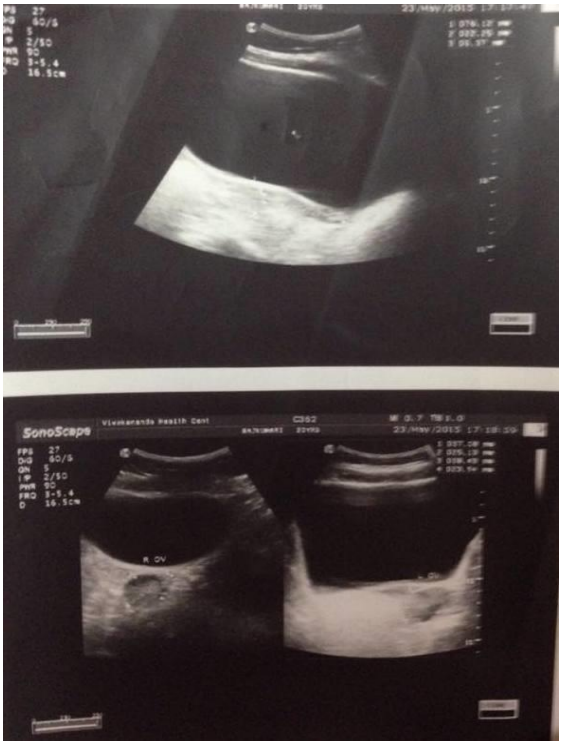

Figure 6: Ultrasonography showing bilateral polycystic ovaries, Right measuring: 3.7 x 2.5 cm and Left measuring: 3.8 x 2.4 cm bilateral multiple peripheral follicles noted with e/o multiple interphases.

Urine analysis:

Colour: yellow, Appearance: clear, Reaction: acidic, proteins: present (++), Sugar: nil, Pus cells: 20-30/HPF, Red cells: nil, Epithelial cells: 5-8/HPF, Crystals: nil, Casts: nil.

Other assessments carried out revealed:

The blood sugar levels before treatment were fasting blood sugar at 107 mg/dl, post-prandial blood sugar at 190 mg/dl, after treatment fasting blood sugar at 97 mg/dl, post-prandial blood sugar at 130 mg/dl and after treatment of about one month duration her fasting blood sugar at 97 mg/dl, post-prandial blood sugar at 130 mg/dl; testosteronemia [Chemiluminescence(CLIA)] at 1.07 ng/mL (0.67 for ovulating) which is more than twice the upper normal of the laboratory; the 17 alpha hydroxy progesterone at 1.3 ng/mL (0.2-1.3 follicular phase, 1.0-4.5 luteal phase, 0.2-0.9 postmenopausal); the serum DHEA-S[Chemiluminescence (CLIA) Method] at 500 µg/dl (35-430 µg/dl); the serum cortisol (Each) 8:00 AM at 10.52 µg/dl (7-9 AM: 5.0-25.0 µg/dl) 5:00 PM at 7.46 µg/dl (3-5 PM: 2.5-12.5 µg/dl); the prolactinemia at 8.87 ng/mL [3.6-18.9 ng/ml]; the thyroid profile T3 at 1.16 ng/mL (0.60-2.00 ng/mL), T4 at 13.8 µg/dl (4.50-12.50 µg/dl), TSH at 3.92 µIU/mL (0.30-5.00 µIU/mL); the glycated hemoglobin (HbA1C) at 7.4%; whereas the lipidic assessment indicated serum cholesterol in normal range at 152 mg/dl, serum triglycerides at borderline 216 mg/dl, low high density lipoprotein at 40 mg/dl, low density lipoprotein at normal 69 mg/dl, high very low density lipoprotein 43 mg/dl; the karyotype was normal (46XX).

Further advised ultrasonography of abdomen & pelvis which revealed fatty infiltration of liver Grade-I with Hepatomegaly; enlarged Right adrenal gland measuring 3.1 x 2.9 cm (Figure 5); bilateral polycystic ovaries right: 3.7 x 2.5 cms and Left : 3.8 x 2.4 cm bilateral multiple peripheral follicles noted with e/o multiple interphases (Figure 6).

Multi slice computed tomography scan abdomen (Oral & IV contrast) showed fatty infiltration of liver.

