

## THE HAIR-AN SYNDROME: A REPORT OF A MISDIAGNOSED CASE WITH UNFORTUNATE OUTCOME

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The HAIR-AN syndrome, which consists of hyperandrogenism (HA), insulin resistance (IR) and acanthosis nigricans (AN), is an underdiagnosed endocrinopathy.<sup>2</sup> Hyperandrogenic women are seen frequently in clinical practice, the challenge being to identify a cause and source of the problem. Many such patients are classified, after thorough investigations, as polycystic ovary syndrome (PCOS). The problem with this identification is that the PCOS encompasses a wide range of clinical and laboratory presentations and, therefore, classification into subgroups may help in understanding the process and thereby targeting the management in a more appropriate way.<sup>2</sup>

The HAIR-AN syndrome is an example of a unique entity with a specific molecular basis. It was thought to be a rare syndrome, but recent experience suggests that as many as 5% of hyperandrogenic women have this syndrome.<sup>3</sup> Here we report a classical case of HAIR-AN which had an unfortunate outcome because of initial misdiagnosis.

### Case Report

A 20-year-old girl presented to the Endocrinology clinic with a history of being healthy until the age of 11 years, when she started experiencing right iliac fossa pain, followed by progressive change in voice, increased body and facial hair, increased pigmentation of skin, increased sweating, with heat intolerance and persistent bitemporal headache. She also noticed enlargement of hands and feet in the six years before presentation, prompting her to change shoes and watches frequently. For the previous three years, she had been experiencing polyuria and polydipsia, was told to have diabetes mellitus, and put on a diet. She had primary amenorrhea, and was put on a combination of pills which resulted in oligomenorrhea with dysmenorrhoea. She later stopped the medication.

In 1990, the patient had been seen in another hospital,

had been diagnosed with appendicitis, and appendectomy was performed to remove a mass found in the right iliac fossa (there was no report on the nature of the mass). In 1993, an ultrasound scan revealed a well-defined solid mass in the pelvis, suggestive of a left ovarian tumor, and the right ovary was visualized. The ovarian mass was subsequently excised. A frozen section done at the time was inconclusive. Paraffin sections did, however, show histological features consistent with a right polycystic ovary and mild hyperthecosis (Figure 1).

Upon presentation to the Endocrine clinic, examination of the patient revealed a depressed girl who was not very communicative. She was about 162 cm tall, weighed 62.2 kg and had a BP of 140/80. She had a large face with big nose and macroglossia. Her hands and feet were large and bulky, with mainly soft tissue enlargement and nonpitting edema of the lower limbs. She had significant facial hirsutism with hypertrichosis over the rest of the body and coarse terminal hair over the limbs.

Acanthosis nigricans was positive at the flexor surfaces, neck, axillae, cubital fossae and the base of the neck. Abdominal examination revealed the scars of the previous two operations, with no organomegaly. The rest of the systemic examination was unremarkable. In summary, the patient had features of hyperandrogenism, was diagnosed with diabetes mellitus, and had histopathological confirmation of polycystic ovarian diseases.

### Results

Investigations in 1993 showed fasting blood sugar (FBS) level of 5.7 mmol/L, follicle stimulating hormone (FSH) 11 IU/L (normal 3-12), luteinizing hormone (LH) 11 IU/L (normal 0.5-11), and prolactin (PRL) 415 mIU/L (normal 55-450). Oral glucose tolerance test (OGTT) showed a diabetic curve, while growth hormone (GH) was normal throughout the study. Insulin levels ranged from 8.2  $\mu$ IU/mL at base line to 249  $\mu$ IU/mL at 120 minutes. Thyroid function test (TFT) was normal, and thyrotropin-releasing hormone (TRH) test for GH was normal. She had normal estradiol level of 166.64 pmol/L (normal 37-530), progesterone level of <0.08 mmol/L (normal 0.95-3.5), and testosterone 3.6 nmol/L (normal 0.7-2.8). Dehydroepiandrosterone (DHEAS) was 0.75 mg/mL

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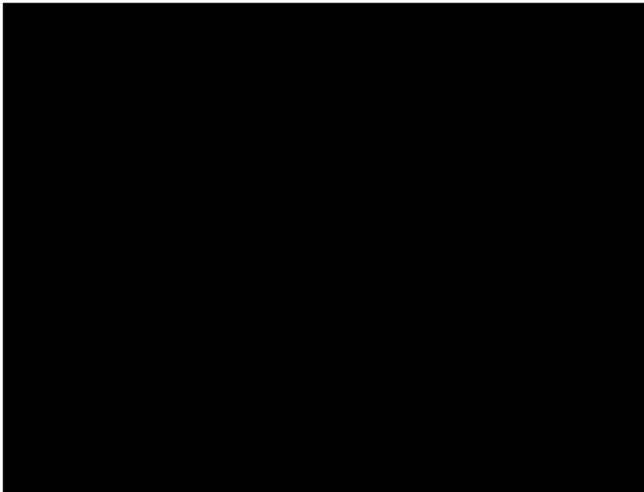


FIGURE 1A. Polycystic ovary. Two large follicular cysts are seen. (H&E, 40x).

