BERARDINELLI-SEIP CONGENITAL LIPODYSTROPHY IN A 5-YEAR-OLD GIRL

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Abbreviation **BSCL** = Berardinelli-Seip congenital lipodystrophy..

Case report. A 5-year-old girl presented to the dermatology clinic with dark, thickened skin on her face, neck, and extremities from the age of 1 year. The little girl, the firstborn of 3rd degree consanguineous parents, was born full term with a normal vaginal birth. There were no similar cases in the family and there was no significant prenatal, perinatal and postnatal history. However, the child had a history of voracious appetite and mild mental retardation.

Physical examination showed gray-black coloration and velvety texture of the skin involving all folds, the gluteal region, the umbilical area, but sparing the external genitalia. There was acromegaloid facies with thickened lower lip (Fig. 1), generalized decrease in subcutaneous fat with prominent muscles and subcutaneous veins, enlarged joints of hands and feet; there was also hypertrophy of the labia majora (Fig. 2) and the clitoris.

The evaluation of the other organs highlighted a protruding abdomen (Fig. 3) with hepatosplenomegaly, while the cardiovascular and respiratory systems were normal and there were no neurological signs.

Laboratory tests showed hemoglobin 8.9 gm/dl (nv 12-16); liver function tests showed AST 52 U/L (nv ≤ 40), ALT 60 U/L (nv ≤ 45) with an albumin/ globulin of 0.9:1. The serum lipid profile showed hypertriglyceridemia (321.61 mg/dl; nv 40-150), VLDL 64.32 mg/dl (nv 2-30), HDL 17.24 mg/dl (nv 35-80); total cholesterol/HDL cholesterol ratio increased to 5.9 (nv ≤ 5). Her glycemic profile showed random blood sugar levels of 130 mg/dl with glycosylated hemoglobin of 8.6% (vnv ≤ 5.6%). Ketone bodies were absent in the urine. Abdominal ultrasound showed moderate hepatomegaly with early alteration of the liver parenchyma and moderate splenomegaly. Serum electrolytes were within normal limits. It was not possible to perform genetic analysis of the patient.

Our patient fulfilled 4 major and 1 minor criteria of BSCL, indicating the diagnosis of Berardinelli-Seip congenital lipodystrophy.

Discussion. Berardinelli reported 2 cases of Berardinelli-Seip congenital lipodystrophy (BSCL) in 1954 and Seip reported another 3 in 1959 (3). BSCL is a rare autosomal recessive disease and affects all ethnicities (2). It is usually diagnosed at birth or in early childhood. BSCL is characterized by the almost absence of adipose tissue and visible hypertrophy of muscle tissue. Over one hundred cases have been reported in world literature (4). The prevalence of this condition is estimated to be less than 1 per 10 million inhabitants (5).

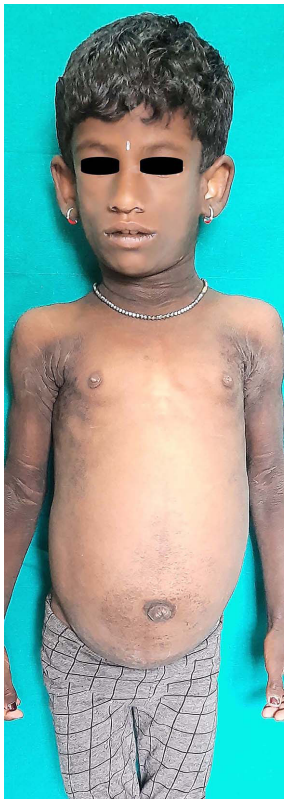

Fig. 1

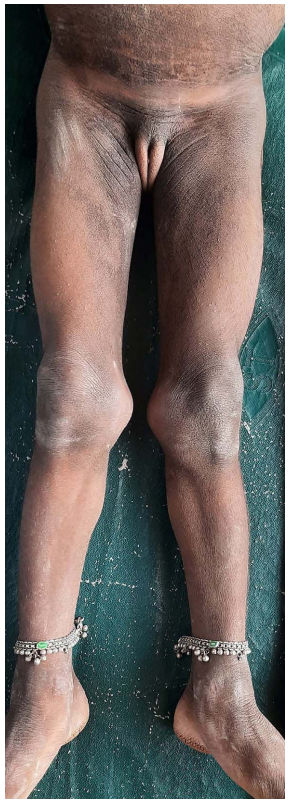

Fig. 2

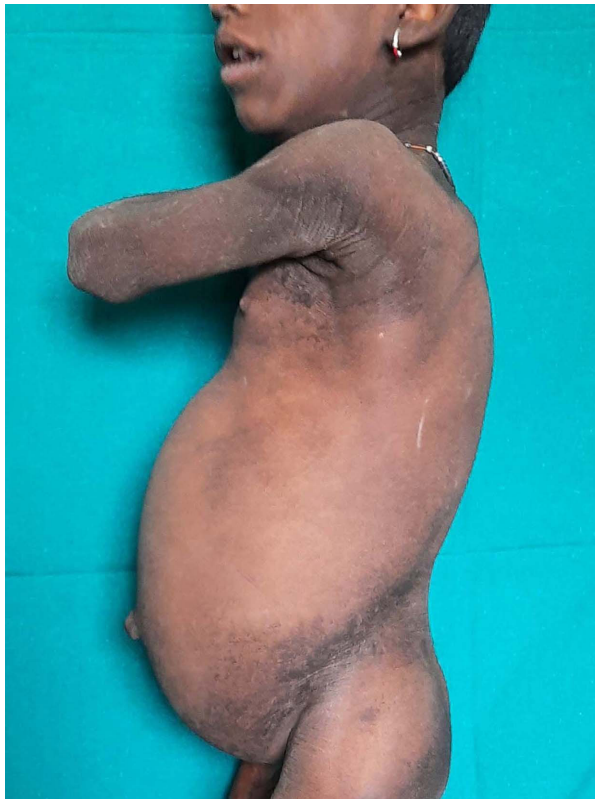

Fig. 3

Fig. 1, 2, 3: Berardinelli-Seip syndrome: acanthosis nigricans of the neck, axillae and cubital cavities; acromegaloid facies with prognathism (Fig. 1). In Fig. 2 acanthosis nigricans of the inguinal folds with sparing of the external genitalia. In Fig. 3 generalized lipoatrophy, evident muscles and protruding abdomen.

