Berardinelli Seip Congenital Lipodystrophy Syndrome: 10 Year Follow-up

Lipodystrophy syndromes are extremely rare disorders of deficient body fat associated with potentially serious metabolic complications. Here, we describe a 10-year-old girl with genetically proven Berardinelli Seip congenital generalized lipodystrophy type 2, diagnosed at 10 months of age. She developed comorbidities like proteinuria, hypertension, diabetes mellitus, and liver fibrosis.

Keywords: *Insulin resistance, Metabolic syndrome, Liver fibrosis*.

Berardinelli Seip Congenital Lipodystrophy (BSCL) is a rare autosomal recessive disorder characterized by generalized lack of adipose tissue, without nutritional deprivation or catabolism [1]. Diagnosis of lipodystrophy syndromes is based on clinical phenotype, and is confirmed by genetic testing.

A 10-month-old, developmentally normal female child born out of non- consanguineous union was brought with failure to gain weight since birth, abnormal facial features and excess generalized hair growth. She had no feeding difficulties or other systemic complaints and diet history revealed no calorie or protein deficit. She was born at term with low birth weight (2.25 kg).

The child had an emaciated appearance, hollowing of cheeks, prognathism, prominent supraorbital ridges, with a generalized lack of subcutaneous fat, more visible over buttocks, abdomen and extremities. She had prominent labia and generalized hypertrichosis. Anthropometric measures were weight 7.1 kg (-1.57 SDS), height 72 cm (0.01 SDS), head circumference 41.5 cm (-2.3 SDS) with a normal upper to lower segment ratio. She had a firm nontender hepatomegaly with a liver span of 8 cm. Other system examination was normal. There was no virilization or acanthosis. Her Fasting Blood sugar was 87 mg/dL, with Simultaneous Insulin of 4.6 m IU/mL. Hepatomegaly with normal echotexture was seen on ultrasonography (USG) abdomen. Both kidneys were of normal size. MRI Brain showed mild ventriculomegaly.

At 4.5 years, she had extensive acanthosis over all flexures along with prominent muscles and significant lack of subcutaneous fat. Her blood pressure and growth parameters were normal, and she had no signs of virilisation or puberty. Liver span was 11 cm with a palpable left lobe of the liver. Investigations revealed impaired fasting glucose (102 mg/dL) and post prandial glucose (188 mg/dL) with a simultaneous serum insulin of 106 mIU/mL (Normal: 2-25) and >300 mIU/mL (Normal:12-82), respectively. Fasting lipid profile revealed raised triglycerides of 257 mg/dL (Normal:30-110), low HDL (16 mg/dL) and normal cholesterol (122 mg/dL) and LDL (54.6 mg/dL). Her liver enzymes were marginally elevated SGOT 65U/L, SGPT 74U/L. Two-dimensional echocardiography and ophthalmologic examination were normal. Her bone age was advanced (6.5 years). USG abdomen revealed B/L raised renal cortical echogenicity. She was advised a low fat, low calorie diet.

A preliminary diagnosis of Congenital Generalized Lipodystrophy was made based on her clinical picture. A Next-generation sequencing (NGS) panel (Illumina TruSight One), consisting of >4800 genes was run on DNA extracted from peripheral blood, using the Illumina MiSeq platform. Bioinformatic analysis was carried out on the *AGPAT2* and *BSCL2* genes which are known to be associated with Berardinelli-Seip congenital lipodystrophy. There was presence of a homozygous 11 bp deletion (produces a shift in the translational reading frame and is predicted to result in nonsense mediated decay) in exon 6 of the BSCL2 gene, classified as pathogenic for the syndrome.

At the age of 9 years, she was noted to have extensive acanthosis (***Fig.* 1**), persistent stage 2 hypertension and hyperglycemia – both fasting and postprandial, with an HbA1c of 11.6%. She had no signs of puberty. USG showed a prepubertal uterus with ovarian volumes being 0.3 mL and 0.5 mL with no cysts/follicles. FSH was 0.32 µIU/mL, LH below 0.09 µIU/mL, estradiol below 10 pg/mL. Her serum leptin levels were in the normal range, 8.7 ng/mL (3.7-11.1).

Coarse liver parenchymal echotexture with mild fibrosis, moderate splenomegaly, and bilateral bulky kidneys with mild increase in parenchymal echogenicity were identified on USG. Portal vein and Renal artery doppler was normal. She had developed significant proteinuria (440 µg/mg of creatinine).

She was started on Basal Bolus Insulin regimen with Glargine and Regular Insulin along with oral Metformin, and Enalapril for hypertension.

At her last follow-up at 9 year 10 months of age, her weight was 28.7 kg (-0.52 SDS); height 135.4 cm (-0.38 SDS)

FIG. 1 *Clinical Photograph showing generalized lipodystrophy and extensive acanthosis nigricans.*

with BMI of 15.7 kg/m^2 (-0.47 SDS). She was still pre-pubertal and had normal intellect. She is now normotensive on Enalapril 2.5 mg OD. Her HbA1c has decreased to 7.4%. She is requiring basal insulin (Glargine 0.4 U/kg/day) along with Metformin (1 g/day) for blood glucose control. Her fasting lipid profile and liver profile were normal. Her platelet count was low at 70,000/µl attributed to hypersplenism, but had no bleeding tendencies. She still had proteinuria (211.3 µg/mg of creatinine) (Normal <30) which had decreased since last visit.

BSCL demonstrates lack of metabolically active adipose tissue within most subcutaneous, intermuscular, bone marrow, intra-abdominal, and intrathoracic sites. However, mechanical adipose tissue in palms, soles, orbits, scalp, and periarticular regions is absent in BSCL2 but not in BSCL1 [2]. BSCL2 is the more severe form of the disease with onset in the neonatal period or early infancy, as was in our child. To date, >12 mutations in the *BSCL2* gene have been identified. However, there is no obvious correlation between mutation severity and phenotype severity [3].

An environment of severe insulin resistance is created by organ infiltration with lipid cells, and this serves as a predecessor to dysglycemia, dyslipidemia, hypertension, and polycystic ovarian syndrome (PCOS) in women [4]. Patients with the early-onset hyperinsulinemia in combination with congenital generalized lipodystrophy develop acromegaloid features, hypertrichosis and soft tissue hyperplasia. As a consequence of low body fat, serum adiponectin and leptin are low as well, leading to hyperphagia and worsening of insulin resistance. Despite this, initially, glucose and glycated hemoglobin can be normal at the expense of very high insulin. Diabetes usually starts at puberty; the mean age of onset in a large series was at 15 years, and arterial hypertension occurred in one-third of patients [5]. Elevations of liver enzymes is also an early finding and occurs due to fat deposition in the liver. Progressive reductions in serum platelets suggest worsening of the liver disease and probable cirrhosis. Index child had all of these features, except for low leptin levels and hyperphagia.

Current therapies prevent or ameliorate the comorbidities of lipodystrophy syndromes [5]. There is no cure for lipodystrophy and management is largely supportive.

Currently, metreleptin (recombinant human methionyl leptin) is the only drug approved specifically for lipodystrophy patients with documented low leptin levels [6]; though, limited by availability and cost. Being an autosomal recessive disorder, genetic counselling is an essential aspect of management.

Declaration of Patient Consent: The authors certify that they have obtained patient's assent and parental consent for her image and other clinical information to be reported in the journal.

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