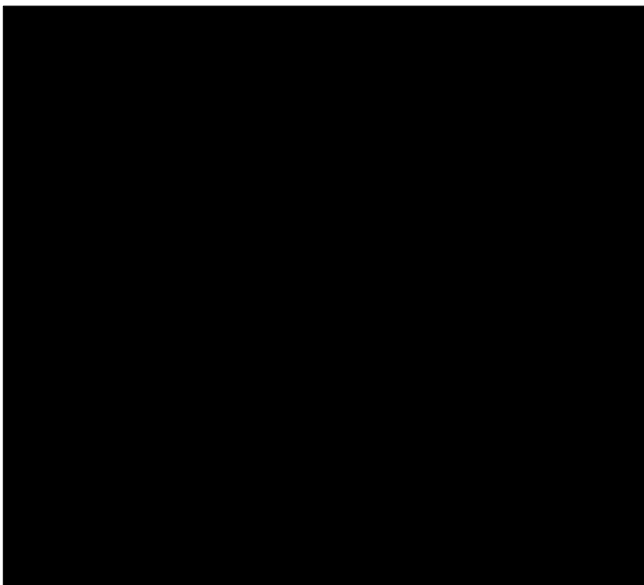


FIGURE 1B. Polycystic ovary. The cysts are lined by granulosa and theca cells (H&E, 200x).

(normal 0.35-4.3), and somatomedin C was 71 ng/mL (normal 182-780).

Ultrasound scan of the pelvis revealed a solid oval mass in the pouch extending to both adnexae, with hypoechoic texture and two small irregular anechoic areas. The mass measured 9x4.6x4.4 cm of questionable left ovarian tumor. The right ovary measured 3.1x1.6 cm.

Repeat investigations upon admission in 1996 revealed the following: FSH was 47.05 IU, and LH 31.29 (postmenopausal levels). OGTT showed a worsening of the patient's diabetic curve, with high insulin levels of 31.6, 23.9, 37.2, 348, 431 (7-34)  $\mu$ IU/mL. Free testosterone was 0.9 pg/mL (normal 0.1-3.5), DHEAS 1.34  $\mu$ g/mL (normal 0.35-4.30), triglyceride 1.2 (normal 0.4-1.48 mmol/L).

Cholesterol was 6.02 mmol/L (normal 2.9-5.2), FBS 7 mmol/L, and post-meal blood sugar was 18 mmol/L.

The patient was subjected to bilateral oophorectomy, which did not improve her insulin resistance status, but her androgens (mainly testosterone) came down. She remained symptomatic, troubled by the hirsutism and acral changes and started on the combined pills which regulated her periods. She was also started on metformin for her blood sugar, and to help in enhancing the peripheral insulin action. Her blood sugar remained fairly controlled, with fasting levels of 6 mmol/L and postprandial levels of 11-12 mmol/L. Later on, a trial of cyproterone acetate with ethinyl estradiol in a reverse sequential rhythm was tried for her hirsutism and she continued to have regular periods. The effect on the hirsutism is yet to be evaluated after adequate duration of therapy.

### Discussion

The HAIR-AN syndrome is one of the most underdiagnosed clinical entities in endocrinology. The reason for this is that women with hyperandrogenism are not usually screened for insulin resistance and acanthosis nigricans. It probably accounts for 1%-3% of women with hyperandrogenism.<sup>2</sup> Barbieri and Ryan have described the salient features of this syndrome, which include signs of androgen excess, amenorrhea, acanthosis nigricans, acral changes suggestive of acromegaly, and presentation around menarche, with most patients being slender.<sup>3</sup> The patients have abnormally elevated insulin levels and some have abnormal OGTT, but many may have normal circulating glucose levels in the fasting and postprandial state. Basal gonadotropins are normal and they respond to LHRH normally. Testosterone and androstenedione levels were high normal to markedly elevated.<sup>4-7</sup>

Pathologically, stromal hyperthecosis is common but is not pathognomonic, and no histological marker is yet available for this syndrome. In 1921, Achard and Thiers<sup>8</sup> were among the earliest investigators to describe a relationship between hyperandrogenism and hyperinsulinemia ("the bearded diabetic"), but the HAIR-AN syndrome as a separate entity was only fully and clearly described in 1983,<sup>2</sup> with more reports on similar cases and their relation to the type A insulin resistance being proposed in the last decade.

