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Case Report

Tale of Hairy Toddler with Masculine Appearance: Berardinelli-Seip Congenital Lipodystrophy Syndrome - A case Report

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Abstract

Berardinelli-Seip congenital lipodystrophy syndrome is an autosomal recessive metabolic disorder characterised by severe generalised lipodystrophy, insulin resistance and hypertriglyceridemia since early infancy. Here we report a boy presenting with generalised lack of adipose tissue, tall stature, muscular body habitus, penile hypertrophy, acanthosis nigricans, hypertrichosis and venous prominence. Diagnosis was made by clinical phenotype, biochemical abnormalities and genetic evaluation. Customised low-fat diet was given along with physical activities. This case report creates awareness regarding this rare metabolic syndrome as early recognition and customised medical therapy is essential to control and prevent the complications.

Introduction

Berardinelli-Seip congenital lipodystrophy (BSCL) is a rare autosomal recessive metabolic syndrome, with a prevalence of less than 1 in 12 million population.[1] Homozygous or compound heterozygous mutations of the AGPAT2, BSCL2, CAV1 and PTRF genes are responsible.[2,3] There is marked lipodystrophy seen either at birth or during early infancy, along with diabetes mellitus, hypertriglyceridemia, hepatic steatosis, acanthosis nigricans and muscular hypertrophy.[4] Treatment is primarily symptomatic. Early recognition is essential to ameliorate the complications. Near three hundred cases have been reported globally, but there is scarcity of data about this syndrome from south-east Asia. Considering the rarity and therapeutic challenges, we report this case of a toddler boy with BSCL presenting with early insulin resistance.

Case Report

A 16-months old toddler boy, first born, out of non-consanguineous marriage, was brought to our institute with the chief complaints of abnormal body habitus and excessive hair growth all over the body since six months of age. Mother also noticed patchy hyperpigmentation over acral areas and nape of neck since nine months of age. On examination, he had generalized absence of fat including buccal pad of fat. There were dysmorphic features such as triangular coarse face, abundant thick scalp hair, long fingers and toes, large hands and feet, prominent musculatures over face and limbs, prominent superficial veins over hands and feet (Figure 1). Patchy hyperpigmentation over nape of neck, axilla, excessive body hairs (sparing the face, axilla and pubic area) were found. In addition, enlargement of genitalia with a penile length of 6 cm (expected size according to Tanner stage 1 - penis of 3 cm or less) was present. His weight was 12 kg (between 0 to +2 standard deviation),

length was 94 cm (above +3 standard deviation) and head circumference was 46.5 cm (between -2 standard deviation to 0). Systemic examination revealed protuberant abdomen and firm hepatomegaly (4 cm below the right costal margin with span 11 cm) with a palpable left lobe.

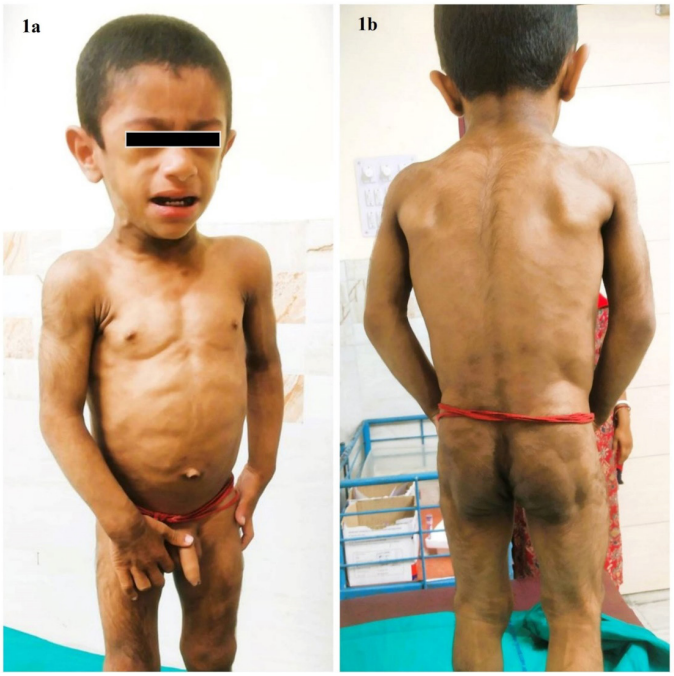

Figure 1: (a) Child with "hollow cheek" appearance, enlarged penis and protuberant abdomen. (b) back of child showing prominent musculature and hyperpigmentation over neck

Laboratory investigations revealed elevated liver enzymes with hypertriglyceridemia along with borderline high total cholesterol, high VLDL and low HDL [Table 1]. Abdominal ultrasound showed hepatomegaly with grade 2 fatty liver. Psychometric analysis revealed mild intellectual impairment. In view of the clinical findings and laboratory parameters, clinical diagnosis of BSCL syndrome was made. Whole exome sequencing (WES) showed probable compound heterozygous, likely pathogenic single nucleotide variant (SNV) involving exon 7 of the BSCL2 gene c.968G>A (p. Trp323Ter) and copy number variant (CNV) [chr:11_?62469928_?62470031_del] in BSCL-2 gene – consistent with our index phenotype.

