

## Berardinelli – Seip Congenital Lipodystrophy

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### Abstract

Berardinelli-Seip Congenital lipodystrophy is a rare autosomal recessive disorder characterized by acanthosis nigricans, loss of subcutaneous fat, hepatosplenomegaly, mental retardation, hypertriglyceridemia, insulin resistance. An inability to store energy in adipose tissue is one of the important pathogenetic mechanisms. In congenital lipodystrophy, insulin resistance is present from birth, resulting in hyperlipidaemia, hyperinsulinaemia, insulin resistance diabetes and acanthosis nigricans. We report here a case of congenital lipodystrophy presenting with seizure and acanthosis nigricans in absence of insulin resistance.

**Keywords:** Lipodystrophy; Acanthosis nigricans; Seizure; BSCL; Insulin resistance; Acromegaly

### Introduction

Berardinelli-Seip Congenital Lipodystrophy (BSCL) is a rare autosomal recessive disorder characterized by generalized loss of fat involving face, trunk and limbs. Approximately 120 patients of various ethnic backgrounds have been reported [1]. Apart from decrease in adipose tissue lipodystrophy is also characterized by generalized muscular hypertrophy, tall stature, hypertriglyceridaemia, diabetes mellitus, insulin resistance and hepatosplenomegaly. We report here a case of BSCL because of its rarity and unusual features.

### Case Report

A 7-year-old girl child, born of nonconsanguineous marriage was admitted with complaints of abdominal enlargement and gradually increasing discoloration of skin since early infancy. There was no history of jaundice, swelling of the body or any breathlessness. Her bodyweight was 15 kg and the height was 119 cm. Five days prior to hospitalization the girl had an attack of generalized seizure associated with loss of consciousness lasting for about ten minutes. No history of vomiting or fever during or prior to the episode of convulsion was present. On examination the girl had generalized loss of subcutaneous fat including cheeks, generalized pigmentation over skin, which was more prominent over axilla and neck. The skin was coarse and the hairs were curly and coarse. Abdominal examination revealed the liver, which were firm, nontender and 6 cm palpable below the right costal arch. The spleen was firm, 3 cm palpable below the left costal arch (Table 1). There was no jaundice or edema. No evidence of ascites was found. Rest of the systemic examination did not reveal any abnormality.

Age	7 years
Sex	Female
Weight	15 Kg.

Height	119 cm.
Seizure	Generalized
Loss of consciousness	Present
Skin	Generalized pigmentation, coarse
Scalp hairs	Coarse and curly
Abdomen	Hepatosplenomegaly

**Table 1:** Clinical features

On investigation, haemoglobin was found to be 12.0 gm/dl, total leukocyte count 9,300/cu.mm with polymorphs 58%, lymphocytes 38% and eosinophils 4%. Her biochemical profile revealed slightly raised total serum cholesterol (observed value: 213 mg/dl normal value 150-200 mg/dl), normal LDL (observed value 116 mg/dl; normal value 60-140 mg/dl), raised VLDL (observed value 62 mg/dl; normal value 5-20 mg/dl), normal HDL (observed 35 mg/dl; normal value 35-84 mg/dl), raised serum triglyceride (observed value 313 mg/dl; normal value 35-114 mg/dl), fasting blood sugar 79 mg/dl and postprandial blood sugar 113 mg/dl. Blood urea and creatinine were normal. Her liver function study revealed raised SGPT (ALT) (observed value 169 U/L; normal value 5-45 U/L), raised SGOT (AST) (observed value 180 U/L; normal value 5-45 U/L), normal alkaline phosphatase (observed value 346 U/L; normal value 130-560 U/L) and serum bilirubin 0.6 mg/dl. CT scan of brain, EEG and echocardiography showed no abnormality. Serum cortisol and insulin levels were normal, (cortisol observed value 18.5 µg/dl; normal value 4.2-38.4 µg/dl) and (insulin observed value 11.67 µU/ml; normal 2.6-24 µU/ml) (Table 2). Her bone age was appropriate for the chronological age. Insulin: glucose ratio was 0.104 (normal ratio < 0.2). Genetic study could not be done in view of economic constraint of the parents.

Haemoglobin	12 gm/dl
Total leucocytes count	9300/cu.mm
Serum cholesterol	213 mg/dl (N.V- 150-200 mg/dl)

LDL	116 mg/dl (N.V- 60-140 mg/dl)
VLDL	62 mg/dl (N.V- 5-20 mg/dl)
HDL	35 mg/dl (N.V- 35-84 mg/dl)
Triglyceride	313 mg/dl (N.V- 35-114 mg/dl)
Glucose (Fasting)	79 mg/dl (N.V- 60-100 mg/dl)
Glucose (Post prandial)	113 mg/dl (N.V- 70-120 mg/dl)
SGPT (ALT)	169 U/L ( N.V- 5-45 U/L)
SGOT (AST)	180 U/L (N.V- 5-45 U/L)
Alkaline phosphatase	346 U/L (N.V- 130-560 U/L)
Bilirubin	0.6 mg/dl (N.V- 0.2-0.8 mg/dl)
Cortisol	18.5 µg/dl (N.V- 4.2-38.4 µg/dl)
Insulin	11.67 µU/ml (N.V- 2.6-24 µU/ml)
Insulin:glucose	0.104 (N.V < 0.2)
N.V- Normal Value	

