

Case Report

Berardinelli-Seip Syndrome: A Rare Autosomal Disorder

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Abstract

Berardinelli-Seip syndrome or congenital generalized lipodystrophy, is a rare autosomal recessive disease caused by dysregulation of lipid and glycemic metabolism. Common clinical signs are acanthosis nigricans, acromegaloid features, hepatomegaly, hyperandrogenism, altered glucose intolerance, cardiomyopathy and hypertriglyceridemia. We report an 11-year-old boy presenting with generalized lack of adipose tissue, generalized muscular hypertrophy and brownish colored skin on the neck, axillae and inguinal folds associated with hyperglycemia. The clinical diagnosis of Berardinelli-Seip syndrome was made.

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Introduction

Berardinelli–Seip congenital lipodystrophy syndrome was first described in 1954 by Berardinelli in a 2-year-old boy in Brazil as generalized congenital lipoatrophy.¹ Later in 1959, Seip² described the same syndrome in three other patients. Berardinelli–Seip syndrome is a rare syndrome with an estimated prevalence of 1 in every 10 million births. It is inherited as an autosomal recessive trait, with frequent parental consanguinity. At least three molecularly distinct forms of Berardinelli–Seip syndrome have been defined, with the mutations of AGPAT2 and BSCL2 being responsible for 95% of reported cases.³

Berardinelli–Seip syndrome is characterized by the lack of adipose tissue with its consequent deregulations in lipid and carbohydrate metabolism. Absence of adipose tissue is responsible for extremely low levels of leptin, an adipocytokine responsible for the regulation of energy metabolism. This plays an important role in the pathophysiology of the disease characterized by hypertriglyceridemia, hepatic stea-

tosis, hyperglycemia, insulin resistance, development of diabetes mellitus and microvascular complications. There is no standardized treatment.^{4,5}

Berardinelli–Seip syndrome has been reported from Lebanon, Portugal, Norway and USA, as well as in a few families from Asian, African and Brazilian. International literature reports around 300 of Berardinelli–Seip syndrome.⁶ The first case report from Pakistan has recently been reported from Pakistan by Cheema et al.⁷ We report here an 11 years old boy with Berardinelli–Seip syndrome which is being followed in our unit.

Case Report

An 11 year old boy presented to our tertiary care hospital with history of fever, cough for 2 weeks and respiratory distress few hours before presentation. His chest x-ray was suggestive of right sided pleural effusion and was treated with appropriate antibiotics as guided by pleural tap examination.

Besides these presenting complaints, boy has

hyperpigmented skin with loss of pads of fats on body which mother dates back to 2.5 years of age, followed by development of dry scaly lesions but she never got any consultation for that. For last one year, he gradually developed abdominal distension too. He was product of consanguineous marriage and eldest among three siblings with no family history of such disorder. On examination he was developmentally normal child with acromegaloid features, hyperpigmented skin, loss of buccal pad of fat, long limbs and large hands, hepatosplenomegaly. His weight was 40 kg, height of 147 cm and BMI of 18.5kg/m². Pubertal stage was Tanner I. Detailed Eye examination was normal. Cardiac examination was normal. Abdominal examination has distended abdomen with massive hepatosplenomegaly. Chest has reduced air entry on right base.

His laboratory values showed Serum Cholesterol of 51 mg/dl, Serum triglycerides 459 mg/dl, Serum HDL-Cholesterol 12 mg/dl, Serum LDL-Cholesterol 21mg/dl, VLDL Cholesterol 92 mg/dl, fasting blood sugar 242 mg/dl, random blood sugar 549 mg/dl and HBA1c 9.5 with normal C-peptide levels. His urine complete, complete blood count, liver and renal function tests came out to be normal. Echocardiography showed mild left ventricular hypertrophy and mild pulmonary hypertension with good ejection fraction. Abdominal ultrasound showed enlarged liver and spleen. CT abdomen showed hepatosplenomegaly with multiple small cysts in both lobes of liver with porta hepatis lymphadenopathy but was neither causing any symptoms nor any derangements in hepatic function. He was treated for acute complaint with appropriate antibiotics. Parents were provided detail counseling for the disease. For hyperglycemia,

