

Berardinelli syndrome. A case report with fatal outcome.

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Key words: Berardinelli syndrome, congenital generalized lipodystrophy, insulin resistance.

Abstract. The aim of this paper is to present the main clinical findings and evolution of a fatal case of Berardinelli Syndrome (congenital generalized lipodystrophy). A 15-year-old girl, followed since the age of three months in the Genetic outpatients' clinic, developed insulin resistance when she was eight years old. She had hyperchloremic metabolic acidosis, bilateral retinopathy, proteinuria and hydronephrosis. She was hospitalized several times due to urinary infections. In her last admission she had fever, abdominal pain and was diagnosed urinary sepsis. She presented hemodynamic instability and died, despite all therapeutic measures adopted. Considering the rarity of this syndrome it is important to describe the clinical presentation and evolution of this patient with Berardinelli Syndrome, which developed renal dysfunction and had a fatal outcome.

Síndrome de Berardinelli. Reporte de un caso con evolución fatal.

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Palabras clave: Síndrome de Berardinelli, lipodistrofia congénita generalizada, resistencia insulínica.

Resumen. El objetivo de este trabajo fue relatar las principales manifestaciones observadas en un caso de evolución fatal de Síndrome de Berardinelli (Lipodistrofia congénita generalizada). Una niña de 15 años, con seguimiento clínico desde los tres meses de edad en el Servicio de Genética, desarrolló resistencia insulínica cuando tenía ocho años de edad. Presentaba además acidosis metabólica hiperclorémica, retinopatía bilateral, proteinuria e hidrone-

frosis. Había sido hospitalizada varias veces debido a infecciones urinarias a repetición. En su última hospitalización presentó sepsis urinaria. Evolucionó con inestabilidad hemodinámica y falleció, a pesar de todas las medidas terapéuticas adoptadas. Considerando la poca frecuencia de este síndrome se hace importante el reporte de la presentación clínica y de la evolución de esta paciente con Síndrome de Berardinelli, que desarrolló disfunción renal y tuvo una evolución fatal.

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INTRODUCTION

Congenital generalized lipodystrophy is a rare autosomic recessive disorder characterized by the absence of adipose tissue and insulin resistance (1-3). It was first described in Brazil in 1954 by Berardinelli and further characterized by Seip, being subsequently named Berardinelli-Seip Syndrome (4, 5).

The prevalence is less than one case per 12 million individuals. There are approximately 250 cases registered all over the world and it is more frequent in some ethnic groups, mainly in Latin Americans and Arabians (individuals of Portuguese and Norwegian ancestry) (1-3, 6, 7).

The main manifestations of this syndrome are generalized lipodystrophy, muscle hypertrophy, acanthosis nigricans, psychomotor and mental retardation, insulin resistance, variable degrees of hyperinsulinemia, hepatomegaly, splenomegaly, hypertrophic cardiomyopathy, hirsutism, acromegaly and hypertriglyceridemia (6-8). Renal involvement and an adverse outcome, which were seen in the case presented here, are not common. Considering the rarity of this syndrome it is important to describe the clinical presentation and evolution of a patient with Berardinelli Syndrome.

CASE REPORT

After an authorization was given by the parents of the patient, we report a fatal

case of Berardinelli Syndrome. A 15-year-old girl was followed in the Genetic outpatients' clinic with initial diagnosis of Leprechaunism Syndrome due to muscle atrophy since the age of three months. She had psychomotor retardation and hepatomegaly, associated with cutaneous lesions (erythematous-descamative lesions in her elbows and knees), with diagnosis of Psoriasis. At five years of age she presented the bone age of an eight-year-old. At the age of eight, she developed insulin resistance, hyperglycemia (fasting plasma glucose 332mg/dL), and hypertriglyceridemia (270mg/dL), requiring insulin therapy. Thyroid hormones were normal. Anti-insulin, antimicrosomal and anti-thyroglobulin antibodies were negative. The echocardiogram was normal. She was diagnosed as having Berardinelli Syndrome. She had a characteristic phenotype, with lipodystrophy affecting both trunk and limbs, prognatism, salient orbital ridges, enlarged hands and feet and muscular hypertrophy (Fig. 1).

She presented, at the age of 11, a 24h proteinuria of 178 mg, in the occasion of an episode of urinary infection, which was successfully treated with antibiotics. The proteinuria increased to 582mg/24h in the year after. The ultrasonography showed hepatic steatosis, splenomegaly and signs of nephropathy (hidronephrosis and severe pyelocaliectasis). She also had anemia (Hb 6 g/dL) and thrombocytopenia (80,000-90,000/mm³), but the myelogram was normal. She had in that occasion, another uri-



Fig. 1. Patient with Berardinelli-Seip Syndrome (Congenital generalized lipodystrophy).

nary infection, which also remitted after administration of the appropriate antibiotics. The urine culture did not isolate any pathogen. Hemoculture was also negative. At the age of 14, she had oligomenorrhea.

Two years later, she was hospitalized with pyelonephritis. The urinalysis showed proteinuria (2+), glycosuria (+), leukocyturia (10 cells per high power field) and hemoglobinuria (3+). She had urea 54mg/dL and creatinine 1.2mg/dL. The computed tomography showed enlargement of the left kidney, with low excretion of contrast. The excretory urography showed exclusion of the left kidney and a right megaureter. A severe diabetic proliferative retinopathy was also diagnosed in the occasion.

One year later she presented proteinuria (3+), glycosuria (1+) and hemoglobinuria (1+). The miccional uretro-cystography showed bilateral vesico-ureteral reflux. The urodynamic study showed a flacid neurogenic bladder (autonomic neuropathy).

