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Acanthosis nigricans vulgaris. A marker of hyperinsulinemia.

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Summary Acanthosis nigricans (AN) is a syndrome with variable clinical significance ranging from marker of moderate endocrine imbalance to marker of malignancy. The most frequent form of AN, which therefore could be called AN vulgaris, is AN associated to obesity. Here is reported a case of AN associated to obesity. Physicians should be aware that this form is due to insulin resistance secondary to obesity and that insulin resistance, when the pancreas works, is responsible for hyperinsulinemia. The latter is responsible in males for AN and in females for AN and hyperandrogenemia (HA). The treatment of AN vulgaris is based, besides the topical therapy, on the correction of obesity. When the latter goal cannot be achieved, metformin hydrochloride should be given. This biguanide drug increases both the peripheral response to insulin and the cellular glucose metabolism. Moreover, it decreases the delayed glucose intestinal absorption and inhibits hepatic glucogenesis.

Key words Acanthosis nigricans, insulin resistance, hyperinsulinemia, hydrochloride metformin.

Acanthosis nigricans (AN) is the term proposed by Unna (17) to indicate a disorder characterized clinically by thickened, dark brown skin with greater evidence of the groove and relief pattern and histologically by hyperkeratosis and hyperplasia of the dermal papillae in absence of true acanthosis, melanic hyperpigmentation and inflammatory infiltrate. Thus, the brownish discoloration is due to the thickened horny layer and not to melanin excess. AN affects whatever cutaneous and mucosal site, although it has a preference for armpits, neck, both behind on the nape and on the latero-cervical regions, groins, the folds of elbows and knees and finally the umbilicus. The keratinocyte and fibroblast hyperplasia is probably due to the presence of growth factors for these cells (15).

The causative factors of AN are extremely complex, as shown by the high number of reports facing this subject (18). However, we can grossly distinguish a form associated with malignancy, the first to be identified (17) and probably due to the presence of tumor growth factors, and a second form non associated to malignancy. In the latter the factor stimulating the keratinocyte and fibroblast growth is probably insulin in subjects with insulin resistance. The latter term means a decreased biological response, in this case the elimination of excessive sugar of the peripheral tissues. The decreased peripheral response to circulating insulin stimulates, when the pancreas works normally, a compensatory insulin hypersecretion aimed at keeping the glycemic level constant and therefore hyperinsulinemia. Insulin resistance is therefore subdivided into two variants (2) as follows: 1- insulin resistance of diabetic subjects, who require 200 or more insulin units to control hyperglycemia and to prevent ketosis and 2- insulin resistance of normoglycemic subjects with associated hyperinsulinemia.

The classification of AN is much more complex as shown by that one of Schwartz (18) in 8 types (see table 1) as follows: 1- benign familial (3), autosomal dominant with variable penetran-

ce, increasing till puberty and then stabilizing; 2- associated to obesity, in the past known as pseudoacanthosis nigricans (5). This usually moderate variant is clearly related to obesity, regressing when obesity regresses. It is the most frequent type of AN and thus the term acanthosis nigricans vulgaris should be appropriate; 3- syndromic, subdivided into type A affecting young women with signs of virilization or accelerated growth and type B autoimmune due to autoantibodies directed against the insulin receptors (12). Besides these variants there are other numerous syndromes, the most well known of which are Hirschowitz syndrome (11), familial, characterized by early onset, deafness and gastrointestinal disorders and Lawrence-Seip syndrome (14, 20) with lipodystrophy associated to AN; 4- associated to malignancy. It is characterized by sudden onset and it is sometimes associated to other cutaneous markers of malignancy such as eruptive seborrheic warts, florid cutaneous papillomatosis and hyperkeratosis of the palms and soles; 5- acral, on the dorsal aspect of the hands and feet, which is almost physiological in dark-skinned subjects. It is also named acral acanthotic anomaly (19); 6- unilateral or nevoid, which can be the initial sign of the benign familial variant and then gets bilateral or persists as monolateral; 7- induced by drugs such as steroid hormones (4), nicotinic acid (6)

Table 1: Classification of acanthosis nigricans according to Schwartz, 1994.

