Case Report

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HAIR-AN Syndrome: A Rare Cause of Hyper Insulinemic State

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ABSTRACT

Insulin resistance is categorized as type A or type B, depending on the etiology. HAIR-AN syndrome is a subtype of type A insulin resistance. It is characterized by high insulin resistance, hyperandrogenemia, and hyperinsulinemia.

Here, we present a 12-year-old girl who was lean during her first decade of life and came with complaints of gradual-onset weight gain, darkening of her neck and limbs, and roughening of her skin. Menarche had not been attained. She had Grade 4 acanthosis nigricans, thick coarse skin, and hirsutism.

Investigations revealed raised blood glucose, elevated testosterone, elevated fasting insulin, and raised HOMA-IR. With biochemical evidence of hyperandrogenemia, insulin resistance, and the presence of acanthosis nigricans, the diagnosis of HAIR-AN syndrome was made.

Introduction

Insulin resistance is categorized as type A or type B, depending on the etiology. Type A syndrome is an inherited form of severe insulin resistance caused by mutations in insulin receptors or various target cell disorders affecting insulin response. Type B insulin resistance is acquired, resulting from autoantibodies against insulin receptors. This type of insulin resistance occurs in patients with less severe acanthosis nigricans and may accompany other immunologic abnormalities. It is associated with a positive antinuclear antibody screen.

HAIR-AN syndrome, a subtype of type A insulin resistance, is an acronym for an unusual multi-system disorder in women that consists of hyperandrogenism (HA), insulin resistance (IR), and acanthosis nigricans (AN). It is characterized by high insulin resistance, obesity, and hyperinsulinemia [1].

Here, we report a rare case of a 12-year-old female with HAIR-AN syndrome.

Case presentation

A 12-year-old female presented with complaints of gradual-onset weight gain over the last 3–5 years. She

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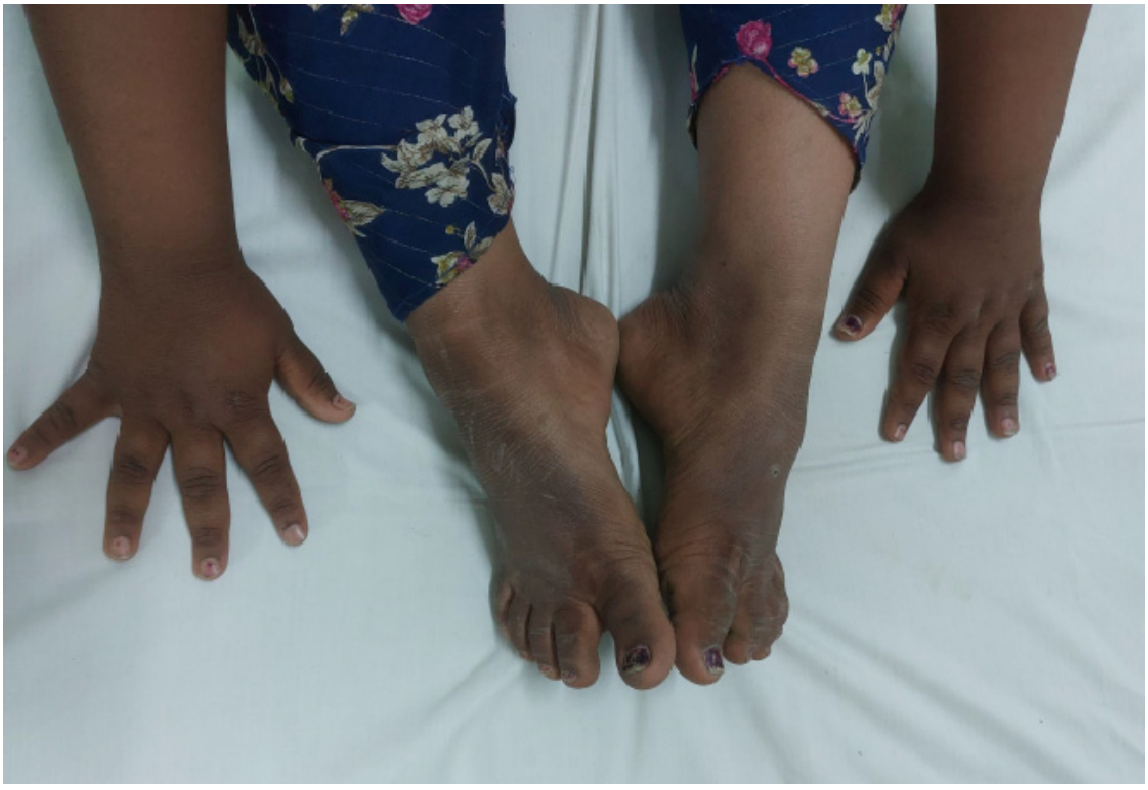

