

ACANTHOSIS NIGRICANS: A NEW ANALYSIS OF ASSOCIATED ENDOCRINE AND MALIGNANT DISORDERS

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The association of acanthosis nigricans (AN) with malignant tumors, obesity, insulin resistance and diabetes, hyperandrogenism, and other endocrinopathies has received the attention of many investigators for the past 100 years.¹⁻¹³

Most malignant tumors reported in the earlier literature were gastrointestinal. Recent literature, however, points to more association of malignancies with AN involvement of eyelids, conjunctiva^{2,7,14-17} and oral cavity, palate or esophagus.^{3,18,19} Insulin resistance is considered to be the underlying pathomechanism of AN by many workers.^{4,6-8,11} Different types of insulin receptor gene mutations have been described recently.^{20,21} Other investigators described excess insulin binding to insulin-like growth factor receptors,²² thus inducing various forms of growth effects. One report established certain keratin patterns in AN²³ which could have contributed to the etiology of skin lesions of AN, and another described acromegaly-like features in some patients with AN and hyperinsulinemia.⁴

Some or all of these mechanisms, as well as others not yet established, could result in insulin resistance, hyperinsulinemia with its growth-promoting influences on the skin, ovaries and possibly other tissues. Other endocrinopathies associated with AN, such as thyroid,^{13,14,24} pituitary^{12,25,26} and adrenal disorders,^{27,28} were frequently reported, but no clear pathomechanisms were established in these reports.

This is a cross-sectional observation study of the prevalence of associated endocrinopathies with AN in certain age and sex groups, along with an attempt to explain such associations. The lack of malignant tumors in this series is also discussed.

Materials and Methods

The study group included 138 patients (95 females and 43 males), ranging in age from three to 62 years. They

were followed between three months and 10 years in our endocrinology out-patient clinics.

The patients were divided into three subgroups, taking into consideration the average ages of puberty and menopause in females who represented the majority of patients in this series: 1) under 15 years; 2) between 15-45 years; and 3) over 45 years of age.

All patients had acanthosis nigricans, with velvety, hyperpigmented thickening of skin over the nape of the neck, with or without involvement of axillae and other flexure areas. Papillomatous formation was present in most cases. No eyelids, conjunctiva or oral cavity involvement with AN was found in any of these patients.

Diagnosis of associated disorders was established by history, physical examination, body mass index (BMI), hormone measurements by radioimmunoassays of thyroid function tests, free testosterone, 17 (OH) progesterone, dehydroepiandrosterone sulfate (DHEAS), cortisol, gonadotropins, prolactin, immunoreactive insulin, and C-peptide levels. Further work-up of polycystic ovary syndrome included ultrasonography of ovaries. Obesity was diagnosed when BMI exceeded 27 kg/m². In this series, BMI of obese patients ranged from 27-51 kg/m².

Acromegaly was diagnosed clinically by the presence of acral hypertrophy and coarsening of facial features; biochemically by failure of elevated immunoreactive serum growth hormone to suppress, following ingestion of a standard dose of glucose administered in the AM fasting state, and the presence of a pituitary adenoma by CT scanning.²⁹ These criteria were also used in the work-up of one male patient with severe AN, severe hyperinsulinemia and acromegaly-like features.

Thyroid nodules were further studied with RAI scans and/or cytologic examination of fine-needle aspiration biopsies.

With variations of phenotypic expressions of various components of the polycystic ovary syndrome (PCOS), the presence of a clinically significant number of the following criteria was considered in diagnosing PCOS in this series,³⁰⁻³² provided that entities such as Cushing's syndrome, adult onset congenital adrenal hyperplasia, ovarian tumors and hyperprolactinemia were excluded: 1) history of menstrual irregularities and/or anovulation; 2)

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hirsutism and/or temporal balding, oily skin and acne; 3) elevated serum-free testosterone and/or elevated LH/FSH ratio; and 4) ultrasonographic finding of polycystic ovaries.

Results

Of the 95 female patients with AN, 12 were below 15 years of age. All were obese (100%), and the only endocrinopathy was one case of precocious puberty (8.3%). In the age group above 45 years, there were 10 patients who were all obese (100%). Nine (90%) had non-insulin-dependent diabetes mellitus (NIDDM). The only endocrinopathy was one case of primary hypothyroidism (10%).

In the age group 15-45 years, there were 73 patients and 69 were obese (94.5%). Of these patients, 61 (83.9%) had endocrinopathies. Twenty-one patients (28.8%) were found to have NIDDM. Nine of these diabetic patients also had other endocrinopathies. Seventeen patients (23.3%) had thyroid disorders, and all of them were obese. Five patients (6.8%) had unexplained primary or secondary amenorrhea, and four of them were obese. Of these five patients, three had secondary amenorrhea, and two had menstrual irregularities. They were evaluated along the same lines as outlined previously. None of them revealed evidence of any endocrinopathy. Twenty-four patients (32.9%) had polycystic ovary syndrome, and 22 of them were obese. Three patients had pituitary adenomas, and all were obese.

Of the 43 male patients with AN, eight were below the age of 15 years. Six of them were obese (75%). None of them showed associated endocrinopathies. Of the remaining 35 patients in the 15-45-year age group, 34 were obese (97%). The only nonobese patient was a 21-year-old man with severe AN, acromegaly-like features, markedly elevated immunoreactive insulin levels without diabetes, and normal growth hormone studies. Thirteen patients (37%) were found to have NIDDM, and two of these diabetic patients also had other endocrinopathies. Two patients (6%) had thyroid disorders, and both were obese. Five patients (15.2%) had hypothalamic pituitary disorders and all were obese.

None of the 138 patients in this series showed any associated malignant tumors.

Discussion

Analysis of data from these 138 cases with AN leads us to several significant conclusions. Obesity was almost universal in all age and sex groups. Different types of endocrinopathies were prevalent in the 15-45-year age group, especially in females. These included PCOS, thyroid, and pituitary-hypothalamic disorders. The vast

majority of patients with these endocrinopathies were obese, including both sexes. The literature is rich in data pointing to obesity, insulin resistance, and hyperinsulinism as being the underlying pathomechanism for growth-promoting effects on several organs, including the skin, ovaries, and possibly other systems. In this context, it is prudent to postulate that such pathomechanisms could explain the high prevalence of AN in our patients with thyroid and pituitary-hypothalamic endocrinopathies. Further work is needed to clarify this association. Greater numbers of cases with such endocrinopathies need studying, including the roles of insulin resistance and of other growth factors, to elucidate the bases of their association with AN.

No malignant tumors were encountered in this series. Careful analysis of literature in this area could provide an explanation. Many reports described increased frequency of malignancies associated with AN, involving eyelids, conjunctiva, oral cavity and esophagus. All patients in this series had AN of the nape of neck, axillae or other skin flexures. None of them had involvement of eyelids, conjunctivae or oral cavities. This finding may be suggestive that AN, excluding the above areas, is not significantly associated with malignant tumors.

The findings in this study stress the importance of screening patients for the presence of AN and its distribution, in the adoption of comprehensive disease discovery and prevention programs. Patients with AN should be screened for the presence and type of associated endocrinopathies. If AN involves eyelids, conjunctiva, oral cavity or esophagus, patients should be carefully screened for possible associated malignancies.

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