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Case Report

Hairan syndrome as a rare cause of primary amenorrhea, hyperandrogenism, insulin resistance and acanthosis nigricans in adolescents: A case report and review of literature

Erdinc Saridogan[1], Serkan Kahyaoglu[1,*], Yasemin Tasci[1], Sebnem Ozyer[1], Omer Hamid Yumusak[1], Salim Erkaya[1]

[1]Zekai Tahir Burak Women's Health Education and Research Hospital, Department of Reproductive Endocrinology, Ankara, Turkey

Abstract

HAIRAN syndrome is a very rare syndrome which manifests with hyperandrogenism, insulin resistance and acanthosis nigricans. The syndrome usually presents with symptoms during adolescent period of life time. These pattients can easily be misdiagnosed as polycystic ovary syndrome both of which has resembling signs and symptoms. Clinical examination, gynecological evaluation and laboratory investigations are mandatory to differentiate these two syndromes. Metabolic consequences of the syndrome increases the risk of cardiovasculary disease in the future life of these adolescent patients. Counseling about the importance of weight reduction and control of insulin resistance by utilization of medical treatment for menstrual irregularies and hirsutism are key steps during management of this syndrome.

Key Words:

HAIRAN syndrome, hyperandrogenism, insulin resistance, acanthosis nigricans

Introduction

HAIRAN syndrome is an acronym for a rare multisystemic disorder in adolescents that consists of hyperandrogenism (HA), insulin resistance (IR) and acanthosis nigricans (AN). The precipitating abnormality is thought to be insulin resistance accompanied by increased insulin levels and subsequent overproduction of androgens in the ovaries. Being exposed to high insulin levels for a long time and probably hyperandrogenism can result in the cutaneous manifestation of acanthosis nigricans [1]. Hirsutism is the most common manifestation of hyperandrogenism and defined as the growth of pigmented hair on a part of body where is depended on androgens such as chest, face, back and lower abdomen. Acanthosis nigricans is a common condition characterized by velvety, hyperpigmented plaques on the skin. Hyperkeratosis, epidermal papillomatosis and increased melanin in the basal layer of epidermis are the major histopathological features of acanthosis nigricans [2]. Primary amenorrhea is defined as absence of menarche by age 15 years which is a primary symptom of PCOS. About 1 to 3 percent of women with hyperandrogenism are thought to have this rare condition, with many cases remaining undiagnosed during management of primary amenorrhea and severe hirsutism [3,4]. Here we reported a case that presented to our adolescent unit with HAIRAN syndrome which lead to primary amenorrhea. We have taken permission from the patient and her parents for publishing this clinical situation by exhibiting external views of dermatological man-

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***Correspondence:** Dr.Serkan Kahyaoglu
Address: Serhat Mahallesi 1292. Sokak Nevbahar Botanik 2 Konutlari C Blok No:7/49 Yenimahalle- Ankara/TURKEY
Phone: +905058868040
E-mail: mdserkankahyaoglu@gmail.com

ifestations of the syndrome without exposing her identity.

Case Presentation

A 17-year-old girl referred to us with primary amenorrhea. Physical examination revealed a patient in good general condition, no fever with heart rate of 82/minute, normotensive at 120/75 mmHg with a body mass index (BMI) at 36.2 kg/m2 and a waist measurement of 110 cm, a moderate hirsutism assessed to be with a score of 27 according to Ferriman Gallwey scale (Figure 1). Her pubertal state was established as stage 4 breast development and stage 5 pubic hair development according to the Tanner staging scale. She had acanthosis nigricans on her neck and nape (Figure 2). Laboratory results were listed on Table 1. Her pelvic ultrasound showed a 38x17x22 mm anteverted uterus, 3 mm endometrium, normal myometrium, 22x21 mm left ovary and 27x25 mm right ovary. Both ovaries were polycystic. The karyotype was normal (46, XX). There was no mutation on polymerase chain reaction analysis for Fragile X syndrome. Progestin withdrawal test was negative thus estrogen-progestin challenge test was performed and she had uterine bleeding. She was been diagnosed with central hypothyroidism and HAIRAN syndrome and administered by levothyroxine, metformin and combined oral contraceptive pill in addition to dietary therapy accompanied with laser depilation for severe hirsutism.