Benign acanthosis nigricans
Acanthosis nigricans associated to obesity
Syndromic acanthosis nigricans
Malignant acanthosis nigricans
Acral acanthosis nigricans
Unilateral acanthosis nigricans
Drug-induced acanthosis nigricans
Mixed acanthosis nigricans

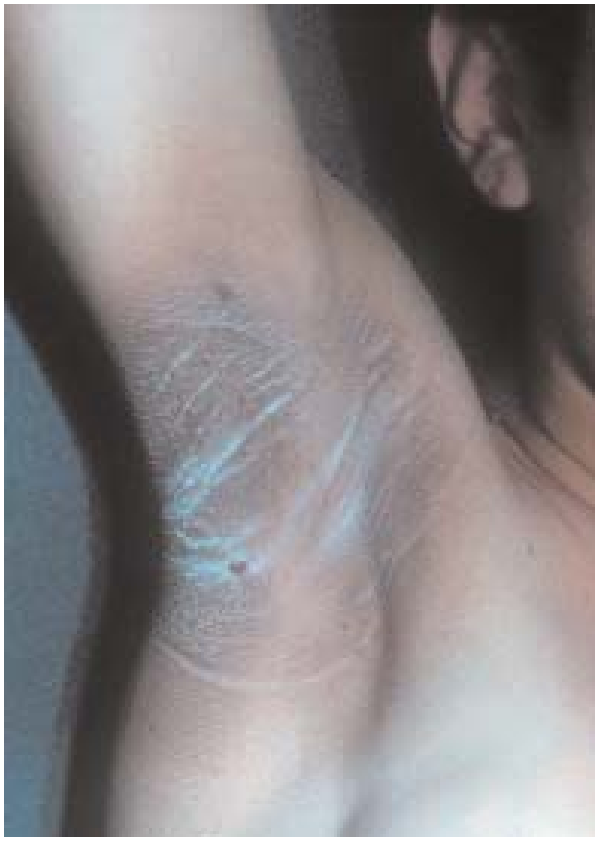

Fig. 1

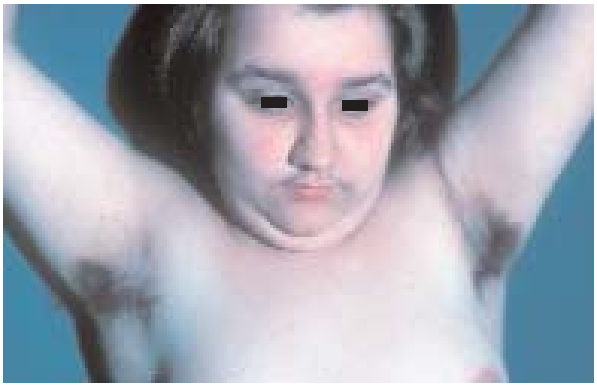

Fig. 2

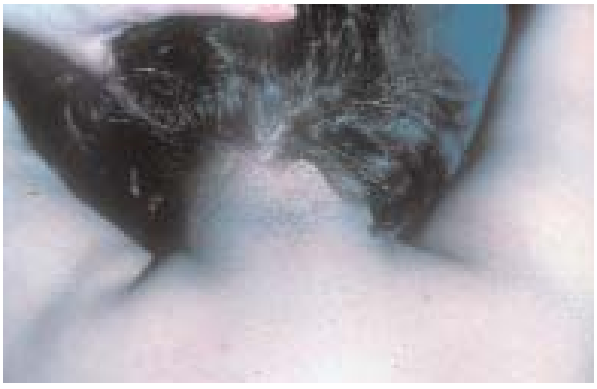

Fig. 3

Fig. 1, 2, 3: Clinical features of acanthosis nigricans on the armpit (Fig. 1). In Fig. 2 and 3 acanthosis nigricans associated to obesity in a 14-year-old girl. Notice the hypertrichosis of the upper lip.

and topical fusidic acid (22) and finally 8-mixed, characterized by 2 associated variants of AN (10).

Here is reported a case of AN associated to obesity, insulin resistance and hyperinsulinemia and its pathogenesis is discussed.

