

Berardinelli-Seip Syndrome: A Case Report and Review of Literature.

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1. Abstract

Berardinelli-Seip syndrome is a congenital disorder of metabolism. It is characterized by insulin-resistant diabetes mellitus and deficiency of adipose tissue. The clinical and laboratory features of the syndrome are mostly due to fat deficiency, diabetes, or to manifestations of secondary hyperinsulinemia. Muscles appear hypertrophic, with flat feet. The combination of clinical and laboratory findings is characteristic and readily recognized once the components of the syndrome are known.

2. Keywords: Berardinelli-Seip syndrome; Congenital

3. Introduction

Berardinelli-Seip syndrome is a disorder of metabolism that results in lipodystrophy, endocrine abnormalities, and characteristic skeletal changes.

It was originally described in Brazil by Berardinelli in 1954 [1] and subsequently confirmed in Norway by Seip in 1958 [2]. Since the initial description, 60 cohorts have been reported. The prevalence appears to range from 1 in 200,000 (Portugal) to 1 in 12,000,000 (USA) [3-13]. Berardinelli-Seip congenital lipodystrophy is also known as congenital generalized lipodystrophy, Seip syndrome, and lipoatrophic diabetes. The entity named lipodystrophic muscular hypertrophy [14] may also represent the same condition.

Muscles appear hypertrophic. In addition, characteristic, but idiopathic, periarticular lytic lesions may be seen in some individuals.

The combination of imaging, clinical, and findings is characteristic and readily recognized once the components of syndrome are known. We report a case of a 3-year-old male, with a history of

disease, who demonstrated many of the typical clinical and laboratory features of BSCL2.

4. Case Report

A 3-year-old male, came to our out patient department, with the presenting complaints of abdominal distension, abnormal facies, darkening of the skin and excessive hair all over the body since early infancy (Figure 1).

The child had a height of 96 cm and a weight of 15 Kg. He has lack of subcutaneous fat in all body parts, apparent muscular hypertrophy, coarse and hyperpigmented skin, acanthosis nigritans in the nape of the neck, with flat feet, excessive body hairs, hypertrophic genitalia and large superficial veins. He had epatomegaly



Figure 1: A 3-year-old male, came to our out patient department, with the presenting complaints of abdominal distension, abnormal facies, darkening of the skin and excessive hair all over the body since early infancy.

and splenomegaly without features of cirrhosis or hypertension. Mental retardation was present in child (Figure. 1). Laboratory investigations revealed normal hemogram. Liver enzymes were elevated (SGOT=80 IU/l, SGPT=143 IU/l, ALP=1717 IU/L); serum triglycerides was elevated (280 mg/dL); serum total cholesterol was normal. Blood sugar was normal. Plasma insulin levels were elevated, suggesting insulin resistance (fasting= 30 μ IU/mL and post-prandial = 38 μ IU/mL).

X-ray of skull, trunk and limbs has shown normal bones. Echocardiography was normal.

In view of the typical dysmorphology, age of onset and hypertriglyceridemia, the diagnosis of BSCL2 was kept.

The child is coming for follow-up since the last one-year. As per recommendations the child is put on low fat diet. The child has developed overt diabetes and serum triglycerides has somewhat decreased with dietary restriction. Special education of the child has been advised because of the associated mental retardation.

5. Discussion

Berardinelli-Seip congenital lipodystrophy is a rare autosomal recessive disorder. It has been variously described as generalized lipodystrophy, congenital lipodystrophy, Seip-Lawrence syndrome and lipotrophic diabetes (in USA).

BSCL families are classified into BSCL1, BSCL2 and BSCLX [8]. BSCL1, prevalent in African-American population, is the milder variety presenting in the second or third decade of life. Garg, et al. [4] first identified the gene for BSCL1 on chromosome 9q34. BSCL2 is more severe with onset in the neonatal period or early infancy. Most have mental retardation. It is prevalent in Portugal, Lebanon, Norway and Middle East. The locus for BSCL2, has been identified on chromosome 11q13 by Magre, et al. [6], the prevalence of BSCL2 is somewhat more than that of BSCL1. BSCLX families are very rare; they show evidence against co-segregation with either 9q34 or 11q13. Agarwal, et al [7] have been detected different mutations of the gene encoding 1-acylglycerol-3-phosphateO-acyltransferase 2 in 20 affected individuals showing linkage to chromosome 9q34 (BSCL1). The AGPAT2 enzyme is involved in the biosynthesis of triacylglycerol and glycerophospholipids.