Laboratory tests showed: creatinine 1.7mg/dL; urea 127mg/dL; K 6.8mEq/L; Albumin 2.8g/dL; AST 23UI/L, ALT 24UI/L; Hb 5.8g/dL; Ht 17.4%; white blood cells 6850/mm³ (neutrophils 4790/mm³,

eosinophils 342/mm³, basophils 137/mm³, lymphocytes 1451/mm³, monocytes 130/mm³); Platelets 168000/mm³. She was on insulin and captopril.

Seven months later she was re-hospitalized with fever, abdominal pain and increased abdominal volume. She was with tachycardia (124bpm) and had signs of peritonitis. A nephrostomy was performed and urinary sepsis diagnosed. She presented, in the post-surgery period, hemodynamic instability and died despite all therapeutic measures adopted.

DISCUSSION

Berardinelli Syndrome is an autosomic recessive disease, with mutation in the gene which codifies the AGPAC II protein, in the chromosome 9 (9q34), and in the *SEIPIN* gene, which codifies the seipin protein, in the chromosome 11q13 (1, 8). The disease was described in all ethnic groups, but it is more frequent in Portuguese and Norwegian descendents (1). The patient showed here had Portuguese ancestry, as have the majority of the Brazilian population. Her parents were not consanguineous. Genetic counseling is very important in these cases, considering the risk of

recurrence and the importance of prenatal diagnosis.

The patient presented here was diagnosed as having Berardinelli Syndrome when she was eight years old. She presented all major diagnostic criteria and two minor criteria for the syndrome. These criteria are summarized in Table 1. Enlarged extremities, loss of adipose tissue, accelerated growth, increase in food intake, advanced bone age, achantosis nigricans, mental retardation, hyperinsulinemia and hypertriglyceridemia are characteristics of this syndrome (2, 3, 6, 9). Enlarged extremities (hands, feet) were observed in our patient, giving her an acromegalic appearance. The occurrence of achantosis nigricans can be due to insulin resistance (2, 3, 6, 9). Differential diagnosis in the infant include: short syndrome, neonatal progeroid syndrome, neurometabolic lysosomal storage disorder (Gaucher type 2, Krabbe disease), Russell diencephalic syndrome; in older children, Dunningan lipodystrophy, Rabson-Mendenhall syndrome, insulin-dependent diabetes mellitus; and in adults, Barraquer-Simons syndrome, AIDS, partial lipodystrophy and Lawrence syndrome (9).

The morphologic and functional study of the muscles in these patients suggests that the increase in muscle mass results from hyperplasia, and not from hypertrophy (2). Hepatomegaly can be observed since childhood and is caused by steatosis. Hepatic function is usually normal. Some patients develop cirrhosis in adult life (6). Dyslipidemia is also common, and is characterized by increase in triglycerides and decrease in HDL (2, 8). Our patient had hepatomegaly and hypertriglyceridemia diagnosed in childhood.

The carbohydrate metabolism is characterized by peripheric insulin resistance, associated with hyperinsulinemia, which results in secondary diabetes mellitus. The course of diabetes among women with

TABLE I
DIAGNOSTIC CRITERIA FOR BERARDINELLI SYNDROME

Major
Lipoatrophy affecting both trunk and limbs, giving an athletic appearance
Acromegaloid features (prognatism, salient orbital ridges, enlarged hands and feet and others)
Hepatomegaly
Elevated serum concentration of triglycerides
Insulin Resistance
Minor
Hypertrophic cardiomyopathy
Psychomotor or mental retardation
Hirsutism
Precocious puberty
Bone cysts

Adapted from Van Maldergem (9).

Berardinelli Syndrome may be dramatic when combined with early complications (retinopathy, nephropathy and cardiovascular events). These patients presents resistance to insulin and to oral antihyperglycemic drugs (2, 10).

Hypertrophic cardiomyopathy can be an expression of insulin action in cardiac receptors of IGF-1. The occurrence of myocardial hypertrophy is frequent in children from diabetic women and in patients with Beckwith-Wiedemann Syndrome (11). In the present case, it was not identified any abnormality with an echocardiogram.

Some kinds of nephropathies can be seen in Berardinelli Syndrome and are mainly due to complications of anabolic processes, diabetes or hyperlipidemia. Our patient presented proteinuria and had sings of chronic kidney disease, developing urinary sepsis. She initially presented microalbuminuria (proteinuria < 300 mg/

24 h) and later developed proteinuria. She did not have hypertension. In a recent study by Javor et al (12), which included 25 patients with generalized lipodystrophy, aged 8 to 67 years, it was observed elevated urine albumin excretion in 22 cases (88%), macroalbuminuria (> 300 mg/24 h) in 15 (60%), and nephrotic range proteinuria (> 3500 mg/24 h) in 5 (20%). Twenty-three (92%) had elevated creatinine clearance (> 125 mL/min/1.73 m²). Renal biopsy findings were remarkable for focal segmental glomerulosclerosis in 4 patients, membranoproliferative glomerulonephritis in 2, and diabetic nephropathy in 1 case. The authors concluded that generalized lipodystrophy is associated with proteinuria and unique renal pathologies, including focal segmental glomerulosclerosis and membranoproliferative glomerulonephritis. The majority of patients treated with recombinant leptin demonstrated reduction in proteinuria and hyperfiltration (12).

Patients with Berardinelli Syndrome must have a multidisciplinary follow-up. They should consume a low-fat diet, with reduction of saturated, trans fats and cholesterol intake. It is also important to practice daily physical activity (6).

The present case reinforces the importance of recognizing lipodystrophies by physicians of different specialties. Berardinelli Syndrome is a rare disease which causes important metabolic abnormalities, which can complicate and have a fatal outcome if optimal therapeutic and preventive measures are not adopted.

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