Acanthosis nigricans, insulin resistance and cutaneous virilism

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Accepted for publication 26 November 1987

SUMMARY

Thirteen patients with the syndrome of acanthosis nigricans and insulin resistance are described. They all had a combination of dermatoses related to hyperandrogenism (cutaneous virilism): hirsuties (11), acne vulgaris (6), hidradenitis suppurativa (5) and androgenic alopecia (4). In addition, 9 out of 13 had keratosis pilaris. The patients had raised fasting plasma insulin levels compared with matched normal controls ($P<0.01$) and increased insulin resistance ($P<0.02$). Insulin resistance correlated with total serum testosterone ($r_s=0.65$; $P<0.02$).

Acanthosis nigricans (AN) and insulin resistance are features of many congenital, metabolic and endocrine disorders, for example, Cushing’s disease, acromegaly, leprechaunism, Laurence-Moon-Bardet-Biedel and Prader-Willi syndromes and congenital lipodystrophy.

A relationship between diabetes and hyperandrogenism in women or diabetes of bearded women has been recognized for many years. However, it is only in the past few years that the cause of the disordered carbohydrate metabolism has been defined as resistance to insulin; and that the combination of AN and insulin resistance (IR) is found in as many as 5% of women with hyperandrogenism (HA). The acronym HAIR-AN has been used to describe this syndrome; even though, as we found in the present study, not all the women are hirsute.

We have studied hyperandrogenized women, most of whom have presented to a dermatology department with hirsuties, in order to determine the features of cutaneous virilism associated with AN and insulin resistance and the relationship of the latter with serum androgens.

METHODS

Patients

Two hundred and twenty seven patients were referred for assessment of hirsuties. Seventy four (33%) were both sufficiently hirsute (Ferriman and Gallwey grade $>15$) and adequately motivated to undergo prolonged anti-androgen therapy. Sixteen (22%) of the 74 patients had

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Acanthosis nigricans and nine (12%) were studied for insulin resistance. Four further hyperandrogenized women with acanthosis nigricans (two with hidradenitis suppurativa and two with generalized keratosis pilaris) were also studied. The study had the approval of the Central Oxford Research Ethical Committee.

Grading schemes
Hirsuties was measured by the Ferriman and Gallwey scale;\(^5\) and androgenic alopecia by Ludwig grades.\(^6\) Obesity was measured as the body mass index (BMI)\(^7\) calculated as weight/height\(^2\) in kg/m\(^2\). The diagnosis of polycystic ovary syndrome was based on menstrual cycle lengths > 35 days and non-midcycle luteinizing hormone > 10 U/l.

Laboratory methods
Sex hormone binding globulin (SHBG) was measured by the method of Iqbal and Johnson.\(^8\) Insulin was assayed by radio-immunoassay;\(^9\) the coefficient of variation for this assay is 6% and the sensitivity 2 mU/l.

The insulin resistance for each subject was determined from the fasting plasma insulin and glucose levels using a computer solved model [homeostasis model assessment (HOMA)]. This model calculates the insulin resistance in the fasting state which is assumed to be a steady-state where glucose production equals glucose disposal. HOMA uses the best available physiological data for the effects of glucose and insulin on hepatic glucose production, glucose uptake by muscle, adipose and nervous tissue. A near approximation for calculating insulin resistance is:

\[
I/22.5 \times e^{-lnG}
\]

where I is fasting insulin and G is fasting glucose. A healthy individual of normal weight is arbitrarily allocated an insulin resistance value of 1.0. The insulin resistance thus calculated correlates well with that derived from the hyperinsulinaemic euglycaemic clamp.\(^10\)

Statistics
The Oxstat statistical package was used. Mann Whitney U tests and Spearman correlation coefficients for non-parametric data were used. Median values and ranges are quoted and \(P\) values are two-tailed.

RESULTS

Clinical features
The clinical details are summarized in Table 1.

Acanthosis nigricans. AN was recorded in 7% of the 227 cases (although its presence was not recorded for 153 of these cases who were not studied). The AN was identical in appearance to the form associated with malignant disease. There were verrucous plaques which varied from soft light brown velvety areas to thickened dark brown rough plaques with deep pseudo-fissures (Fig. 1). They principally affected a thin necklace-like band on the lateral and dorsal aspects of the neck; the majority of the patients also had AN of the axillae and inner thighs. The more obese subjects had AN in the intertriginous areas under the breasts and in the fatty fold around the waist and in two cases the skin overlying the sternum was affected. There were pigmented verrucous plaques over the elbow tips in two cases and on the dorsal aspects of the interphalangeal joints in a further case; these were all considered to be examples of AN. The palms were not involved in any patient.
**TABLE 1. Clinical details and laboratory findings in 13 patients with HAIR-AN syndrome**

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Age years</th>
<th>BMI*</th>
<th>Total testosterone nmol/l</th>
<th>SHBG ng DHT bound/l</th>
<th>Insulin resistance HOMA</th>
<th>PCOS‡</th>
<th>Acne vulgaris**</th>
<th>Hirsuties†</th>
<th>Androgenic alopecia Ludwig grade</th>
<th>Hidradenitis suppurativa</th>
<th>Extensive keratosis pilaris</th>
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<td></td>
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<td>...</td>
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</table>

* BMI = Quetelet Index, weight/height²
** Acne: + mild ++ moderate +++ severe
† Hirsuties, Ferriman and Gallwey scale³ (maximum score 44)
‡ PCOS: Polycystic ovary syndrome
**Obesity.** The median BMI was 34.6 (range 24.2–46.8), which indicated that the group was considerably overweight (BMI 25.8 is approximately 120% and BMI 30 is approximately 140% of ideal body weight).

