

## Case Report

# Hyperandrogenism insulin resistance-acanthosis nigricans syndrome in a female adolescent with migraine: A case report

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## ABSTRACT

The case study explores the extreme manifestation of polycystic ovary syndrome known as hyperandrogenism insulin resistance-acanthosis nigricans (HAIR-AN) syndrome in patients with migraine, which is marked by hyperandrogenism (HA), insulin resistance (IR) and acanthosis nigricans (AN). Typically affecting women during their reproductive years, with a higher prevalence observed among adolescents, HAIR-AN syndrome's aetiology is multifaceted, involving genetic and environmental factors, including the related seborrhoea, acne, hirsutism and alopecia syndrome. The report details the case of an 18-year-old female presenting with HAIR-AN syndrome, demonstrating symptoms such as migraine, obesity, acne, hirsutism and AN, which manifested during puberty. Despite symptom onset in adolescence, diagnosis was delayed until adulthood. Clinical evaluation revealed obesity, HA and IR, with laboratory tests confirming diabetes. The case suggests a potential link between IR-induced diabetes and the development of migraine symptoms. Treatment encompasses a multifaceted approach involving antiandrogen therapy, weight management strategies, migraine treatment and medications such as metformin used to address IR and orlistat, targeting obesity. Emphasis is placed on the significance of early diagnosis and intervention in endocrine disorders with HA to enhance treatment efficacy. The complex interplay between hormonal and metabolic dysregulation in HAIR-AN syndrome is highlighted, advocating for a multidisciplinary treatment approach. Continued research efforts are required to refine diagnostic modalities and treatment strategies, particularly in the adolescent population.

**Keywords:** Acanthosis nigricans, Adolescent health, Diagnosis, Hyperandrogenism insulin resistance-acanthosis nigricans syndrome, Insulin resistance, Obesity, Polycystic ovarian syndrome, Hyperandrogenism, Treatment

## INTRODUCTION

As per the Rotterdam consensus, polycystic ovarian syndrome (PCOS) is defined by the presence of at least two out of the following three criteria: oligo- or anovulation, clinical or biochemical signs of hyperandrogenism (HA) and polycystic ovaries characterised by 12 or more follicles measuring 2–9 mm in diameter and/or an ovarian volume >10 mL in at least one ovary.<sup>[1]</sup> Affecting 6–13% of women in their reproductive years and stretching up to 6–18% of adolescent girls. Hyperandrogenism insulin resistance-acanthosis nigricans (HAIR-AN) syndrome, an extreme PCOS phenotype, presents with HA, insulin resistance (IR) and acanthosis nigricans (AN), typically manifesting during adolescence.<sup>[2]</sup> Around 5–10% of females with elevated androgen levels receive a diagnosis of HAIR-AN syndrome, and it is noted that the syndrome

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may be present in up to 40% of adolescents with irregular periods.<sup>[2]</sup> The exact causes of HAIR-AN remain unclear, with suggestions of a combination of genetic and environmental factors. HAIR-AN syndrome may be considered a variant or extreme phenotype of seborrhea, acne, hirsutism and alopecia (SAHA) syndrome, as they share overlapping clinical features such as HA-related dermatologic manifestations.<sup>[3]</sup>

First described by Barbieri and Ryan in 1983, HAIR-AN syndrome has been recognised for over four decades as a distinct multisystem disorder involving HA, IR and AN.<sup>[4]</sup> This syndrome reflects a complex interplay of hormonal and metabolic dysregulation. Key pathophysiological factors include IR and HA, with AN as a secondary outcome. The continuous cycle of positive feedback between IR and HA sustains the progression of the disease.<sup>[5]</sup>

HAIR-AN syndrome presents with obesity, acne, hirsutism and AN, typically arising during puberty. The combination of IR and obesity increases the risk of type 2 diabetes, especially in teenagers with HAIR-AN syndrome, which often leads to severe IR and rapid weight gain. These metabolic disturbances can accelerate  $\beta$ -cell dysfunction and glycemic degeneration during an important developmental window.<sup>[3,6,7]</sup> Despite symptom onset in adolescence or earlier, diagnosis often occurs in adulthood.<sup>[8]</sup> While there is no established treatment regimen, antiandrogen therapy and weight loss are considered beneficial for HAIR-AN syndrome management.