Fig. 1. Dark rough skin

noticed that her weight had increased by 20 kilograms in the last two years. She also observed darkening of her neck and limbs [Figure 1] and roughening of her skin over the past year. Menarche had not been attained. She reported hair growth over her chin for the past six months.

She admitted to having a sedentary lifestyle with a sleep duration of nine hours per day and a screen time of approximately eight hours per day. There was no attempt at physical activity or exercise throughout. She was born at full-term via normal vaginal delivery. Birth history and developmental history were normal. There was no history of prior hospital admissions or any indication of ambiguous genitalia at birth, salt-losing crisis, or hypoglycemic episodes to date.

She also confirmed that she consumed junk food, including chips, Kurkure, Lays, and street food, almost daily. She consumes both vegetarian and non-vegetarian diets.

She denied any history of daily intake of medicines or alternative medicines. Her mother had a history of hypothyroidism and had been taking thyroxine supplementation daily for the past nine years. There was no other significant family history.

On examination, her weight was 72 kilograms, her height was 148 cm, with a BMI of 32.87 kg/m^2. She had Grade 4 acanthosis nigricans [Figure 2], thick coarse skin, and hirsutism (Ferriman-Gallwey score of 8). Thelarche was present, and external genitalia were appropriate for age with Tanner staging of B3 and P3. The clitoral index was 20 mm^2 (normal <35). However, there were no striae over the abdomen or features such as large lips, large limbs, prognathism, or hyperhidrosis. There were no other discriminatory features of Cushing's syndrome or acromegaly. Blood pressure, pulse, and other systemic examinations were normal.

Renal and liver function tests were normal. Serum electrolytes were also normal.

Ultrasound of the pelvis showed an ovarian volume of 7 mL and five follicles, with the largest follicle measuring 6 mm. The uterus and other Müllerian structures were normal on ultrasound.

As the patient presented with weight gain, Grade 4 acanthosis nigricans, and mild hirsutism, differential diagnoses of polycystic ovarian syndrome, hypothyroidism, and Cushing's syndrome were considered. On biochemical evaluation, thyroid function tests were normal. The 08:00 cortisol level was normal. An overnight dexamethasone suppression test (ONDST) was performed, ruling out