Abbreviations: HAIR-AN: Hyperandrogenism-insulin resistance-acanthosis nigricans syndrome, PCOS: Polycystic ovarian syndrome.

DISCUSSION

HAIR-AN syndrome

HAIR-AN syndrome is a subphenotype of Polycystic Ovary Syndrome (PCOS)[6] and is characterized by hyperandrogenism, insulin resistance, and acanthosis nigricans. It is one of the most common causes of menstrual disorders, hyperandrogenic symptoms, and insulin resistance among young women. The annual incidence worldwide is estimated at around 5% of adolescent girls. Approximately 5-10% of females with hyperandrogenism, and up of 40% of adolescent patients with irregular periods, may have HAIR-AN syndrome. Symptoms occur from adolescence, but diagnosis is often delayed until adulthood. Hyperandrogenism manifests as acne, slowly progressive hirsutism (Ferriman and Gallwey score of 8 or higher), and sometimes virilization including temporal balding, voice deepening, and clitoromegaly. Many patients have menstrual dysfunction, infrequent or absent ovulation, and polycystic ovaries. Insulin resistance may lead to obesity, numerous skin tags (achrochordons), and acanthosis nigricans. Acanthosis nigricans is characterized by the presence of velvety, verrucous, hyperpigmented skin, found most frequently on the back of the neck, axillae, and in other skin fold areas. HAIR-AN syndrome can cause acute psychological distress with morbidity, depression (24% of cases), and self-esteem problems. Due to insulin resistance, obesity, and menstrual dysfunction, patients have a significantly increased risk of type 2 diabetes mellitus and infertility. Etiology is still unknown but the syndrome may be associated with mutations of the tyrosine kinase domain of the insulin receptor gene (INSR). Diagnosis is based on the presence of the triad: hyperandrogenism, insulin resistance, and acanthosis nigricans. However, women with insulin resistance may not present with acanthosis nigricans. Fasting insulin levels, fasting glucose-to-insulin ratio, glucose challenge testing, and the euglycemic hyperinsulinemic clamp tests may be useful to confirm the diagnosis, but no solid consensus has been established so far. Differential diagnoses include late-onset congenital adrenal hyperplasia, Cushing's syndrome, and ovarian and adrenal hormone producing tumors.

In this case we report you all the features hyperandrogenism, insulin resistance and acanthosis nigrans at back of neck and in skin folds (Figure 2), Hyperandrogenism manifestation as hirsutism (Ferriman and Gallwey score of 27), insulin resistance with type-II diabetes mellitus, enlarged Right adrenal gland measuring 3.1 x 2.9 cm (Figure 5) and bilateral polycystic ovaries right: 3.7 x 2.5 cm and left: 3.8 x 2.4 cm bilateral multiple peripheral follicles noted with e/o multiple interphases on ultrasonographic scanning (Figure 6). Also the patient has dyslipidaemia, hypertension.

Polycystic ovary

Polycystic ovaries are commonly detected by ultrasound or other forms of pelvic imaging, with estimates of the prevalence in the general population being in the order of 20-33%.[7,8]

Although the ultrasound criteria for the diagnosis of polycystic ovaries have not, until now, been universally agreed, the characteristic features are accepted as being an increase in the number of follicles and the amount of

stroma as compared with normal ovaries, resulting in an increase in ovarian volume. The term 'polycystic ovary' in some respects adds to the confusion that surrounds its diagnosis. The 'cysts' are not cysts, in the sense that they do contain oocytes. So truly it should be called a polyfollicular ovary, to reflect the finding that the 'cysts' are actually follicles whose development has been arrested. Indeed, the prerequisite of a certain number of cysts may be of less relevance than the volume of ovarian stroma or of the ovary itself, which has been shown to closely correlate with serum testosterone concentrations.

Jonard et al.[9] studied 214 women with PCOS (oligo- or amenorrhoea, elevated serum LH and/or testosterone, and/or ovarian area greater than 5.5 cm^2) and 112 with normal ovaries to determine the importance of Follicle Number Per Ovary (FNPO). A FNPO of ≥12 follicles 2-9 mm gave the best threshold for the diagnosis of PCOS (sensitivity 75%, specificity 99%). The authors suggest that intraovarian hyperandrogenism promotes excessive early follicular growth up to 2-5 mm, with more follicles able to enter the growing cohort which then become arrested at the 6-9 mm size.