He received proper nutritional counselling. Complex carbohydrates, plant proteins, animal proteins were advised. For a low-fat diet- skimmed / semi skimmed milk, cottage, curd cheese, low fat yoghurt, sunflower / olive oil was given. After six months follow up, child weighed 13.5 kg (between 0 to +2 standard deviation), height 99 cm (above +3 standard deviation) and head circumference 47.5 cm (between -2 standard deviation to 0). Biochemical parameters also improved [Table I]. Periodic screening for diabetes mellitus, dyslipidaemia and yearly echo-cardiography, liver ultrasonography has been planned. They have been counselled about the disease, risk of recurrence in subsequent pregnancies. Carrier testing for parents have been advised.

Table 1: Trends of laboratory parameters of child having Berardinelli-Seip congenital lipodystrophy

Parameter	At admission	6 months	Reference range
Total bilirubin	0.3	0.4	0.2 - 1 mg / dl
Serum protein	8.1	6.9	6.1 - 7.9 g / dl
Serum albumin	5.0	4.3	3.5 - 5 g / dl
ALT / AST / ALP	85 / 98 / 280	55 / 81 / 246	12 - 45 / 22 - 63 / 145 -230 U/L
PT / aPTT	12 / 30	11 / 32	10 – 13 / 24 - 36 (sec)
INR	0.9	1.0	
Urea / creatinine	20 / 0.3	24 / 0.4	20 - 40 / 0.03 - 0.50 mg / dl
FBS / PPBS	99 / 132	82 / 119	60 - 100 / < 140 mg / dl
HbA1c	5.7	5.2	4.8 - 5.9 %
Fasting insulin	15.9	13.2	0.00 - 28.4 uIU / ml
Serum triglyceride	282	253	High: > 100 mg /dl
Total cholesterol	171	162	High: > 200 mg / dl
HDL	27	23	Low: < 40 mg / dl
LDL	99	96	High: > 130 mg/ dl
VLDL	56.4	50.6	High: > 30 mg / dl
Cortisol (8.00 am)	18	-	5 - 23 mcg / dl
TSH / fT4	1.96 / 1.65	2.1/1.76	0.4- 4 uIU / ml / 0.8- 1.76 ng / dl
GH / IGF-1	2.47 / 65.9	-	0.01 - 3.00 / 14 - 193 ng / ml
LH / FSH	0.125 / 0.792	-	0.8 - 7.6 /0.7 - 11.1 mIU / ml

Discussion

BSCL was first described by W. Berardinelli from Brazil in 1954 and later confirmed by Seip from Norway in 1959. According to the order of discoveries for causative homozygous or compound heterozygous mutations of the AGPAT2, BSCL2, CAV1 and PTRF genes - four subtypes are called BSCL1,

BSCL2, BSCL3 and BSCL4 respectively. AGPAT2, BSCL2 mutations are responsible for 95% of the cases.[2,3] The absence of functional adipose tissue leads to loss of energy storage function and leptin deficiency - an important determinant of the metabolic abnormalities.[5] The excess energy leads to ectopic lipid accumulation in non-adipose tissues like liver, pancreas and skeletal muscles. As a result of hypertriglyceridemia and ectopic fat accumulation, insulin resistance develops. Pancreatic abnormal accumulation also leads to impaired insulin secretion. Both of these lead to diabetes mellitus.

The diagnosis is made by 3 major criteria or 2 major criteria plus 2 or more minor criteria and / or by the identification of biallelic pathogenic variants in responsible genes.[5] In our index case, all major criteria (generalised lipoatrophy, pseudo-acromegalic features, hepatomegaly, hypertriglyceridemia and insulin resistance) and 3 minor criteria (psychomotor retardation, hypertrichosis, phlebomegaly) were fulfilled. In our case, even if the child had normal fasting, postprandial blood sugar and fasting insulin level, HOMA-IR ratio was 3.9 which indicated mild insulin resistance. From the genetic point of view, only a single case report previously reported the identified SNV and CNV to be disease causing.[6]

Unfortunately, there is no curative treatment for lipodystrophy syndromes till now. So, therapeutic interventions aim to correct metabolic abnormalities and prevent end organ damages. Diet and physical activity are mainstay of therapy. Balanced macronutrient diet consisting of 50 - 60% carbohydrates, 15 - 20% fat and 20 - 25% protein is recommended. MCT and omega- 3 fatty acid-based fat diet is another approach to cut down the triglycerides.[7] When lifestyle modifications are insufficient, statins and fibrates may be used. Metformin is certainly the best drug to reduce insulin resistance and improves hyperglycemia. FDA recently approved recombinant human leptin (Metreleptin) therapy for the treatment of generalized lipodystrophy (non-HIV-related) patients aged > 2 years, where standard treatments have failed to achieve adequate metabolic control.[8]

Conclusions

BSCL is a multisystemic and progressive disease. Regular follow-up with yearly echocardiogram, ECG, ultrasonogram of liver, lipid profile and liver enzymes are important to identify lethal complications. Early diagnosis and diet control can bring about a favourable outcome.

Conflict of Interest: None

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