This disease is caused by the mutation of *AGPAT2* located on chromosome 9q34 in the type 1 variant or of *BSCL-2* located on chromosome 11q13 in the type 2 variant (6, 7). The AGPAT2 protein belongs to the acyltransferase family and catalyzes an essential reaction in the biosynthetic pathway of glycerophospholipids and triacylglycerols in eukaryotes (6). Patients with BSCL have elevated levels of circulating triglycerides and develop ectopic fat deposits that lead to severe complications early in life (8). In type 1 disease there is complete loss of metabolically active adipose tissue of the subcutaneous, intra-abdominal, intra-thoracic and bone marrow areas, with well-preserved mechanical adipose tissue under the scalp, in the retro-orbital, peri-articular, and palmar-plantar region, palms. In type - 2 disease, loss of both types of adipose tissue occurs (5).

Clinical features include acanthosis nigricans manifesting as symmetrical gray-brown or blackish pigmentation and velvety skin texture on the neck, folds, and around the navel. Acromegaloid features are present including prognathism, salient orbital ridges, enlarged hands and feet, macrogenitosomia, gigantism, and muscle hypertrophy. Muscle hypertrophy is present from birth and leads to increased production of muscle glycogen and creatinine (2). Our patient presented with acanthosis nigricans involving all folds, acromegaloid facies, lipoatrophy with muscle hypertrophy, enlarged hands and feet.

Liver abnormalities in BSCL include abnormal liver function tests, hepatomegaly, hepatic steatosis, and cirrhosis. Hepatomegaly is usually associated with splenomegaly (9). Mental retardation, diabetes mellitus, and insulin resistance generally manifest around 12 years of age, with the development of

ketosis-resistant diabetes mellitus, associated with hypermetabolism and increased appetite (5). In our case, hepatoslenomegaly with abdominal distension and diabetes mellitus were observed.

Cardiac abnormalities include hypertrophic cardiomyopathy, ventricular dysfunction leading to congestive heart failure, and cardiomegaly. This is due to the high levels of IGF-1 and the high concentration of IGF-1 receptors on the myocardial tissue or to the direct effect of the mutant gene (1). No cardiac abnormalities were detected in our patient.

Other features include polycystic ovary disease, hirsutism, oligomenorrhea (1), increased size of penis, clitoris, and labia majora secondary to hyperandrogenism (6), curly and kinky hair, hyperhidrosis, xanthomas, umbilical hernia, pancreatic disease, mental retardation (2) immunodeficiency (12). In our patient, enlarged clitoris and labia majora were observed; there was no evidence of pancreatic disease or umbilical hernia.

BSCL is diagnosed based on the presence of three major criteria or two major and two or more minor criteria (2). Major criteria – lipoatrophy, acromegaloid features, hepatomegaly, elevated serum triglycerides – and minor criteria – phlebomegaly – were the clues to diagnose our case.

BSCL should be differentiated from other congenital generalized lipodystrophies such as Rabson-Mendenhall syndrome: this syndrome presents clinical features similar to BSCL such as acanthosis nigricans, lack of subcutaneous fat, enlargement of the genitals; however, patients with BSCL have more severe liver disease and hyperlipidemia (12, 13); furthermore, ketoacidosis is not observed in BSCL.

Mandibulacral dysplasia, in addition to lipodystrophy, presents mandibular and clavicular hypoplasia, acroosteolysis, delayed closure of the cranial suture, and joint contractures (14). In addition to lipodystrophy, Hutchinson-Gilford progeria presents premature aging, macrocephaly, alopecia, loss of eyebrows and eyelashes, and micrognathia (15).

Patients with BSCL should receive multidisciplinary treatment. Treatment is usually symptomatic and aims to delay the progression of the disease. Diet and exercise are important factors in the management of these patients. A low-fat diet with essential supplements like fish oil can help control acanthosis nigricans, hyperpigmentation, and hirsuitism (16). Metformin is the drug of choice, it helps in glucose metabolism, helps reduce appetite and improves symptoms of polycystic ovarian disease and hepatic steatosis (17).

Leptin treatment benefits non-diabetic patients, but with insulin resistance, hepatic steatosis and hypertriglyceridemia; it has also been shown to reduce triglyceride levels, increase insulin sensitivity and decrease liver volume, decrease appetite, reduce food intake and improve metabolic profile; it is also useful for eliminating or reducing dosages of antidiabetic drugs (18). Other treatment options include fibric acid derivatives, n-3 polyunsaturated fatty acids, and fish oil. Patients with BSCL should limit their diet to trans saturated fats and low in fat and cholesterol. Along with the therapies mentioned above, increasing physical activity is recommended (7). Patients with BSCL should be followed every 3-4 months with regular monitoring of blood sugars, lipid profile, liver function tests, abdominal echo, and echocardiogram.

Conclusion. We report this case because of its rarity and to alert physicians to the need for rigorous diabetes control in these patients.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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