We aim to underscore the significance of early diagnosis in endocrine disorders presenting HA features, as this emphasis can markedly improve clinicians' effectiveness in managing underlying conditions.

## CASE REPORT

An 18-year-old female visited the neurology outpatient department (OPD) highlighting her chief complaint of a persistent headache localised to the occipital region, which had been ongoing for 15 days and radiating to the neck. In addition, she reported experiencing heaviness in the head, nausea and a recent episode of fever the night before admission. Notably, the patient had a history of head trauma 15 days before the onset of her symptoms. The headache initially manifested intermittently but progressively worsened, particularly in the evening, preventing her from getting adequate sleep. Bending forward exacerbated the pain, leading to dizziness and occasional blackouts. The headache did not respond to over-the-counter medications, including Combiflam® (Ibuprofen 400 mg + Paracetamol 325 mg) and tablet magrium (containing magnesium, ubidecarenone and riboflavin), indicating a more severe or refractory migraine pattern. The patient also reported a history of burning micturition associated with chills, photophobia and nosebleeds, and the patient had a history

of transient visual obscurations. Based on the chief complaint and medical history, it appears that the patient presented with symptoms consistent with migraine.

Furthermore, the patient disclosed an increase in skin pigmentation over the past 2–3 months, accompanied by a rapid weight gain from 75 kg to 99 kg within a month. She had irregular menstrual cycles for the past 5 months, with a normal duration of 7 days. The onset of menstruation occurred at the age of 13 years. Notably, the patient had been taking unidentified Ayurvedic medications.

On a detailed clinical assessment, the patient was determined to be obese, with a recorded body mass index (BMI) of 37.1 kg/m<sup>2</sup> and a waist measurement of 112 cm. She was normotensive at 130/80 mmHg, with a capillary glycaemia level of 128 mg/dL as shown in Table 1. Physical examination revealed skin pigmentation, a buffalo hump, linea nigra and Cushingoid facies as shown in Figure 1. These features prompted consideration of Cushing's syndrome in the differential diagnosis. However, further evaluation, including normal blood pressure, lack of muscle wasting or purple striae and absence of other classical stigmata, made exogenous or endogenous Cushing's syndrome less likely. Signs of HA were evident, including excess hair on the face and body, and AN was positive with dark, velvety patches over the neck, armpits and elbow flexor as shown in Figure 2. Laboratory assessments showed normal follicle-stimulating hormone levels of 3.45 mIU/ml (normal range 1.40–9.90 mIU/ml), placing the patient in the follicular cycle stage, normal luteinising hormone (LH) levels of 4.48 mIU/ml (Normal range 1.80–11.78 mIU/ml) and a slightly elevated fasting blood glucose level of 129 mg/dL (normal range 70–100 mg/dL). The oral glucose tolerance test (OGTT) findings pointed to an abnormal curve, suggesting the presence of diabetes with a high glycated haemoglobin (HbA1C) level of 6.70% (normal range 4–5.6%) as shown in Table 2. The patient experienced migraine, which showed a correlation with IR, especially in women with PCOS and HAIR-AN syndrome. IR can affect cerebral glucose metabolism and vascular regulation, which contributes to migraine pathophysiology. Studies suggest that women with PCOS and metabolic disturbances, including IR, can experience more frequent and serious migraine episodes than those without such conditions.<sup>[8]</sup> Renal and hepatic function were within normal limits, while the lipid profile revealed elevated levels of triglycerides, very-low-density lipoprotein and a high cholesterol-to-high-density lipoprotein (HDL) ratio with decreased HDL levels. Imaging studies, including abdominal and pelvic ultrasound, revealed that the right ovary was mildly bulky in size and contained a simple anechoic cystic lesion measuring 36 × 34 mm, with no septations or solid components, consistent with a simple ovarian cyst. However, brain magnetic resonance

imaging, both plain and contrast, showed no significant abnormalities in the neuroparenchyma. The overarching clinical evaluation led to the conclusive diagnosis of HAIR-AN syndrome, distinguished by the coexistence of HA, IR and the manifestation of AN.