Case report

S.N., born on 1989, was first observed in autumn 2003 due to the presence of brownish lesions of the neck and armpits. She is 1.78 m tall and weighs 97 kg. She had the first menstruation at the age of 12 and her menstrual interval is very irregular. Her obesity is of the high type, mainly affecting shoulders, thorax and abdomen. There is slight hypertrichosis (Fig. 2) whereas there is not acromegaly, acne and enlargement of clitoris.

Routine laboratory examinations were within normal limits, included glycemia 98 mg/dl (n.v. 70-110), triglyceridemia 74 mg/dl (n.v. 0-150) and cholesterolemia 159 mg/dl (n.v. <220). Plasma androgens and markers of malignancy were within normal limits. Insulinemia at fasting is 69 mU/ml (n.v. 4-19).

Pelvic ultrasonography showed an anteverted and bended uterus and micropolycystic ovary bilaterally.

Dietary control and metformin hydrochloride 1g daily, then increased to 1g twice a day were associated to topical keratolytic drugs, leading to significant improvement of the lesions.

Discussion

Insulin carries on its activity through its receptor located on the plasma membrane. When insulin links to its receptor, the complex receptor-insulin enters the cytoplasm. Then the receptor is recycled and goes back to the plasma membrane or it is degraded. This complex process may go wrong at various levels and lead to insulin resistance. The latter may be prereceptor -for instance due to antiinsulin antibodies-, receptor -for instance due to reduced number of receptors- or postreceptor -for instance due to abnormal transduction of signals or reduced sensitivity of the peripheral tissues to insulin, as observed in obesity-. The insulin resistance associated to obesity is probably initially due to a reduced number of receptors, but later on a postreceptor defect occurs (18). The insulin resistance and the consequent hyperinsulinemia are associated to AN in the male, to AN and hyperandrogenemia in the female (12, 21). AN is related to increased level of plasma insulin. The latter can bind to insulin-like receptors functioning as growth factors (9). High insulin concentrations could activate these receptors and be responsible for the proliferations of keratinocytes and fibroblasts occurring in acanthosis nigricans.

Hyperinsulinemia is also responsible for hyperandrogenemia, by stimulating the ovary production of androgens (1). The latter occurs only in presence of LH and thus it occurs only in females after puberty (9). Hyperandrogenemia can manifest itself after puberty with hirsutism, acne, oligomenorrhea or amenorrhea, enlargement of clitoris and androgenic alopecia.

Obesity associated to insulin resistance in females is of high type, affecting shoulders, thorax and abdomen rather than thighs and buttocks (7).

The treatment of acanthosis nigricans associated to obesity does not require insulin because most affected subjects have not diabetes mellitus. The reduction of weight can really improve acanthosis nigricans, but is not easily obtained, also because of the scarce clinical evidence of AN in these subjects. Retinoids, both topical and oral, temporarily improve AN (16) as well as calcipotriol and keratolytic drugs.

Oral metformin hydrochloride is a first choice drug in the treatment of AN associated to obesity and insulin resistance. This biguanide drug increases both the peripheral response to insulin and the cellular glucose metabolism. Moreover, it decreases the delayed glucose intestinal absorption and inhibits hepatic glucogenesis. Metformin does not induce hypoglycemia but prevents hyperglicemia. Its mechanism of action is probably related to an increased activity of insulin level with the peripheral tissues. Metformin is absorbed in the enteron, is not

metabolized and excreted unchanged with urine with a half-life of 1.3-4.5 hours. The maximum dose useful is 3 g a day in 3 refracted doses, which should be taken during meals. Its side effects consist of intestinal problems and can be reduced by taking the drug during meals and in low initial dose to be increased gradually.

In conclusion, after having diagnosed acanthosis nigricans, physicians should try to clarify its causes. When diagnosing the most frequent variant associated to obesity and insulin resistance, a weight reduction of the patient should be the goal of treatment. In the mean time oral metformin hydrochloride at increasing doses can be useful. Symptomatic topical drugs such as keratolytics, retinoids and calcipotriol can be also useful.

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