

Do you know this syndrome?*

*Você conhece esta síndrome?**

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CASE REPORT

Female patient, 14, brown, from Felisburgo, state of Minas Gerais. She was seen due to complaint of velvety hyperchromic lesions in the cervical, inguinal, and axillary regions, begun at two years of age and recently worsened. She reported increased appetite and amenorrhea. She had a good school performance and denied having had previous diseases. The parents were distant cousins and there was no similar case in the family.

Acantosis Nigricans could be noted in the perioral, cervical, axillary, inguinal and antecubital regions (Figure 1). She also presented acromegaly and absence of Bichat fat (Figure 2), axial and limb muscular hypertrophy, hepatomegaly and notable scarcity of subcuta-



FIGURE 1:
Acantosis
Nigricans in
the axilla

neous tissue (Figure 3), except in hands and feet. The breasts were hypotrophic due to the lack of fat, and the clitoris was salient (Figure 3). She weighed 45 kg and was 1.56 m tall.

Laboratory tests showed increased blood sugar (125 mg/dl), triglycerides (537mg/dl), aminotransferases (AST 69u/L; ALT 112u/L), gamma-GT (113 u/L, reference values 12-43u/L), insulinemia (48,6μU/ml; reference values 2-27μU/ml). Hemogram, ionogram, alkaline phosphatase, total and fractioned cholesterol, kidney and thyroid function, urinalysis, dehydroepiandrosterone sulphate, testosterone, prolactin, GH, LH, and FSH were all within normal ranges.

The abdominal ultrasound showed liver enlargement with steatosis and colecystolithiasis. ECG showed indirect signs of hypertrophy of the left ventricle. Thoracical and long bone X-rays displayed no abnormality and neither did the echodopplercardiogram.

A restrictive diet for fats and sugars was prescribed. She developed diabetes mellitus, and insulin therapy was initiated. Later glibenclamide was introduced, without control of the clinical picture. Aminotransferases were still high.

The Acantosis Nigricans was treated with urea cream and salicylic acid, with partial improvement. Yellowish papular lesions appeared on upper limbs, and the histological test confirmed the clinical suspicion of eruptive xanthoma (Figure 4).

The patient also presented albuminuria, glycosuria, hematuria, and systemic high blood pressure, controlled by hyposodium diet.

Multidisciplinary follow-up was interrupted after one year by the patient's own initiative.

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Conflict of interests: None

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FIGURE 2:
Mentum
salience
(acromegaly);
absence of
Bichat fat

WHAT IS THIS SYNDROME?

Berardinelli-Seip Syndrome

Lipodystrophies comprise a group of congenital or acquired disorders characterized by partial or nearly total loss of adipose tissue.

Congenital generalized lipodystrophy, known as Berardinelli-Seip Syndrome, of an autosomic regressive inheritance, is characterized by scarcity of adipose tissue seen already at birth or

early childhood.¹⁻⁴ The genetic defect probably results in the bad development of metabolically active adipose tissue.^{5,6} Adipose tissue is scarce in most subcutaneous areas, in the abdomen, thorax, bone marrow and malar region.^{3,5,7} It is found to be normal in the palms of hands, soles of the feet and other sites that have a mechanical function.^{5,7}

Hyperlipidemia is an almost constant finding and it may lead to xanthomatosis.³

Serum leptin, an important hormone for energy homeostasis, is low, thus contributing to the occurrence of insulin resistance and other metabolic abnormalities.⁸⁻¹⁰

Carbohydrate metabolism disorders are probably a result of the limited capacity of its storage as fat. Carbohydrate surplus leads to hyperinsulinemia and intense anabolism, and glycemia may be kept at normal levels. However, peripheral insulin resistance is likely to be observed since childhood.³

Affected individuals generally present accelerated linear growth, excessive appetite, advanced bone age in childhood, acromegaly and muscular hypertrophy.^{3,8}

More serious lipid and carbohydrate metabolism normally does not occur until puberty, due to the protecting effect of the growth speed.³ With the end of growth in stature, dyslipidemia becomes more serious and diabetes mellitus is manifested.^{3,11}

As a consequence of hyperinsulinemia, Acantosis Nigricans develops.³ Steatosis occurs with hepatomegaly, which may progress to steatohepatitis and cirrhosis.³ Women may show clitoris enlarge-



FIGURE 3:
Muscle
hypertro-
phy, scarcity
of subcuta-
neous tis-
sue,
hypotrophic
mammae,
salient cli-
toris



FIGURE 4:
Elbow xan-
thomas

ment, hirsutism, polycystic ovaries and reduced fertility. Men are likely to maintain normal reproductive potential.^{3,8} Mammary gland tissue is well developed, but there is a scarcity of subcutaneous tissue around the mammae.⁵

Systemic hypertension and myocardial hypertrophy are common.^{12,13} Neurological disorders may also be reported,⁴ as well as bone disorders.¹⁴

As for treatment, there is no diet able to revert lipodystrophy, even though fat and carbohydrate restriction is fundamental.³

Fibrates and statins may be attempted in order to control hypertriglyceridemia.⁹

Normally, insulin use does not allow for adequate glycemic control. Tiazolydinediones seem to be the most effective therapy, even though they are not

ideal.⁹ Metformin may be tried.⁹ In a recent study, leptin-replacement therapy resulted in an improvement of metabolic and glycemia control.⁹ In the case reported, glibenclamide was the choice of endocrinology due to the alteration of liver enzymes, which, theoretically, would constitute a contraindication for the use of metformin.