Barbieri and Hornstein stated in the second review in 1988 that if all women with significant ovarian hyperandrogenism were properly studied, approximately 50% would have associated insulin resistance and hyperinsulinemia, while if women with stromal hyperthecosis were studied, approximately 90% could be demonstrated to have insulin resistance and hyperinsulinemia.<sup>3</sup>

The primary abnormality in the HAIR-AN syndrome is postulated to be insulin resistance with secondary hyperinsulinemia, which leads to a cascade of pathological

events, including induction of ovarian androgen overproduction, mainly through stimulation of IGF-I receptors or other receptors from the family of insulin-like growth factors. Insulin may also have a direct short-term effect on the regulation of steroidogenesis.<sup>2</sup>

Macnatty et al. have found that the ovaries are the site of androgen production.<sup>9</sup> Kahn, Bar and colleagues found a marked decrease in the insulin receptors on the white blood cells of some patients with the HAIR-AN syndrome (type A insulin resistance), and in a patient with the HAIR-AN syndrome and Kahn type-c insulin resistance the insulin receptors themselves appeared to be normal and post-receptor defects in insulin action were postulated.<sup>4,10</sup> So the HAIR component of the HAIR-AN syndrome is very common, the AN being an epiphenomenon of the hyperandrogenism and hyperinsulinemia. It has been documented by many investigators that 5% of the hyperandrogenic women have acanthosis nigricans.<sup>3,11</sup>

Many authors have confirmed the role of insulin and IGF-I as important regulators of thecal and stromal androgen production.<sup>12,13</sup> Some authors have postulated that the effect of hyperinsulinemia is most likely exerted by a non-classical pathway, with a specificity spillover, i.e., the pathologically elevated insulin levels interact with many insulin-like peptide receptors, e.g., somatomedins, IGF, and relaxin, even though with low affinity accounting for the hyperandrogenism effect on the adrenals, and the muscularization which is common in all insulin resistance syndromes.<sup>14</sup> It may also account for the acral enlargement through cross-reactivity with IGF-I receptors and somatomedin-like peptide receptors, as well as for the renal and adrenal enlargement.<sup>7</sup> The hyperandrogenism itself may increase the severity of insulin resistance, and this positive feedback loop helps propagate the disease and lead to an increase in severity with time.<sup>2</sup>

The painful muscle cramps are probably explained by an unknown disorder of altered membrane function sensitivity of the muscle to insulin through alternation of insulin-mediated ion transport.<sup>7</sup> Also, a relation between hypomagnesemia and the muscle cramps has been suggested.

Gonadotropins are likely to play a permissive role for the effects of insulin in prepubertal girls with the HAIR-AN syndrome. Mild hyperandrogenism is usually present at the time of puberty, but with the onset of the pulsatile secretion of the gonadotropins, the hyperandrogenism often becomes severe, demonstrating the importance of LH in the stimulation of ovarian androgen production.<sup>2</sup>

The tendency for severe hyperinsulinemia to be associated with stromal hyperthecosis, rather than polycystic ovaries, is further evidence that the HAIR-AN syndrome is a unique subclassification of hyperandrogenism.<sup>3</sup> The hyperandrogenism and hyperinsulinemia together stimulate the epidermis and result in acanthosis nigricans.<sup>2</sup>

Barbieri and associates have subgrouped the syndrome into two types of ovarian hyperandrogenism. The first group is hyperandrogenic insulin-resistant (HA-IR) women who have marked insulin resistance with slightly elevated or normal leutinizing hormone (LH) and normal prolactin (PRL), who have ovarian stromal hyperthecosis. The second sub-group are the hyperandrogenic non-insulin-resistant (HA-nonIR) women with minimal insulin resistance, markedly elevated LH and slightly elevated PRL, who often have polycystic ovarian morphology.<sup>3</sup> Women with the HA-IR probably have a primary hypothalamic pituitary abnormality that leads to hyperandrogenism, while women with HA-nonIR probably have a primary metabolic abnormality that causes the hyperandrogenism.<sup>3</sup>

Current management is controversial and not adequate. In obese patients, loss of weight,<sup>2,15</sup> as well as exercise,<sup>16</sup> helps in reducing the insulin resistance. Gonadotropin suppression by the combined pills has been reported by many to help in reduction of ovarian hyperandrogenism.<sup>2</sup> Work is still needed to validate the use of gonadotropin antagonists and/or agonists to desensitize the pituitary, and help in ovarian suppression.<sup>2</sup>

Bilateral wedge resection can produce a transient decline in ovarian androgen production, but in most patients the hyperandrogenism returns to preoperative status in a few months.<sup>2</sup> Removal of the ovaries does not improve the insulin resistance, as this is mainly a genetic metabolic defect,<sup>3</sup> as was observed in our reported patient. Operation in conjunction with hormonal gonadotropin suppression is probably the most effective therapy currently available.<sup>2</sup>

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