In the 11q13 linked families (BSCL2) various homozygous and compound heterozygous mutations were found in a previously unidentified gene, termed seipin. More than 15 different allelic variations of the BSCL2 gene have been described [6, 8]. The seipin gene encodes for a 398-amino acid protein of unknown function.

Magre, et al. [6] in 2001 indicated that this protein could be a transmembrane protein. Windpassinger, et al [9] in 2004 showed that seipin is an integral membrane protein of the endoplasmic reticulum. This gene is widely expressed, with particularly high expression levels in brain and testis.

In all BSCL subjects, there is near total absence of adipose tissue.

Dietary and endogenous fat is aberrantly stored in metabolically important tissues like muscle and liver. This leads to severe insulin resistance and ultimately a difficult to control diabetes mellitus. Other metabolic consequences include hypertriglyceridemia leading to hepatic steatosis and ultimately to cirrhosis and death due hepatic failure. For unknown reasons many subjects develop hypertrophic cardiomyopathy that can lead to death from cardiac failure [8]. Association with bone cyst has been reported; it was previously described as Brunzell syndrome [5].

Most of the clinical features of the syndrome can be explained as being due to either the consequences of the fat deficiency, diabetes, or to manifestations of secondary hyperinsulinemia, which results from the failure of the tissue to respond to insulin.

Hyperinsulinemia results in an elevated basal metabolic rate and excessive food intake. It has been recently recognized that the central nervous system can sense and respond to input from hormones such as insulin and leptin that are usually secreted in proportion to body energy stores [10]. Children with BSCL experience rapid increases in height, weight, muscle mass, and skeletal mineralization.

Growth may confer some protection against the hyper metabolic effects as metabolic disorders tend to become more severe after puberty. Children with BSCL may also demonstrate advanced bone age on radiographs. Hands and feet are large, as in acromegaly, although growth hormone levels are normal. Patients with BSCL also frequently suffer from acanthosis nigricans, a hyperpigmentation disorder that is generally thought to be caused by elevated levels of insulin or insulin-like growth factors.

In absence of adequate reservoirs of adipose storage, dietary and endogenous fat is aberrantly stored in other tissues such as muscle and liver [3]. Therefore, although it may seem counter-intuitive given the general absence of fat, hepatomegaly and muscle enlargement may result from fatty infiltration. A recent work indicates that insulin resistance is associated with increased levels of lipid within skeletal muscle cells [11]. It is thought that these increased levels result in impaired energy metabolism and may play a central role in the pathogenesis of insulin

resistance. Morphological and functional of the skeletal musculature of patients with this disease suggests that increased muscle mass should more properly be termed hyperplasia rather than hypertrophy, since patients with BSCL do not demonstrate increased strength. Musculoskeletal symptoms in BSCL are probably due to the combined effects of muscle hypertrophy and impaired energy metabolism.

Laboratory findings of BSCL are due to diabetes and to abnormalities of hepatic, renal, and pancreatic function.

Despite hepatomegaly, in most patients the liver function is well preserved. However, hepatic dysfunction may cause triglyceride and glycogen levels to increase and severe cases of cirrhosis have been reported. Decreased renal function is due to diabetes mellitus. Proteinuria is often present. As in patients with the common insulin resistance syndrome, individuals with BSCL are subject to an increased risk of atherosclerosis [12]. Hyperglycemia due to diabetes mellitus and low HDLC may be observed as early as in infancy.

Leptin is a peptide hormone that is secreted by fat cells. It has many physiological effects, one of which is oxidation of fatty acids, reducing the lipid content of cells. It has been shown that leptin therapy may help to reverse the effects of insulin resistance. Unfortunately, the usefulness of leptin is limited by side effects and the rapid occurrence of tachyphylaxis [13].

In our case, we suspected generalized lipodystrophy. The diagnosis was confirmed after the typical dysmorphology was noted and hypertriglyceridemia and hyperinsulinemia were detected. In conclusion, we have presented a patient with features of classic type 2 BSCL. The condition can be recognized by a characteristic combination of clinical, laboratory features, and sheds light on some of the physiological functions of adipose tissue.

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