During her hospitalisation, the patient received a comprehensive treatment plan, including medications such as tablet rosuvastatin 20 mg daily, tablet metformin hydrochloride sustained release 500 mg twice daily, injection paracetamol 1 gm as needed, tablet topiramate 25 mg twice daily for migraine prophylaxis, tablet magrium, taken twice daily, combines magnesium, ubiquinone (coenzyme Q10) and riboflavin (Vitamin B2) to reduce migraine frequency and severity, tablet domperidone and naproxen sodium) 500 mg as needed, tablet orlistat 60 mg once daily for obesity management. The Food and Drug Administration has approved orlistat for use in adolescents aged 12 years and older, and paediatric trials have shown it to be effective in reducing BMI and improving metabolic outcomes when combined with dietary and lifestyle changes.

On discharge, the patient was deemed vitally stable with no new complaints. The prescribed medications included tablet metformin hydrochloride sustained release 500 mg once daily, tablet rosuvastatin 20 mg once daily. Statin therapy is supported in high-risk paediatric populations by current guidelines from the American Academy of Paediatrics, particularly when lipid abnormalities persist despite non-pharmacologic interventions, tablet orlistat 60 mg twice daily for 1 month to support weight loss efforts in the setting of severe obesity (BMI 37.1 kg/m<sup>2</sup>) and accelerated weight gain over a short period, which are known contributors to worsening IR. The patient was advised of dietary changes and exercise for weight reduction.

Following the OPD visit after 1 month, it was observed that she had lost 3 kg in weight, indicating initial success in the management of her condition, and on follow-up, she also reported a noticeable decrease in both the frequency and severity of migraine episodes.

## DISCUSSION

This case contributes meaningfully to the limited literature on HAIR-AN syndrome in adolescents, particularly by illustrating its co-occurrence with refractory migraine, a relationship that is underexplored but clinically relevant due to the shared pathway of IR. Unlike typical presentations, this patient demonstrated rapid-onset metabolic deterioration, with nearly 24 kg of weight gain and clinical signs of HA within 1–2 months, an unusually aggressive course for HAIR-AN. By presenting a rare constellation of rapidly evolving HAIR-AN syndrome with neurologic and metabolic overlap in an adolescent, this report adds clinical depth to the

diagnostic and management framework of hyperandrogenic conditions in young females.

HAIR-AN syndrome, a rare form of PCOS primarily affecting adolescent females, involves an intricate interplay of HA, IR and AN.<sup>[4]</sup> The clinical presentation of HAIR-AN syndrome typically includes symptoms such as obesity, moderate-to-severe acne, hirsutism, irregular menstrual cycles and AN.<sup>[3]</sup> This syndrome shares similarities with SAHA syndrome, characterised by seborrhoea, acne, hirsutism and alopecia in women, and may also be associated with PCOS, cystic mastitis, obesity and infertility.

Barbieri and Hornstein (1988) reported that around 50% of women with ovarian HA display concurrent IR and hyperinsulinemia on thorough examination. In addition, approximately 90% of women with stromal hyperthecosis are suggested to have IR and hyperinsulinemia.<sup>[7]</sup> Hatim *et al* (2006) conducted a cohort study involving 1002 young women, of whom 50 adolescents were diagnosed with HAIR-AN syndrome, constituting 5% of the total attendees and 36.8% of those with irregular menses. The average age at diagnosis was 15.5 years, with initial mean weight and BMI of 94.5 kg and 33.1 kg/m<sup>2</sup>, respectively.<sup>[8]</sup>