At the joint ASRM/ESHRE consensus meeting, a refined definition of PCOS was agreed, encompassing a description of the morphology of the polycystic ovary. According to the available literature, the criteria fulfilling sufficient specificity and sensitivity to define the polycystic ovary are the presence of 12 or more follicles measuring 2-9 mm in diameter and/or increased ovarian volume (>10 cm^3).[10] If there is a follicle greater than 10 mm in diameter, the scan should be repeated at a time of ovarian quiescence in order to calculate volume and area. The presence of a single polycystic ovary is sufficient to provide the diagnosis. The distribution of the follicles and the description of the stroma are not required in the diagnosis. Increased stromal echogenicity and/or stromal volume are specific to polycystic ovaries but it has been shown that the measurement of the ovarian volume (or area) is a good surrogate for the quantification of the stroma in clinical practice. A woman having polycystic ovaries in the absence of an ovulation disorder or hyperandrogenism (asymptomatic polycystic ovaries) should not be considered as having PCOS, although she may develop symptoms over time, for example if she gains weight.

In this case the patient has bilateral polycystic ovaries right: 3.7 x 2.5 cm and left: 3.8 x 2.4 cm bilateral multiple peripheral follicles noted with e/o multiple interphases on ultrasonographic scanning

Endocrine profile

Women with PCOS usually have a normal serum FSH concentration.

LH is the second gonadotrophin which, like FSH, is released by the gonadotrophs in the anterior pituitary gland, under the influence of pulsatile release of gonadotrophin-releasing hormone (GnRH). The differential control of FSH and LH secretion relies upon the need for priming of the pituitary by oestradiol before it will become responsive to GnRH and release LH. FSH secretion, on the other hand, is under tonic inhibitory control by inhibin acting in a negative feedback loop from the ovaries. Therefore, in times of oestrogen deficiency, such as weight-related amenorrhoea, LH concentrations in the circulation are lower than FSH, whilst the mid-cycle surge that is primed by rising oestradiol secretion from the ovary results in a greater release of LH than FSH.

An elevated serum concentration of LH in the follicular phase of the cycle suggests that the patient has PCOS, usually associated with a concentration of more than 10 IU/l in the early to mid-follicular phase of the cycle. In a series of over 1700 women with PCOS, approximately 40% of patients were found to have an elevated serum concentration of LH, which was associated with a significantly higher risk of infertility than in those with normal LH levels (Balen et al. 1995). Other causes of an elevated LH serum concentration are the mid-cycle surge and ovarian failure. LH stimulates ovarian production of androgens, and LH is most commonly elevated in slim women with PCOS. In overweight women, hypersecretion of insulin is the main cause of androgen secretion by the ovaries. The normal female range for total serum testosterone is 0.5-3.5 nmol/l. The most usual cause of an elevated serum testosterone level is PCOS. Most women with PCOS, however, have a normal total serum testosterone concentration. Measurement of the Sex-Hormone-Binding Globulin (SHBG) concentration (normal range 16-119 nmol/l) will permit calculation of the 'free androgen index' [(testosterone × 100)/SHBG], which should be less than 5. Women who are obese have high circulating levels of insulin which reduces synthesis of SHBG by the liver, so the free androgen index is often elevated when total testosterone is in the normal range. If the serum testosterone concentration is greater than 5 nmol/l, it is necessary to exclude other causes of hyperandrogenaemia, such as late-onset CAH, Cushing's syndrome and androgen-secreting tumours. Women with the most common form of CAH (21-hydroxylase deficiency) will have an elevated serum 17-hydroxyprogesterone concentration (17-OHP >20 nmol/l) and an exaggerated response to an intravenous bolus of adrenocorticotrophic hormone (250 mg tetracosactrin will cause an elevation of 17-OHP, usually between 65 and 470 nmol/l).

In this case on assessment her serum testosterone [Chemiluminescence (CLIA)] at 1.07 ng/mL (0.67 for ovulating) which is more than twice the upper normal of the laboratory, the 17 alpha hydroxy progesterone at 1.3 ng/mL (0.2-1.3 follicular phase, 1.0-4.5 luteal phase, 0.2-0.9 postmenopausal), the serum DHEA-S [Chemiluminescence (CLIA) method] at 500µg/dl (35-430 µg/dl).