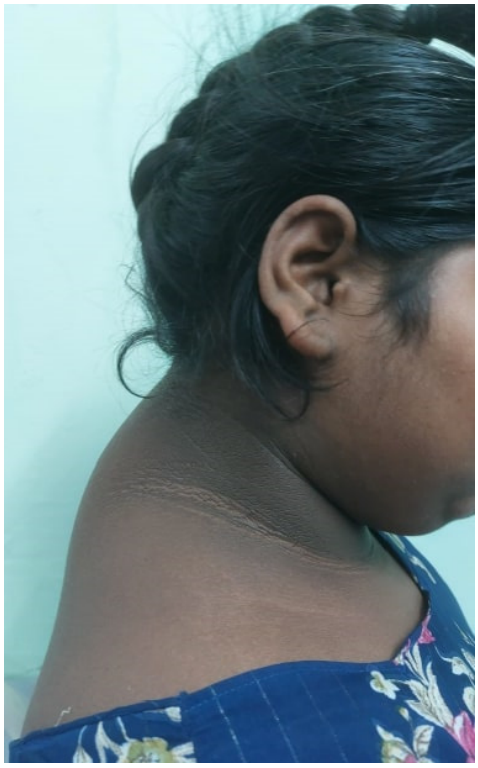

Fig. 2. Grade 4 acanthosis nigricans

Table 1. Laboratory findings

PARAMETER	RESULT	REFERENCE RANGE
Hemoglobin (g/dL)	12.8	12 – 14
Thyroid Stimulating Hormone (µIU/mL)	4.1	0.27 – 4.2
Total T3 (ng/dL)	1.18	0.8 - 2
Total T4 (µg/mL)	10.6	5.1 – 14.1
HbA1c (Glycosylated hemoglobin)	8.4%	<5.7%
Fasting blood sugar (mg/dL)	101	70 - 100
Postprandial blood sugar (mg/dL)	212	100 - 140
Fasting insulin (mIU/L)	39	<25
HOMA-IR	9.7	>2 indicates insulin resistance
8AM -Cortisol (µg/dL)	14.2	4.82 – 19.5
Post overnight 1mg dexamethasone suppression cortisol (µg/dL)	0.42	<1.6
Follicle-stimulating hormone (mIU/mL)	2.7	3.5 – 12.5
Luteinizing hormone (mIU/mL)	5.2	2.4 – 12.6
Total testosterone (ng/dL)	92	15 - 70
DHEAS (µg/dL)	164	70 - 395
Total Cholesterol	130	<200
Serum LDL Cholesterol (mg/dL)	46	60-130
Serum HDL Cholesterol (mg/dL)	48	50-80
Serum triglycerides (mg/dL)	200	<150
Vitamin B12 (pg/mL)	462	200-900

Cushing's disease. Serum testosterone was marginally elevated, while DHEAS, FSH, and LH levels were normal [Table 1]. However, ultrasound morphology was not suggestive of PCOS. The Rotterdam criteria were applied, but scores were not clearly indicative of PCOS. Fasting insulin and HOMA-IR suggested severe insulin resistance.

With biochemical evidence of hyperandrogenemia, insulin resistance, and the presence of acanthosis nigricans, the diagnosis of HAIR-AN syndrome was made. The patient was advised to adopt lifestyle modifications. A dietitian's advice was taken, and standard dietary changes were implemented. She was advised to engage in at least one hour of physical

activity per day and to remain active. Metformin and dapagliflozin were initiated.

At the two-month follow-up, the patient confirmed adherence to dietary changes and medications. She also actively participated in physical activities and an exercise program. She had lost 3 kilograms in two months, and her blood glucose was within the normal range. Metformin was continued, and dapagliflozin was stopped.

At the six-month follow-up, she had lost 10.5 kilograms. HbA1c had decreased to 5.9%, and blood glucose remained within the normal range. She noticed significant lightening of her skin color and smoothing of her skin. She felt fresh and enthusiastic. She also attained menarche five months after starting treatment.

Discussion

Depending on the cause, insulin resistance is classified as either type A or type B. Mutations in insulin receptors or various target cell abnormalities in insulin response result in type A syndrome, an inherited form of severe insulin resistance. Autoantibodies against insulin receptors cause type B insulin resistance, which is acquired. This kind of insulin resistance can coexist with other immunologic disorders and is seen in people with less severe acanthosis nigricans. It is associated with a positive antinuclear antibody screen [1].

The prevalence of HAIR-AN syndrome is about 1–5% in women with hyperandrogenism [1]. It is characterized by high insulin resistance, obesity, and hyperinsulinemia compared to PCOS. It is still unclear whether HAIR-AN syndrome and polycystic ovarian syndrome (PCOS) are distinct entities or represent a phenotypic spectrum of the same syndrome [2].

The precipitating abnormality is thought to be insulin resistance, with a secondary increase in insulin levels and subsequent overproduction of androgens in the ovaries. Long periods of hyperinsulinism and hyperandrogenism can result in the cutaneous manifestation of acanthosis nigricans. Occasionally, patients with autoimmune disorders such as Hashimoto's thyroiditis and Graves' disease also have HAIR-AN syndrome. Other nonmalignant endocrine disorders with features of androgen excess include Cushing's syndrome, polycystic ovarian syndrome, acromegaly, and congenital adrenal hyperplasia [1].