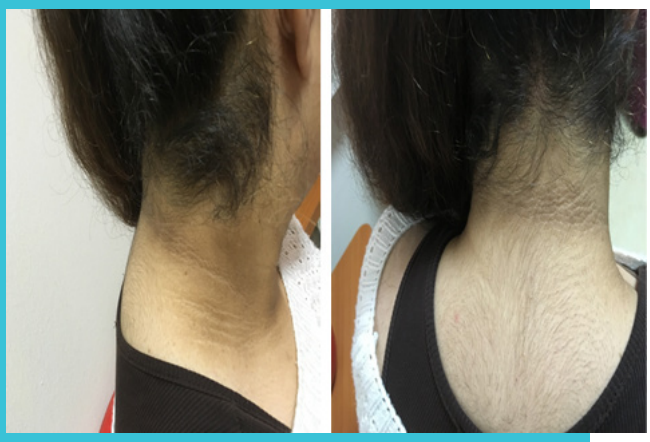
Figure 1.

Significant hirsutism score on the right arm of the patient.

Discussion

PCOS is a condition that may cause various clinical manifestations such as type 2 diabetes mellitus [7], obesity [13], hypertension, dyslipidemia [9], coronary artery disease [8], endometrial [10] and ovarian [14] neoplasm and infertility [15] due to ovulatory dysfunction, hyperandrogenism and insulin resistance [6]. The syndrome originally was described by Stein and Leventhal as the association of amenorrhea and polycystic ovaries [5] and defined by international consensus in adults [11,12]. There is no consensus about diagnosis of PCOS in adolescents although a suggestion from the Endocrine Society includes hyperandrogenism, preferably confirmed by spesific biochemical testing and anormal menstrual pattern for a given gyneacologic age [16]. The American College of Obstetrician and Gynecologists (ACOG) described normal menstrual cycles in adolescent girl as 21-45 days menstural cycle interval, 7 days or less menstrual flow length and 3-6 pads per day menstrual product use [17].

Figure 2.



Acanthosis nigricans with intense pigmentation around the neck of the patient which is a typical region of this dermatological sign for HAIRAN syndrome.

HAIRAN syndrome is a subtype of PCOS that characterized by severe insulin resistance and hyperinsulinism, possibly affecting up to 5% of androgen excess patients [12,18] and a rare cause of primary amenorrhea. Hyperinsulinism due to insulin resistance is the basic pathophysiologic mechanism of the syndrome and leading to increased androgen production and secretion from ovarian

Table 1. Laboratory results of the patient which were detected during evaluation of hirsutizm			
Hemoglobin (g/dl)	14,8 (12-15)	Prolactin (ng/ml)	15,1 (3,34-26,7)
Platelets (x1000/mm3)	259 (150-450)	Beta HCG (mIU/mL)	0 (0-5)
White blood cells (x1000/mm3)	7,7 (4-10,5)	Homa-IR	4,35 (<3,6)
Sodium (mEq/L)	138 (135-150)	**75 gr OGTT**	
Potassium (mEq/L)	4,3 (3,5-5)	0' Glucose (mg/dl)	84 (<100)
Hemoglobin A1c (%)	5,7 (<6,5)	120' Glucose (mg/dl)	128 (<140)
Urea nitrogen (mg/dl)	33 (17-43)	0' Insulin (ulU/mL)	21,64 (2-25)
Creatinine (mg/dl)	0,81 (0,6-1,1)	120' Insulin (ulU/mL)	221,55
AST (U/L)	22 (0-35)	**Low-dose ACTH stimulation test**	
ALT (U/L)	16 (0-35)	0' Cortisol (mcg/dl)	11,66 (3,09-16,66)
Total protein (g/dl)	8,3 (6,6-8,3)	30' Cortisol (mcg/dl)	12,88
Albumin (g/dl)	4,96 (3,5-5,2)	60' Cortisol (mcg/dl)	13,53
Triglycerides (mg/dl)	130 (<200)	0' 17 alpha hydroxyprogesterone (ng/ml)	2,72 (0,4-4,28)
HDL-cholesterol (mg/dl)	52 (>65)	30' 17 alpha hydroxyprogesterone (ng/ml)	2,94
LDL-cholesterol (mg/dl)	102 (<155)	60' 17 alpha hydroxyprogesterone (ng/ml)	2,57
Total cholesterol (mg/dl)	180 (<200)	0' Total testosterone (ng/dl)	107,62
FSH (mIU/mL)	8,5	30' Total testosterone (ng/dl)	119,14
LH (mIU/mL)	14,9	60' Total testosterone (ng/dl)	96,36
Estradiol (pg/ml)	34	0' DHEA-SO4 (mcg/dl)	341,1 (65-368)
ACTH (pg/ml)	77,8 (0-46)	30' DHEA-SO4 (mcg/dl)	335
TSH (mcIU/mL)	1,86 (0,34-5,6)	60' DHEA-SO4 (mcg/dl)	345
Free T4 (ng/dl)	0,55 (0,58-1,25)		