Features of hyperandrogenism

Signs of hyperandrogenism (acne, hirsutism, balding) are suggestive of PCOS, although biochemical screening helps to differentiate other causes of androgen excess. Hirsutism can be graded and given a 'Ferriman and Gallwey score'. It is useful to monitor the progress of hirsutism, or its response to treatment, by making serial records, either using a chart or by taking photographs of affected areas of the body. It is important to distinguish between hyperandrogenism and virilization, which is associated with high circulating androgen levels and causes deepening of the voice, increase in muscle bulk, breast atrophy and cliteromegaly. Virilization suggests a more profound disturbance of androgen secretion than usually seen with PCOS, and indicates the need to exclude CAH, Cushing's syndrome and androgen-secreting tumours.

In this case the patient presented with hirsutism and is given 27 according to Ferriman & Gallwey scoring. There were no history of increase in muscle bulk, breast atrophy and cliteromegaly.

Hyperinsulinaemia

The association between insulin resistance, compensatory hyperinsulinaemia and hyperandrogenism has provided insight into the pathogenesis of PCOS. The cellular and molecular mechanisms of insulin resistance in PCOS have been investigated extensively, and it is evident that the major defect is a decrease in insulin sensitivity secondary to a postbinding abnormality in insulin-receptor-mediated signal transduction, with a less substantial, but significant, decrease in insulin responsiveness (Dunaif 1997). It appears that decreased insulin sensitivity in PCOS is potentially an intrinsic defect in genetically susceptible women, since it is independent of obesity, metabolic abnormalities, body fat topography and sex hormone levels. Although the insulin resistance may occur irrespective of Body Mass Index (BMI), the common association between PCOS and obesity has a synergistic deleterious impact on glucose homeostasis, and can worsen both hyperandrogenism and anovulation. An assessment of BMI alone is not thought to provide a reliable prediction of cardiovascular risk. It has been reported that the association between BMI and coronary heart disease almost disappeared after correction for dyslipidaemia, hyperglycaemia and hypertension. Some women have profound metabolic abnormalities in the presence of a normal BMI, and others have few risk factors with an elevated BMI. It has been suggested that rather than BMI itself, it is the distribution of fat that is important, with android obesity being more of a risk factor than gynaecoid obesity. Hence the value of measuring the waist:hip ratio or waist circumference, which detect abdominal visceral fat rather than subcutaneous fat. It is the visceral fat which is metabolically active and, when increased, results in increased rates of insulin resistance, type 2 diabetes, dyslipidaemia, hypertension and left ventricular enlargement. There is a closer link between waist circumference and visceral fat mass, as assessed by computer tomography, than waist:hip ratio or BMI (Lord and Wilkin 2002). Waist circumference should ideally be less than 79 cm, whilst a measurement of greater than 87 cm carries a significant risk. Exercise has a significant effect on reducing visceral fat and reducing cardiovascular risk; indeed, a 10% reduction in body weight may equate to a 30% reduction in visceral fat. Insulin acts through multiple sites to increase endogenous androgen levels. Increased peripheral insulin resistance results in a higher serum insulin concentration. Excess insulin binds to IGF-1 receptors which enhances androgen production by theca cells in response to LH stimulation. Hyperinsulinaemia also decreases the synthesis of SHBG by the liver. Therefore, there is an increase in the serum free testosterone concentration, and consequent peripheral androgen action. Intraovarian androgen excess is responsible for anovulation by acting directly on the ovary, promoting the process of follicular atresia. This latter process is characterized by apoptosis of granulosa cells. As a consequence, there is an increasingly larger stromal compartment, which retains LH responsiveness and continues to secrete androgens. Hyperinsulinaemia also stimulates trophic changes in the skin that results in acanthosis nigricans in the skin creases. Insulin resistance is defined as a reduced glucose response to a given amount of insulin and may occur secondary to resistance at the insulin receptor, decreased hepatic clearance of insulin and/or increased pancreatic sensitivity. Both obese and non-obese women with PCOS are more insulin resistant and hyperinsulinaemic than age- and weight-matched women with normal ovaries. Thus, there appear to be factors in women with PCOS which promote insulin resistance and that are independent of obesity. Insulin resistance can be measured by a number of expensive and complex tests, but it is not necessary to measure it routinely in clinical practice; it is more important to check for impaired glucose tolerance. Simple screening tests for risk of Impaired Glucose Tolerance (IGT) include an assessment of BMI and waist circumference. If the fasting blood glucose is less than 5.2 mmmol/l, the risk of impaired glucose tolerance is low. The 2-h standard 75 g oral glucose tolerance test may be conducted in those at high risk (BMI >30 kg/m^2 in Caucasian women and >25 kg/m^2 in women from South Asia, who have a greater degree of insulin resistance at a lower body weight).