Ovarian HA has been classified into two types by Barbieri and Hornstein. The hyperandrogenic insulin-resistant (HA-IR) group typically exhibits marked IR with slightly elevated or normal LH and normal prolactin (PRL), along with ovarian stromal hyperthecosis. On the other hand, the hyperandrogenic non-insulin-resistant (HA-nonIR) group shows minimal IR, significantly elevated LH and slightly elevated PRL, often accompanied by polycystic ovarian morphology. It is suggested that HA-IR women may have a primary hypothalamic-pituitary abnormality, while HA-nonIR women likely have a primary metabolic abnormality causing HA.<sup>[6]</sup>

The primary pathophysiological disruptions in HAIR-AN syndrome involve IR and HA, with AN considered a secondary outcome.<sup>[9]</sup> The underlying mechanism of HAIR-AN syndrome involves symptoms induced by HA, driven by elevated testosterone levels and mechanisms propelled by IR. IR fosters hyperinsulinemia, triggering increased ovarian androgen production primarily through the stimulation of IGF-I receptors or other receptors within the insulin-like growth factor family, intensifying HA. In addition, IR contributes to the onset of AN by interacting with insulin and keratinocyte surfaces, resulting in skin hyperpigmentation.<sup>[5,9,10]</sup> The inclination for severe hyperinsulinemia to be linked with stromal hyperthecosis, rather than polycystic ovaries, further supports the assertion that HAIR-AN syndrome is a distinct sub-classification of HA.<sup>[5]</sup> Insulin plays a crucial role in regulating brain metabolism and blood flow through brain receptors. Peripheral IR can extend to the brain, reducing receptor

levels and disrupting glucose metabolism. This disruption in glucose homeostasis may result in a chronic deficit in brain energy, contributing to the chronification of migraines over time.<sup>[11]</sup> In addition, IR is increasingly proposed as a mechanistic link between obesity and migraine, particularly through its effects on glucose metabolism, neurovascular regulation and inflammatory pathways.<sup>[11,12]</sup> Obesity has been linked to the development of IR and subsequent HA. However, existing literature indicates that Asian Indians face an elevated risk of developing dysmetabolic disorders even at a lower BMI.<sup>[5]</sup>

Pathologically, stromal hyperthecosis is a prevalent finding, but it lacks pathognomonic characteristics, and as of now, there is no identified histological marker specific to this syndrome. Diagnosis of HAIR-AN syndrome relies on a comprehensive clinical assessment, specific laboratory tests and imaging studies to rule out other potential causes. Laboratory evaluations, including fasting plasma glucose, insulin and HbA1c levels, along with hormonal profiling and ovarian ultrasound, play a crucial role in confirming the diagnosis.<sup>[9,10]</sup>

There are no specific protocols for the treatment of this syndrome. Treatment strategies for HAIR-AN syndrome involve a multifaceted approach targeting underlying hormonal and metabolic dysregulation. In our patient, a multidisciplinary treatment approach was adopted, incorporating pharmacological interventions targeting IR, obesity and headache symptoms. Metformin, a cornerstone in the management of IR, was prescribed to improve insulin sensitivity and regulate menstrual cycles.<sup>[9]</sup> Limited research has explored its application in adolescents, but in small-scale trials, there is evidence suggesting that it may diminish weight gain and normalise menstrual cycles. Lipase inhibitors were administered to decrease free fatty acid absorption, aiming to reduce weight. Weight loss proves effective in alleviating HAIR-AN syndrome manifestations and reducing the risk of other conditions, including diabetes and heart disease. In addition, lifestyle modifications, including dietary changes and exercise, were emphasised to facilitate weight reduction and improve metabolic parameters.<sup>[4,9]</sup> The guidelines of the German Headache and Migraine Society and the American Academy of Neurology recommend antiepileptic agents such as topiramate and valproic acid, along with certain antidepressants, as first-line therapies for migraine prevention. In addition, nutraceuticals such as Vitamin B2 (riboflavin), magnesium and coenzyme Q10 have been identified as effective non-pharmacological alternatives. These options are particularly favoured by patients who prefer natural or better-tolerated treatments for long-term migraine management.<sup>[13]</sup> Hormonal therapies such as oral contraceptives were prescribed to regulate menstrual cycles and mitigate the effects of HA.<sup>[4]</sup> Beyond the physical treatment, addressing the psychosocial aspects