The other features of cutaneous virilism are summarized in Table 1. The median hirsuties grade 34 (range 17–37)—excluding the two non-hirsute women—is artificially high as the source of referral produced an inevitable bias towards severe hirsutism.

**Metabolic data**
The thirteen hirsute women with AN were compared with 13 controls matched for age (median age, patients 35 years, range 16–39; controls 40 years, range 20–57) and BMI (mean patients 34.6, range 24.2–46.8; controls 32.2, range 21.7–57.6, difference not significant). Median fasting insulin was 33 mU/l (range 7.7–65.0 mU/l) in the patients and 10.4 mU/l (range 1.5–33.3 mU/l) in the controls (P<0.01). Median fasting glucose was 5.1 mol/l (range 4.4–8.0) for patients and 5.1 mmol/l (range 4.4–6.9 mmol/l) in the controls; this difference was not significant. Median insulin resistance (HOMA) in arbitrary units was 8.03 (range 1.71–17.16) in the patients and 2.44 (range 0.33–8.62) in the controls (P<0.02) (Fig. 2).

The control group were slightly, although not significantly, older. This would have the effect of reducing the difference demonstrated, as insulin resistance increases with age.11

**Endocrine data**
Median serum testosterone was 2.7 nmol/l (range 1.1–8.8); SHBG 22.9 ng DHT bound/l (range 7.0–62.9). Testosterone levels correlated with insulin resistance, r_s = 0.65 (P<0.02) (Fig. 3), but not with BMI, r_s = 0.46 (P = 0.12).
FIGURE 2. Insulin resistance (HOMA) in arbitrary units in patients with HAIR-AN syndrome and in age and weight matched controls.

FIGURE 3. The relationship between insulin resistance (HOMA) in arbitrary units and the total serum testosterone in patients with HAIR-AN syndrome. $r_s = 0.65 (P < 0.02)$.
DISCUSSION

We have studied patients with acanthosis nigricans (AN) who have presented with features of cutaneous virilism. In the group of hirsute patients the incidence of AN and insulin resistance was at least 7% (16 of 227) as this figure represents the number of patients in whom AN was recorded. This figure may be falsely low as only a third of the total group of patients was studied; however, the incidence of 7% is similar to that in the report by Flier et al. which suggested an incidence of 5%, but did not include a definition of AN.

The features of cutaneous virilism are quite pronounced and reflect the degree of hyperandrogenism which has been demonstrated to be directly proportional to insulin resistance. An unusual aspect of this series is that only half the patients had polycystic ovary syndrome (as defined by oligomenorrhea and increased luteinizing hormone levels) whereas this is usually considered to be a prerequisite feature. The features of cutaneous virilism are quite pronounced and reflect the degree of hyperandrogenism which has been demonstrated to be directly proportional to insulin resistance. An unusual aspect of this series is that only half the patients had polycystic ovary syndrome (as defined by oligomenorrhea and increased luteinizing hormone levels) whereas this is usually considered to be a prerequisite feature. The pathophysiological mechanism associating hyperandrogenism, insulin resistance and acanthosis nigricans is not known. Neither is it known whether hyperandrogenism precedes the insulin resistance. There is clearly a close relationship between the level of serum testosterone and insulin resistance as demonstrated in the present and previous reports. This relationship is not dependent upon obesity, as shown in two of our cases and one previous report.

The development of acanthosis nigricans at puberty with the normal surge of androgen production would suggest that androgens have an aetiological effect. It is not known whether androgens act directly on the epidermis to produce AN or indirectly by the induction of a state of insulin resistance. There are two possible mechanisms for an insulin mediated effect; insulin may directly stimulate epidermal transformation or it may enhance ovarian androgen production. Both these effects may be created by the binding of insulin to receptors for insulin-like growth factors in the epidermis or ovary. Increased ovarian production of androgens would aggravate the condition with the formation of a positive feedback mechanism.

Treatment of acanthosis nigricans with anti-androgenic agents has been unsuccessful in our experience (five of the patients in the present series received 12 months of anti-androgen therapy with no remission of their acanthosis nigricans). However, there have been isolated case reports of temporary remissions induced by other therapies. In one report, surgical ovarian wedge resection was successful, in another, therapy with cyclical norethindrone and mestranol in conjunction with ovarian wedge resection was effective, and in a third, drug therapy alone with cyproterone acetate was successful at reducing AN. Weight reduction may be effective in reducing insulin resistance, but has only been reported to be effective in reducing acanthosis nigricans in a single case.

ACKNOWLEDGMENTS

We are grateful to Mary A. Gales of the Regional Assay Laboratory, Radcliffe Infirmary, Oxford for the testosterone and gonadotrophin assays and to Schering Health Care for financial support.

REFERENCES

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