Table 1. *Laboratory results of the patient which were detected during evaluation of hirsutizm*

theca cells by cross-reaction with insulin-like growth factor reseptors. This cross-reaction is also results in acanthosis nigricans [19]. This is supported by a case report that observed a virtually cleared acanthosis nigricans after hemipancreatectomy [31]. Decreased progestin due to chronic anovulation may reduce central opiate tonus and negative feedback on luteinising hormone (LH). Sex hormone binging globulin (SHBG) decreases because of increased androgen production and secretion from ovarian theca cells due to stimulation of LH lead to rise of free androgens in the circulation. Granulosa cell dysfunction is present in addition to this theca cell dysfunction. Premature luteinization and over expressing the LH reseptor of granulosa cells lead to secretion of estradiol in response to LH [20,21]. Hyperandrogenism may result in hirsutism, alopecia, acne, menstrual dysfunction (amenorrhea, infertility), increased libido, voice deepening, male body habitus and clitorimegaly [22]. Acanthosis nigricans and obesity due to hyperinsulinism caused by insulin resistance are the other clinical features of HAIRAN syndrome. Acanthosis nigricans may occur with endocrine diseases such as diabetes mellitus, metabolic syndrome, acromegaly and Cushing's syndrome in addition to some genetic syndromes like Down syndrome, Rabson-Mendenhall syndrome, Berardinelli-Seip syndrome, familial partial lipodystrophy, Alstrom syndrome [19], Costello syndrome[23] and medications. Glucocorticoids[24], injected insulin [25], niacin [26], protease inhibitors [27], palifermin [28], testosteron [29] and aripiprazole [30] may lead to acanthosis nigricans. The paraneoplastic form of acanthosis nigricans can be accompanied by gastric adenocarcinoma, Wilms' tumor or osteogenic sarcoma in adolescents particularly if rapid onset, extensive involvement, lesions in atypical sites and unexplained weight loss are present. Primary amenorrhea is defined as the absence of menses at age 15 years in the presence of normal growth and secondary sexual characteristics or the absence of menses at age 13 years and secondary sexual characteristics such as breast development. Gonadal dysgenesis, mullerian agenesis and PCOS are the most common etiologies of primary amenorrhea [3]. Serum human chorionic gonadotropin (HCG), thyroid stimulating hormone (TSH), prolactin (PRL) and follicle stimulating hormone (FSH) should be evaluated to rule out pregnancy, hypothyroidisim and hyperprolactinemia after medical history, physical examination and pelvic ultrasound. Karyotype should be performed if uterus is absent. Mullerian agenesis (Rokitansky-Küster-Hauser-Mayer syndrome) is probably the reason if the karyotype is 46, XX. The diagnosis may be one of complete androgen insensitivity syndrome and 5-alpha reductase deficiency if karyotype is 46, XY. If uterus is present and FSH is elevated firstly 17-alpha hydroxlase deficiency should be excluded and then karyotype should be determined to distinguish gonadal dysgenesis or primary ovarian insufficiency. A normal FSH in the presence of uterus, hematometra or hematocolpos and cyclic pelvic pain are indicator for outflow tract disorders such as imperforate hymen and transverse vaginal septum. PCOS or functional hypothalamic amenorrhea (weight gain, weight reduction, emotional stres, exercise) and systemic diseases (celiac disease and type 1 diabetes mellitus) should be considered in the differential diagnosis. Both very low FSH and LH may be related to constitutional delay of puberty, congenital GnRH deficiency or other hypothalamic-pituitary space occupying disorders which can be detected with pituitary magnetic resonance imaging (i.e magnetic resonance imaging-MRI). If congenital adrenal hyperplasia is suspected, 17-alpha hydroxyprogesterone and a low-dose ACTH stimulating test may be required. Serum testosteron and dehydroepiandrosterone sulfate (DHEAS) should be assessed for adrenal or ovarian mass and MRI or computed tomography should be considered in further evaluation if rapidly progressing hirsutism and significant virilization are observed. During management of HAIRAN syndrome, lifestyle modification is the first-line treatment for obesity and insulin resistance. Insulin sensitizing drugs such as metformin (biguanide) and pioglitazone (thiazolidinedione) or insulin may be administered when weight loss is not enough. Combined oral contaceptives that containing newer progestins such as drospirenone, norgestimate and desogestrel which have fewer androgenic side effects should be administered for treatment of hyperandrogenism and amenorrhea. Severe and resistant hirsutism may require to be treated by antiandrogens like spironolactone, cyproterone acetate and flutamide which are competitive inhibitors of androgen receptor. Finasteride can also be utilized as an antiandrogen that inhibits 5 alpha reductase enzyme. The key point of treatment is giving information about the complications to the patients by reminding the metabolic consequences of this rare syndrome and importance of close follow-up during life style modification and medical treatment.

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Declaration of Interest
None

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