In this case on examination the patient was hypertensive with blood pressure at 170/110 mmHg with Body Mass Index (BMI) at 40.08 (Obese Class-3, as per WHO 2004) and waist measurement of 106 cm. On assessment of she is hyperglycemic with fasting blood sugar at 107 mg/dl, post-prandial blood sugar at 190 mg/dl, fasting insulin at 13.13 µIU/ml, HbA1C at 7.4%, Oral Glucose Tolerance Test (OGTT) with 75 gm glucose suggestive of type-2-diabetes with hyperinsulinaemia, lipid profile showed serum cholesterol in normal range at 152 mg/dl,

serum triglycerides at borderline 216 mg/dl, low high density lipoprotein at 40 mg/dl, low density lipoprotein at normal 69 mg/dl, high very low density lipoprotein 43 mg/dl.

Health consequences of PCOS

Obesity and metabolic abnormalities are recognised risk factors for the development of ischaemic heart disease in the general population, and these are also recognised features of PCOS. The questions are whether women with PCOS are at an increased risk of ischaemic heart disease and whether this will occur at an earlier age than women with normal ovaries. The basis for the idea that women with PCOS are at greater risk of cardiovascular disease is that these women are more insulin resistant than weight-matched controls and that the metabolic disturbances associated with insulin resistance are known to increase cardiovascular risk in other populations. Insulin resistance is defined as a diminution in the biological responses to a given level of insulin. In the presence of an adequate pancreatic reserve, normal circulating glucose levels are maintained at higher serum insulin concentrations. In the general population, cardiovascular risk factors include insulin resistance, obesity, glucose intolerance, hypertension and dyslipidaemia. There have been many studies demonstrating the presence of insulin resistance and corresponding hyperinsulinaemia in both obese and non-obese women with PCOS.[11,12] Obese women with PCOS have consistently been shown to be more insulin resistant than weight-matched controls. It appears that obesity and PCOS have an additive effect on the degree and severity of the insulin resistance and subsequent hyperinsulinaemia in this group of women. The insulin resistance causes compensatory hypersecretion of insulin, particularly in response to glucose, so euglycaemia is usually maintained at the expense of hyperinsulinaemia. Insulin resistance is restricted to the extra-splanchnic actions of insulin on glucose dispersal. The liver is not affected (hence the fall in sex hormone-binding globulin, SHBG, and high-density lipoprotein, HDL), neither is the ovary (hence the menstrual problems and hypersecretion of androgens) nor the skin, hence the development of acanthosis nigricans. Women with PCOS who are oligomenorrhoeic are more likely to be insulin resistant than those with regular cycles, irrespective of their BMI, with an intermenstrual interval correlating with the degree of insulin resistance. Women with PCOS have a greater truncal abdominal fat distribution as demonstrated by a higher waist to hip ratio. The central distribution of fat is independent of BMI and associated with higher plasma insulin and triglyceride concentrations and reduced HDL and cholesterol concentrations. From a practical point of view, if the measurement of waist circumference is greater than 88 cm, there will be excess visceral fat and an increased risk of metabolic problems. Thus, there is evidence that insulin resistance, central obesity and hyperandrogenaemia have an adverse effect on lipid metabolism, yet these are surrogate risk factors for cardiovascular disease. Pierpoint et al.[13] reported the mortality rate in 1028 women diagnosed as having polycystic ovary syndrome between 1930 and 1979. All the women were older than 45 years and 770 women had been treated by wedge resection of the ovaries. Seven hundred and eighty six women were traced; the mean age at diagnosis was 26.4 years and average duration of follow up was 30 years. There were 59 deaths, of which 15 were from circulatory disease. Of these 15 deaths, 13 were from ischaemic heart disease. There were six deaths from diabetes as an underlying or contributory cause compared with the expected 1.7 deaths. The standard mortality rate both overall and for cardiovascular disease was not higher in the women with PCOS compared with the national mortality rates in women, although the observed proportion of women with diabetes as a contributory or underlying factor leading to death was significantly higher than expected (OR 3.6, 95% CI 1.5-8.4). Thus, despite surrogate markers for cardiovascular disease, in this study, no increased rate of death from cardiovascular disease could be demonstrated.