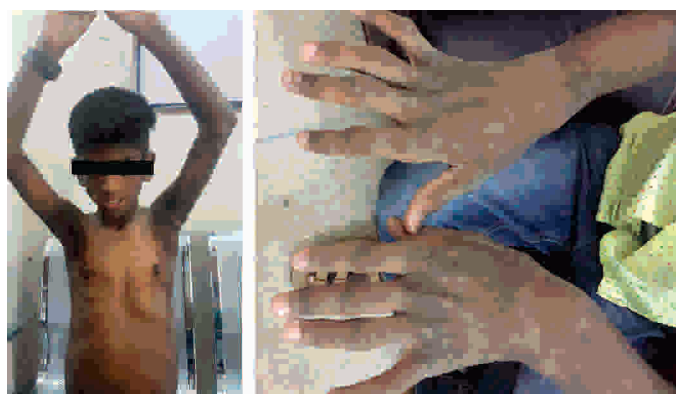


Figure 1: Prognathism, enlarged hands/feet, prominent ears and muscular hypertrophy (Picture taken with permission)

he is on dietary fat restriction with oral metformin and insulin. Child is on our regular follow up now with controlled symptoms on treatment.

Discussion

Three major criteria or two major plus two or more minor criteria make a diagnosis of BSCL likely. Major criteria include lipoatrophy affecting the trunk, limbs, and face; acromegaloid features; hepatomegaly; elevated serum triglycerides; and insulin resistance. Minor criteria include hypertrophic cardiomyopathy, psychomotor retardation, hirsutism, precocious puberty in females, bone cysts, and phlebomegaly. Our patient fulfilled three major criteria (lipodystrophy, hepstomegaly, insulin resistance). Our patient had symptoms suggestive of Berardinelli–Seip syndrome, since early childhood. Although we could not get the genetic analysis done for this patient, however, clinical features were consistent with the syndrome. Fat deficiency leading to failure of the tissues to respond to insulin resulting in hyperinsulinemia mainly leads to the features of Berardinelli–Seip syndrome. Lipodystrophy is present since birth but age at which hyperinsulinemia affects individuals is not well established.

Diabetes mellitus (DM) is reported in 25-30% of the cases between ages 15 and 20 years.⁸ Insulin resistance is present from birth resulting in hyperinsulism, dyslipidemia and insulin resistant diabetes with anabolic syndrome worsened by voracious appetite. As seen in our case, the child had acanthosis nigricans and hyperglycemia but never went in diabetic ketoacidosis. Our patient also showed these features so we had to start insulin after confirming c peptide levels. Liver is usually involved in Berardinelli–Seip syndrome, leading to hepatic steatosis and cirrhosis.³ Hepatomegaly was present in our patient, however, hepatic functions were normal.

Among 20-23% of the affected individuals, hypertrophic cardiomyopathy is reported and is a significant cause of morbidity from cardiac failure and early mortality.⁹ Although our patient did not had cardiac symptoms but showed evidence of mild left ventricular hypertrophy on echocardiography. Our patient also had acromegaloid features in the form of prognathism, enlarged hands/feet, prominent ears and muscular hypertrophy.

Ferraria et al³ has reported case series from Portugal and has highlighted the difficulties in management. Hyperglycemia and lipid disturbances need special attention to be managed. Lipid lowering therapy, Insulin administration, and moderate calorie restrictions (20% -30%) should be the main stay of treatment. Leptin – adipocyte hormone, is a new, therapeutically effective, long-term option for severe forms of lipodystrophy. This may improve the insulin resistance, dyslipidemia and hepatic derangements.⁶ Our patient is on treatment for hyperglycemia and is on regular follow up.

Two hormones are important in the understanding of the physiopathology of this syndrome: insulin and IGF-I, which have in common their own receptors distributed in certain organs and tissues, with similar function and structure, that when activated promote growth and cellular differentiation. The activation of these receptors determines all the clinical and biological responses produced by the link with its hormones. The excess of a hormone may activate the receiver of another hormone. When a receptor is activated by a hormone that is not its homologue, the event is called specificity spillover. In patients who are in an insulin resistant state and therefore, with hyperinsulinemia, the linking of insulin to the IGF-I³ receptors present in the myocardial tissues results in hypertrophy of this organ, as well as other tissues where these receptors are distributed. This explains the high frequency of myocardial hypertrophy in some cases of insulin resistance, like in lipodystrophy. The histological differentiation from the classic hypertrophic cardiomyopathy is made by the absence of rearrangement of fibers in the myocardial hypertrophy associated with lipodystrophy. In conclusion, cardiac involvement seems to be the

bigger influence in the long-term prognosis of patients with the syndrome, with an unfavorable characteristic due to the anatomic and functional changes that occur as a result of the severe myocardial hypertrophy.

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