The treatment of Acanthosis Nigricans and xanthomas requires the crucial control of triggering factors, such as hyperinsulinemia and dyslipidemia.

The case reported reinforces the importance of the knowledge of lipodystrophies by the dermatologist, who may be sought initially because of the presence of skin changes from which one can reach the diagnostic of metabolic syndromes with major systemic affection. □

Abstract: Congenital generalized lipodystrophy (Berardinelli-Seip syndrome) is a recessive autosomal disease characterized by absence of subcutaneous tissue. The fat tissue absence leads to metabolic dysfunction of lipids and carbohydrates, peripheral insulin resistance and increased serum levels of triglycerides and also a higher metabolic rate. Other findings are acanthosis nigricans, acromegaly, hepatomegaly and muscular, bony, cardiovascular and neurological abnormalities. A case of a patient with this syndrome is reported, whose diagnosis was made in a dermatology ambulatory.

Keywords: Acanthosis nigricans; Acromegaly; Hyperinsulinism; Hypertriglyceridemia; Insulin resistance; Lipodystrophy

Resumo: A lipodistrofia generalizada congênita (síndrome de Berardinelli-Seip), doença autossômica recessiva, caracteriza-se por escassez do tecido subcutâneo. A falta de tecido adiposo propicia disfunção metabólica dos lipídeos e carboidratos, resistência periférica à insulina, hipertrigliceridemia e hipermetabolismo. Outros achados são acantose nigricante, acromegalia, hepatomegalia e alterações musculares, ósseas, cardiovasculares e neurológicas. Relata-se o caso de paciente com essa síndrome, cujo diagnóstico foi realizado em um serviço de dermatologia.

Palavras-chave: Acantose nigricans; Acromegalia; Hiperinsulinismo; Hipertrigliceridemia; Lipodistrofia; Resistência à insulina

REFERENCES

1. Magré J, Delépine M, Khallouf E, Gedde-Dahl T Jr, Van Maldergem L, Sobel E, et al. Identification of the gene altered in Berardinelli-Seip congenital lipodystrophy on chromosome 11q13. *Nat Genet.* 2001;28:365-70.
2. Berardinelli W. An undiagnosed endocrinometabolic syndrome: report of 2 cases. *J Clin Endocrinol Metab.* 1954;14:193-204
3. Seip M, Trygstad O. Generalized lipodystrophy, congenital and acquired (lipoatrophy). *Acta Paediatr Suppl.* 1996;413:2-28
4. Das GP, Mehta L. Seip-Berardinelli syndrome. *Indian J Pediatr.* 1991;58:551-3
5. Garg A, Fleckenstein JL, Peshock RM, Grundy SM. Peculiar distribution of adipose tissue in patients with congenital generalized lipodystrophy. *J Clin Endocrinol Metab.* 1992;75:358-61.
6. Klaus S. Functional differentiation of white and brown adipocytes. *Bioessays.* 1997;19:215-23.
7. Chandalia M, Garg A, Vuitch F, Nizzi F. Postmortem findings in congenital generalized lipodystrophy. *J Clin Endocrinol Metab.* 1995;80:3077-81.
8. Garg A, Wilson R, Barnes R, Arioglu E, Zaidi Z, Gurakan F, et al. A gene for congenital generalized lipodystrophy maps to human chromosome 9q34. *J Clin Endocrinol Metab.* 1999;84:3390-4.
9. Oral EA, Simha V, Ruiz E, Andewelt A, Premkumar A, Snell P, et al. Leptin-replacement therapy for lipodystrophy. *N Engl J Med.* 2002;346:570-6.
10. Pardini VC, Victória IMN, Rocha SMV, Andrade DG, Rocha AM, Pieroni FB, et al. Leptin levels, beta-cell function, and insulin sensitivity in families with congenital and acquired generalized lipodystrophy. *J Clin Endocrinol Metab.* 1998;83:503-8.
11. Sovik O, Vestergaard H, Trygstad O, Pedersen O. Studies of insulin resistance in congenital generalized lipodystrophy. *Acta Paediatr Suppl.* 1996;413:29-38.
12. Viégas RFL, Diniz RVZ, Viégas TMRF, Filho EBL, Almeida DR. Envolvimento cardíaco na lipodistrofia total generalizada (Síndrome de Berardinelli-Seip). *Arq Bras Cardiol.* 2000;75:243-8.
13. Bjørnstad BG, Foerster A, Ihlen H. Cardiac findings in generalized lipodystrophy. *Acta Paediatr Suppl.* 1996;413:39-43
14. Westvik J. Radiological features in generalized lipodystrophy. *Acta Paediatr Suppl.* 1996;413:44-51.

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