PCOS in younger women

The majority of studies which have identified the risk factors of obesity and insulin resistance in women with PCOS have investigated adult populations, commonly including women who have presented to specialist endocrine or reproductive clinics. However, PCOS has been identified in much younger populations,[8] in which women with increasing symptoms of PCOS were found to be more insulin resistant. These data emphasise the need for long-term prospective studies of young women with PCOS in order to clarify the natural history and to determine which women will be at risk of diabetes and cardiovascular disease later in life. A study of women with PCOS and a mean age of 39 years followed over a period of six years found that 9% of those with normal glucose tolerance developed impaired glucose tolerance and 8% developed type 2 diabetes[14] while 54% of women with impaired glucose tolerance at the start of the study had diabetes at follow up. The risks of disease progression, not surprisingly, were greatest in those who were overweight.

Hashimoto's thyroiditis

Hashimoto's thyroiditis or chronic lymphocytic thyroiditis is an autoimmune disease in which the thyroid gland is attacked by a variety of cell- and antibody-mediated immune processes, causing primary hypothyroidism. It was the first disease to be recognized as an autoimmune disease.[15]

There are many symptoms that are attributed to Hashimoto's thyroiditis or Hashimoto's disease. The most common symptoms include the following: fatigue, weight gain, pale or puffy face, feeling cold, joint and muscle pain, constipation, dry and thinning hair, heavy menstrual flow or irregular periods, depression, panic

disorder, a slowed heart rate, and problems getting pregnant and maintaining pregnancy.

Hashimoto's disease is about seven times more common in women than in men. It can occur in teens and young women, but more commonly shows up in middle age, particularly for men. People who get Hashimoto's disease often have family members who have thyroid or other autoimmune diseases, and sometimes have other autoimmune diseases themselves.[16]

The thyroid gland may become firm, large, and lobulated in Hashimoto's thyroiditis, but changes in the thyroid can also be nonpalpable.[17] Enlargement of the thyroid is due to lymphocytic infiltration and fibrosis rather than tissue hypertrophy. Physiologically, antibodies against thyroid peroxidase (TPO) and/or thyroglobulin cause gradual destruction of follicles in the thyroid gland. Accordingly, the disease can be detected clinically by looking for these antibodies in the blood. It is also characterized by invasion of the thyroid tissue by leukocytes, mainly T-lymphocytes. A rare but serious complication is thyroid lymphoma, generally the B-cell type, non-Hodgkin lymphoma.[18]

In this case, the anti-thyroid peroxidase antibodies in the serum were elevated but, as she was on medication for hypothyroidism her T3, T4 and TSH titres were in normal range.

Management in this case

Management is multifactorial and includes weight loss, oral contraceptive pills, and antiandrogens (spironolactone, GnRH agonists, and flutamide, used in association with contraception). Treatments for insulin resistance, such as metformin, are controversial but are used frequently. Management should also include consideration of the potential psychological disorders. Early diagnosis and treatment of HAIR-AN syndrome may improve the quality of life of patient. Undiagnosed and untreated insulin resistance is linked to long-term sequelae, such as coronary artery disease, hyperlipidemia, and type II diabetes. In adolescents, depression and potential suicidal behavior should be aggressively addressed.

Her current medications include tablet metformin (Glyciphage Sr) 500 mg thrice daily 15 minutes before food for type-II diabetes mellitus; tablet spironolactone (Aldactone) 25 mg twice daily for hyperaldosteronism; tablet atorvastatin 20 mg once daily for dyslipidaemia, tablet telmisartan (Telma 20) 20 mg once daily for hypertension, eltroxin 50 Mcg for hypothyroidism, advised change of lifestyle, weight loss, exercise and diabetic diet.