In young women, hyperandrogenism manifests as oily skin, hirsutism, acne, menstrual irregularities, and, in some cases, androgenic alopecia, deepening of the voice, clitoromegaly, and changes in muscle mass. Insulin resistance can present in different forms; some individuals have high concentrations of insulin but normal levels of glucose, while others have glucose measurements in the diabetic range. A history of diabetic symptoms such as polydipsia, polyuria, and weight loss may sometimes, but not always, be present. Concomitant vitiligo may also be present [3].

Acanthosis nigricans lesions are velvety, hyperpigmented patches of skin that occur after long-term exposure of keratinocytes to insulin. Human keratinocytes have insulin and insulin-like growth factor receptors on their surface. Stimulation caused by high insulin levels induces the formation of acanthosis nigricans lesions. In fact, acanthosis nigricans occurs in 60–80% of adolescents with type 2 diabetes mellitus [1].

Acanthosis nigricans can also occur in patients who have a malignancy, the most common being adenocarcinoma of the stomach [4]. Malignancy should be suspected in individuals older than 35 years, especially those who are not overweight. The rapid onset and extensive presentation of acanthosis nigricans found during a normal endocrine work-up should prompt a search for malignancy. Obese patients with no other disease can also develop acanthosis nigricans [5].

Two cases of organic mood disorders have been reported in association with HAIR-AN syndrome. In both cases, depression responded to treatment with oral contraceptives. Hypothalamic abnormalities can cause both depression and a disruption in insulin regulation, which may explain the coexistence of both conditions [6,7].

Weight loss may help decrease insulin resistance in overweight patients. Suppression of gonadotropins with estrogen-progesterone oral contraceptives has also been shown to help by reducing ovarian androgen production. Contraceptives containing newer progestins, such as desogestrel and norgestimate, appear to have fewer androgenic side effects and may be safer to use in individuals with abnormal lipid levels or hirsutism [6].

Antiandrogenic agents may also be used, alone or in combination with oral contraceptives. Spironolactone inhibits testosterone action by binding to its receptors. The standard dosage is 50–100 mg twice daily, but higher dosages may be required [8]. Combination therapy with oral contraceptives and spironolactone may be needed in women with severe hirsutism. The irregular menstrual bleeding that can occur with

spironolactone can often be improved by adding an oral contraceptive.

Flutamide is another antiandrogen that can be used, but it is considered more potent than spironolactone and has been associated with hepatotoxic reactions [9]. Finasteride is a 5α-reductase inhibitor that reduces the conversion of testosterone to dihydrotestosterone. It is useful in the treatment of hirsutism at dosages as low as 5 mg per day [8,9].

Patients with HAIR-AN syndrome may experience spontaneous exacerbation and remission of their insulin resistance and must be monitored closely for progression to diabetes. Those with type B insulin resistance generally follow this course, with fluctuations in the symptoms of insulin resistance, secondary acanthosis nigricans, and hyperandrogenism depending on the level of circulating anti-insulin-receptor antibodies [10,11].

Treatment of insulin resistance with an insulin-sensitizing drug such as metformin has shown promising results [10,11]. Malabsorptive bariatric surgery is effective in improving hyperandrogenism and acanthosis nigricans, with noteworthy aesthetic consequences [12].

Conclusion

HAIR-AN syndrome is a rare cause of a hyperinsulinemic state and should be suspected when a patient presents with severe acanthosis nigricans and hyperandrogenic features. Weight reduction and lifestyle modification play important roles in the management of this condition. Early detection and management are crucial, as the condition is partially reversible.

Limitations

Genetic test was not available for this patient.

Ethical Considerations

ETHICAL Approval

There were no ethical concerns related to this article. The patient provided written informed consent to publish this case report and accompanying images.

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Conflict of Interests

The authors have no conflicts of interest to declare.

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