Acromegaly with Polycystic Ovaries, Hyperandrogenism, Hirsutism, Insulin Resistance and Acanthosis Nigricans: A Case Report

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Abstract. We describe a woman with acromegaly who had acanthosis nigricans and hirsutism. Serum growth hormone (GH) and testosterone levels were markedly elevated. Standard oral glucose tolerance test (OGTT) showed a diabetic curve and no suppressed GH levels. Fasting insulin levels were very high while plasma glucose levels were not hypoglycemic. Insulin tolerance test revealed blunted hypoglycemic response. Acanthosis nigricans was present in the right axilla and face. Ultrasonogram demonstrated bilateral polycystic changes in the ovaries. From the above findings this patient's condition is characteristic of a very rare syndrome consisting of acromegaly, polycystic ovaries (PCO), hyperandrogenism, hirsutism, insulin resistance and acanthosis nigricans.

Key words: Acromegaly, Polycystic ovary, Acanthosis nigricans, Insulin resistance, Hyperandrogenism.

INSULIN resistance occurs in many patients with obesity, acromegaly or Cushing's syndrome. Acanthosis nigricans also occurs in many patients with gigantism, Cushing's disease, Addison's disease, polycystic ovary syndrome (PCOS), hyperthyroidism, hypothyroidism and diabetes mellitus [1-5]. PCOS with hyperandrogenism, insulin resistance and acanthosis nigricans is defined as HAIR-AN syndrome [4]. We could not find a report of a patient with acromegaly, polycystic ovaries (PCO) and HAIR-AN syndrome in the literature. Here we report a woman with acromegaly, PCO, insulin resistance, hyperandrogenism and acanthosis nigricans.

Case Report

A 34-year-old married woman was investigated in another hospital because of headache, amenorrhea, and hirsutism 11 years ago. Acromegaly was diagnosed and she underwent hypophysectomy. She was admitted to our clinic for evaluation of hirsutism, headache, dizziness and secondary amenorrhea in 1990. Her menarche occurred at the age of 13 years, with regular menses every 30 days. She married at the age of 16 years and two years later she experienced a successful pregnancy. The menses became irregular and she was amenorrheic at the age of 21 years. Physical examination disclosed acromegalic face, hands and feet. Her pulse rate was 90 beats per minute and blood pressure 160/90 mm/Hg. There was increased hair over the face, chest, upper arms, thighs, back, and abdomen. The modified Ferriman-Gallwey score [6] was 36. Brown pigmented lesions in the right axilla and face suggested acanthosis nigricans (Fig. 1). Histologic examination of the skin confirmed the diagnosis. Bilaterally slightly enlarge ovaries
with ten or more cysts 2 to 10 mm in diameter per ovary and an increased amount of hyperechogenic stroma were seen on transvaginal ultrasound scan (Fig. 2). Computerized tomography demonstrated pituitary macroadenoma. She underwent second pituitary surgery and the tumor was removed. Pathologic examination disclosed a GH secreting adenoma.

Laboratory examination revealed high serum GH and testosterone levels. Table 1 shows the basal hormone levels. TRH (200 µg, iv) stimulation test disclosed blunted TSH response and paradoxical GH response (Fig. 3). Standard oral glucose tolerance test (OGTT, 75 g glucose) showed a diabetic curve and nonsuppressible GH levels (Fig. 4). Fasting insulin levels were 118 and 152 µIU/ml while plasma glucose levels were 120 and 140 mg/dl respectively. Insulin tolerance test (0.3 U/Kg regular insulin) failed to induce hypoglycemia. The last two findings suggested insulin resistance. LH and FSH responses to LHRH (100 µg, iv) challenge were normal (Fig. 5). The LH/FSH ratio was 1.76/5.39. After GnRH agonist buserelin (1000 µg, sc) stimulation, the basal 17-

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Table 1. Basal hormone levels

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Results</th>
<th>Normal Range</th>
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<tbody>
<tr>
<td>Triiodothyronine</td>
<td>152.2 ng/dl</td>
<td>52–175</td>
</tr>
<tr>
<td>Thyroxine</td>
<td>11 µg/dl</td>
<td>4–12.5</td>
</tr>
<tr>
<td>TSH</td>
<td>0.91 µIU/ml</td>
<td>0.3–4.5</td>
</tr>
<tr>
<td>GH</td>
<td>41.97 ng/ml</td>
<td>&lt;5</td>
</tr>
<tr>
<td>FSH</td>
<td>5.39 mIU/ml</td>
<td>&lt;20</td>
</tr>
<tr>
<td>LH</td>
<td>1.76 mIU/ml</td>
<td>&lt;8</td>
</tr>
<tr>
<td>Testosterone</td>
<td>117.71 ng/dl</td>
<td>6–86</td>
</tr>
<tr>
<td>Free Testosterone</td>
<td>7.28 pg/ml</td>
<td>1–3.2</td>
</tr>
<tr>
<td>Sex Hormone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Binding-Globuline</td>
<td>8.83 nmol/l</td>
<td>20–100</td>
</tr>
<tr>
<td>Prolactin</td>
<td>10.27 ng/ml</td>
<td>&lt;20</td>
</tr>
<tr>
<td>Cortisol</td>
<td>33.45 µg/dl</td>
<td>6–27</td>
</tr>
<tr>
<td>Insulin</td>
<td>118 µIU/ml</td>
<td>&lt;30</td>
</tr>
<tr>
<td>Estradiol</td>
<td>16.43 pg/ml</td>
<td>35.6–213.6</td>
</tr>
</tbody>
</table>

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Fig. 1. Acromegalic face, brown pigmented lesion and increased hair over the face.