**Table 1:** Summary of clinical examination findings.

Parameter	Observation
Age	18 years
BMI	37.1 kg/m <sup>2</sup> (obese)
Waist circumference	112 cm
Blood pressure	130/80 mmHg (normotensive)
Skin changes	Acanthosis nigricans, linea nigra
Facial features	Cushingoid facies
Other signs	Buffalo hump, hirsutism
Menstrual history	Irregular cycles for past 5 months
Menarche	Age 13
Weight change	From 75 kg to 99 kg in 1 month
Neurological symptoms	Occipital headache, dizziness, blackouts, transient visual obscurations
GI/GU complaints	Burning micturition, nausea

BMI: Body mass index, GI/GU: Gastrointestinal/genitourinary

**Table 2:** Laboratory and imaging findings.

Test	Result	Reference range
Fasting blood glucose	129 mg/dL	70–100 mg/dL
OGTT	Abnormal curve	-
HbA1c	6.70%	4–5.6%
FSH	3.45 mIU/mL	1.4–9.9 mIU/mL
LH	4.48 mIU/mL	1.8–11.78 mIU/mL
Lipid profile	↑ Triglycerides, ↑ VLDL, ↓ HDL	-
Renal function tests	Normal	-
Hepatic function tests	Normal	-
Abdominal/pelvic ultrasound	Right ovarian simple cyst (36×34 mm), mildly bulky	-
Brain MRI (plain+contrast)	No significant abnormalities	-

OGTT: Oral glucose tolerance test, HbA1C: Glycated haemoglobin, FSH: Follicle-stimulating hormone, VLDL: Very-low-density lipoprotein, HDL: High-density lipoprotein, MRI: Magnetic resource imaging, LH: Luteinizing Hormone, ↑: Increase

of HAIR-AN syndrome is essential. Most adolescent females are concerned about their body image and sensitive to the syndrome's phenotypic manifestations.

Collaboration with a multidisciplinary healthcare team, including endocrinologists and gynaecologists, is crucial in formulating individualised treatment plans and addressing the psychosocial aspects of HAIR-AN syndrome.



**Figure 1:** Buffalo hump, linea nigra.



**Figure 2:** Black, velvety patches of hyperpigmented skin around the neck (acanthosis nigricans).

Furthermore, ongoing research is essential to elucidate the genetic and environmental factors contributing to the syndrome's development and to refine therapeutic strategies for optimal patient outcomes.<sup>[9]</sup>

## CONCLUSION

HAIR-AN syndrome, characterised by HA, IR and AN, presents significant challenges in both diagnosis and

management, profoundly affecting the quality of life of affected adolescents. Symptoms typically manifest during adolescence, yet diagnosis is frequently delayed until adulthood. Despite being recognised for over three decades, ongoing research is crucial, particularly in elucidating genetic factors, addressing obesity and refining diagnostic techniques. Accurate diagnosis relies on practical laboratory assessments, while exploration of treatment options, including insulin-sensitising agents, holds paramount importance, particularly in adolescent cohorts. Long-term studies evaluating the effects of these agents on the development of type II diabetes and cardiovascular disease in HAIR-AN patients are imperative. Early recognition and comprehensive management are pivotal for optimising patient outcomes, underscoring the necessity of tailored approaches informed by a deep understanding of the syndrome's pathophysiology. Physicians must also remain attentive to the psychological impact on patients, offering support, reassurance and clear explanations to promote treatment adherence.

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