After treatment of about one month duration her fasting blood sugar at 97 mg/dl, post-prandial blood sugar at 130 mg/dl and her blood pressure recorded at 140/90 mmHg.

Medications used in this case for management

Metformin 500 mg: Trade name: Glyciphage SR

Metformin is an insulin-sensitizing drug that has also been used in the treatment of HAIR-AN syndrome. Few studies test its use in adolescents, but in small trials it appears to reduce weight gain and regulate menstrual cycles. The effect of metformin on hirsutism has not been adequately studied.[19] The reduction of insulin resistance by metformin could reduce the appearance of acanthosis nigricans on the adolescent.[20] Previous studies have shown that metformin reduces the Body Mass Index (BMI) of HAIR-AN patients and also helps regulate the menstrual cycle.[21]

Dosage: 3 times daily, 15 minutes before meals.

Spironolactone 25 mg: Trade name: Aldactone

Spironolactone is used in the treatment of hyperaldosteronism (the body produces too much aldosterone, a naturally occurring hormone); low potassium levels; heart failure; and in patients with edema (fluid retention) caused by various conditions, including liver, or kidney disease. It is also used alone or with other medications to treat high blood pressure.

Dosage of spironolactone: 25 mg two times daily.

Cyproterone 2 mg with Ethinylestradiol: Trade name: Diane 35

Dosage: Once daily.

Atorvastatin 20 mg: Atorvastatin is used to treat patients with elevated cholesterol, triglyceride or lipoprotein levels in blood, and to reduce the risk of heart diseases, even when blood cholesterol is normal.

Dosage: 20 mg once daily.

Telmisartan 20 mg: Trade name: Telma 20

Telmisartan belongs to a class of medicines known as angiotensin II receptor blockers. It is used to treat high blood pressure, prevention and treatment of heart attack (myocardial Infarction) and heart failure; when heart is unable to pump sufficient blood. It is also used for kidney failure in patients with diabetes.

Dosage: 20 mg once daily.

Thyroxine 50 Mcg: Trade name: Eltroxin/Thyronorm 50 Mcg

Thyroxine (Levothyroxine) is used to treat hypothyroidism, a condition where the thyroid gland does not produce enough thyroid hormone. Thyroxine is also used to treat congenital hypothyroidism (cretinism) and

goiter (enlarged thyroid gland). It is also used with surgery and radioactive iodine therapy to treat thyroid cancer.

Dosage: 50 Mcg once daily before breakfast on empty stomach.

Use of cosmetic methods such as laser hair removal can also be utilized to reduce the severity of existing hirsutism.[15] Weight loss is also an effective way to reduce the manifestations of HAIR-AN syndrome and also reduce the risk for other diseases including diabetes and heart disease. A lower-calorie diet rich in fiber and protein can aid in healthy weight loss for the obese adolescent.[22] It is also recommended that physicians council the adolescent about the importance of exercise and assist in the formation of an exercise program tailored to the individual patient.

Beyond physical treatment of HAIR-AN syndrome, physicians should also be observant of the mental state of the patient. Most adolescent females are concerned with their body image and are sensitive to the phenotypic manifestations of the syndrome.[19] A short evaluation of the patient's concerns and emotions associated with the diagnosis of HAIR-AN syndrome can alert physicians to any problems. Reassurance and thorough explanations of the treatment can comfort and encourage the patient.

CONCLUSIONS

To our knowledge this is the first case report of the HAIR-AN syndrome in 21 year old female associated with Hashimoto's thyroiditis, dyslipidaemia, hypertension and type-2-diabetes and this case also highlights about early diagnosis and management of HAIR-AN syndrome with PCOS and hypothyroidism which could help prevent long-term sequalae such as cardiovascular disease and endometrial cancer and with the advent of knowledge and availability of health resources we can prevent long-term adverse effects (threefold) on health of women. This woman should be observed for these ailments in later life. Obesity in adolescents needs to be avoided and corrected. Lifestyle changes should be recommended. It is suggested that in utero- malnutrition results in intrauterine growth-retarded baby which develops PCOD and X syndrome in later life. This implies that pregnancy should be managed well to maintain a good health of the individual.

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