Fig. 2. Transvaginal ultrasonogram showing ovaries with multiple cysts arranged around a dense stroma.
hydroxyprogesterone (17-OHP) level (0.74 ng/ml) showed a small increase at 1800 h and 2400 h (1.12 ng/ml, 1.29 ng/ml, respectively).

**Discussion**

Acromegaly is an uncommon condition. Disabling and disfiguring skeletal changes are seen in patients who developed acromegaly when they were young and in whose treatment has been delayed. Acromegalic features are believed to be caused by somatomedins, a family of growth promoting peptides whose secretion is controlled by GH. Insulin at high concentration can stimulate GH through low-affinity binding to receptors for some of these somatomedin-like peptides. Acanthosis nigricans is a well-known finding in acromegaly [1]. Acanthosis nigricans is a hyperplastic response of the skin to stimulation by GH, insulin and androgen [3–5, 7]. Levin et al. [8] described the occurrence of acromegaly with acanthosis nigricans in two brothers. Flier et al. [9] reported the appearance of insulin resistance, acanthosis nigricans and muscle cramps in two siblings. These reports suggest a genetic basis for this syndrome. The presence of acanthosis nigricans, or acral enlargement should alert the physician to the possible coexistence of insulin resistance, regardless of the state of glucose tolerance. Our patient can be considered insulin resistant, because of the presence of marked endogenous hyperinsulinemia without concomitant hypoglycemia and failure of hypoglycemia despite high insulin administration. Kahn et al. [10] also reported six patients with acanthosis nigricans, variable degrees of glucose intolerance, hyperinsulinemia and marked resistance to exogenous insulin.

Our case was also characterized by PCO. Nabarro [1] did not mentioned PCO in his report including 153 women with acromegaly. Melmed [11] recently reviewed acromegaly, and polycystic changes in ovaries were not mentioned as a finding in acromegaly. In a well-known textbook of endocrinology, Randall [12] reported that he had seen three patients (not reported) with hormonally active acromegaly and surgically proven polycystic ovaries. In another famous textbook of endocrinology, “Williams Textbook of Endocrinology”, PCO was not included among the clinical findings in acromegaly [13]. Thus, it seems that PCO are an unusual feature of acromegaly. Nagamani et al. [14] reported a rare case of acromegaly and ovarian hyperthecosis. Our patient also had very severe hirsutism due to increased levels of testosterone. All three criteria of HAIR-AN syndrome...
(hyperandrogenism, insulin resistance and acanthosis nigricans) were present. The association of hyperandrogenism, insulin resistance and polycystic ovarian disease is well established. Approximately 50% of women with PCOS are insulin resistant and approximately 10% of these are severely insulin resistant. Multiple dynamic endocrine suppression studies indicate that in both obese and nonobese women with hyperinsulinemia and hyperandrogenism, hyperinsulinemia causes hyperandrogenism, but hyperandrogenism does not cause insulin resistance [5]. Both insulin and insulin-like growth factor-I (IGF-1) receptors have been identified in human ovarian cells [15]. Hyperinsulinemia, regardless of its cause, in the presence of permissible concentrations of gonadotropins, acting via ovarian IGF-1 receptors, stimulates ovarian testosterone and androstenedione production [16, 17]. The basal LH level was low, and not exaggerated but normal LH responses to LHRH challenge were detected. It can therefore be said that overproduction of LH was not a causative factor in the development of PCO. But normal LH responses to LHRH challenge indicate that some LH was present in the circulation, permitting hyperinsulinemia to give rise to hyperandrogenemia. We think that insulin resistance which is seen in some patients with acromegaly, was the primary cause of hyperandrogenemia and PCO. Hyperprolactinemia, which may play a role in the development of hyperandrogenemia, was not present in the patient. Why are PCO not commonly reported in acromegalic patients? Although the question remains to be clarified, we postulate that not all acromegalic patients are insulin resistant, or there may be not enough gonadotropins by which hyperinsulinemia stimulates ovarian androgens, in some patients with acromegaly who are insulin resistant and whose gonadotropin secreting cells are occupied by a GH-secreting tumor. On the other hand, it seems that PCO may develop in patients with acromegaly in the setting of genetic predisposition to PCOS [5].

Barnes et al. [18] suggest that PCOS usually results from hyperfunction of the androgen-forming enzyme (cytochrome P450c17a), and a serum 17-OHP level over 2.20 ng/ml in response to the GnRH agonist nafarelin is a useful diagnostic test for PCOS. However, the 17-OHP response to the GnRH agonist buserelin did not increase adequately in our patient. We think that blunted 17-OHP response to the GnRH agonist might have been caused by the failure of the LH level to increase.

In conclusion, acromegaly may be characterized by hyperinsulinism, hyperandrogenism, hirsutism, acanthosis nigricans and PCO, even if it is very rare.

References