**Table 2:** Laboratory profile

## Discussion

BSCL is a very rare autosomal recessive disease with a prevalence of less than one case per 12 million individuals [1]. BSCL families are classified into BSCL1, BSCL 2 and BSCL X [2]. BSCL 1, prevalent in African-American population, is the milder variety presenting in the second or third decade of life. Garg, et al. [3] first identified the gene for BSCL on chromosome 9q34. BSCL 2 is more severe with onset in the neonatal period or early infancy. Most have mental retardation. The locus for BSCL 2 has been identified on chromosome 11q13 by Magre et al. [4] Worldwide the prevalence of BSCL 2 is somewhat more than that of BSCL 1. BSCL X families are very rare. They show evidence against co-segregation with either 9q34 or 11q13. Acromegalic appearance of face, hands and feet, loss of adipose tissue, accelerated growth, increased basal energy expenditure, advanced bone age, acanthosis nigricans, mental retardation, insulin resistance, hypertriglyceridemia, low levels of high density lipoprotein cholesterol and hepatosplenomegaly are characteristic [5]. The earliest skin manifestation includes acanthosis nigricans, eruptive xanthomas and hirsutism. All patients show acanthosis nigricans to some degree [6].

Adipose tissue is scarce in most subcutaneous areas, in the abdomen, thorax, bone marrow and malar region [7,8]. Acromegalic gigantism with advanced dentition is an early and constant feature. The growth velocity is most remarkable in the first four years. Growth subsequently slows and the adults are normal or may have short stature. Diabetes mellitus usually begins in the teenage years. The diabetes is insulin resistant and despite poor control ketosis is absent. Hyperlipidemia usually precedes the appearance of diabetes. Kidneys may be enlarged without apparent histologic cause and renal failure may ensue. Cardiomegaly with muscular hypertrophy and ventricular dilatation is frequently observed. Common causes of death are renal failure and gastrointestinal haemorrhage from esophageal varices in association with hepatic failure. Serum leptin, an important hormone for energy homeostasis, is low thus contributing to the occurrence of insulin resistance and other metabolic disturbances [9,10]. Neurological abnormality like mental retardation has been documented earlier in BSCL [11]. But in the present case one episode of seizure was the unusual neurological manifestation, which has not been reported earlier probably to the best of our knowledge. Seizure

could be manifested as a result of diabetes mellitus, hypoglycaemia, acute renal failure, hypertension, fulminant hepatic failure in BSCL. But none of these conditions was present in the index case to explain seizure. In individuals with Type 1 congenital generalized lipodystrophy (CGL) the disorder is caused by mutation of the AGPAT 2 gene encoding 1-acylglycerol-3 phosphate O-acyltransferase 2 and located at 9q34. This enzyme is highly expressed in adipose tissue, so it can be concluded that when the enzyme is defective in CGL lipids cannot be stored in adipose tissue [12]. In those who have Type 2 CGL a mutation occurs in the BSCL2 gene encoding the Seipin protein and located at 11q13. This gene encodes a protein Seipin, whose function is unknown. Expression of mRNA for the Seipin protein is high in the brain, yet low in adipose tissue. Additionally patients who have mutation in this protein have higher incidents of mental retardation and lack mechanically active adipose tissue which is present in those with AGPAT 2 mutation [13]. Besides AGPAT 2 and BSCL 2 there may be additional loci for CGL. In the index case type 2 CGL may be considered in view of early onset and presence of neurological manifestation viz. seizure which might be caused by either a novel mutation of the BSCL 2 gene or additional loci for BSCL 2 gene. Genetic heterogeneity is accompanied by phenotypic heterogeneity. Appropriate genetic analysis could have unfolded the interesting facet related to seizure in this case where unfortunately it could not be done. Therefore further genetic study in CGL cases may be warranted in this direction in future. Insulin resistance seen in BSCL might contribute to the abnormal glucose tolerance test, diabetes mellitus, acanthosis nigricans and some other metabolic derangements. In the present case acanthosis was present in absence of insulin resistance, which may be regarded as atypical profile of BSCL.

Therefore the present case highlights that in seizure or epileptic disorders metabolic disorders like BSCL should also be kept in the mind. Secondly apart from insulin resistance the pathogenesis of acanthosis nigricans in BSCL may also be caused by some other ill understood factors which need future study.

## State of Informed Consent

Parents were informed about the suitability of publication of the case in the journal. They gave verbal consent in this regard.

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