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Case Report

Congenital Generalized Lipodystrophy: A Multisystemic Metabolic Disorder

Abstract

Introduction: Congenital generalized lipodystrophy or Berardinelli-Seip syndrome is a rare autosomal recessive multisystem disorder characterized by the near absence of subcutaneous and visceral adipose tissue from birth or early infancy with severe insulin resistance. It is caused by mutations in the gene for AGPAT-2 on chromosome 9 or BSCL-2/Seipin on chromosome 11 resulting in triglyceride-depleted adipocytes. BSCL-2/Seipin is a cell autonomous regulator of lipolysis essential for adipocyte differentiation.

Case: A 6-year-old male child presented with abdominal distention. He was noted to have a characteristic phenotype with generalized absence of subcutaneous fat over the body with acanthosis nigricans and hepatomegaly. His anthropometric indices were above the 75th centile for age and he was in sexual maturity rating Stage II. Investigations revealed hyperglycemia, hypercholesterolemia with fatty infiltration of liver and hyperinsulinemia with normal Growth hormone levels and accelerated bone age. The clinical features, pathogenesis, management and prognosis are discussed.

Conclusion: Congenital generalized lipodystrophy is an exceptionally rare disorder with prevalence of 1 per 12 million population, affecting all ethnic groups. It is characterized by generalized lipodystrophy, acanthosis nigricans, prominent superficial veins, muscle hypertrophy, hirsutism, accelerated skeletal growth with tall stature and genital precocity. Metabolic derangements seen are hyperlipidemia, hepatomegaly and non-ketotic insulin resistant diabetes mellitus. Death occurs in the third decade due to complications of diabetes, cardiomyopathy or cirrhosis. Our case showed all the phenotypic and metabolic features of this syndrome with early appearance of and difficult to control diabetes mellitus.

Abbreviations

AGPAT: Acylglycerol-Phosphate-Acyltransferase; BMR: Basal Metabolic Rate, BSCL: Berardinelli-Seip Congenital Lipodystrophy, GH: Growth Hormone; SMR: Sexual Maturity Rating; US:LS: Upper Segment to Lower Segment ratio;

Introduction

Loss of fatty tissue occurring in a partial or generalized distribution is called as lipodystrophy. Generalized lipodystrophy may be congenital or acquired in nature. Congenital generalized lipodystrophy or Berardinelli-Seip syndrome is a rare autosomal recessive multisystem disorder characterized by the near absence of subcutaneous and visceral adipose tissue from birth or early infancy with severe insulin resistance. Other clinical and biological features include a specific phenotype, cutaneous changes, and an anabolic syndrome with metabolic derangements. Findings seen less commonly include xanthomas, cardiac hypertrophy, hypertension, enlargement of parotid glands, ovarian cysts and clitoromegaly in females [1]. Difficult to control brittle diabetes mellitus may present by the end of second decade. Herein we present a 6 year old child who showed all the phenotypic and metabolic features of this syndrome with early appearance of and difficult to control diabetes mellitus.

Case Presentation

A 6-year-old male child, second sib of a second-degree

consanguineous marriage presented with progressive abdominal distention. There was history of the child having thin limbs and an emaciated look on the face during infancy. Child had a triangular face with loss of the buccal fat pad giving the face a gaunt appearance. His weight was 25 kg (> 90th centile), height was 120.5 cm (>75th centile), weight for height was between 75th to 90th centile with Upper segment to Lower segment (US:LS) ratio of 1.3: 1.0. There was generalized loss of subcutaneous fat over the limbs and the trunk, with hypertrophied limb muscles and prominent veins (Figure 1). Acanthosis nigricans was seen in both axillae and groins. His scalp hair was thick and



Figure 1: Berardinelli – Seip syndrome showing characteristic facies with generalized loss of subcutaneous fat, muscular hypertrophy and abdominal distention.

curly and child was in sexual maturity rating (SMR) stage II. He had a 5 cm non-tender firm hepatomegaly and no splenomegaly. His neurological examination was normal with normal intellectual faculties. Investigations revealed a normal hemogram and urine exam positive for reducing substance. His fasting blood sugar value was 226 mg/dl, and the post-prandial value was 327 mg/dl. Serum cholesterol was 370 mg/dl with Serum Triglycerides of 190 mg/dl. All other biochemical parameters were normal. X-ray of left wrist and hand corresponded with a bone age of 9-10 years. Ultrasound abdomen showed hepatomegaly with fatty infiltration of liver. Echocardiography did not reveal any cardiomyopathy. The fasting plasma Insulin assay showed hyperinsulinemia and was 33 uU/ml (Normal 7-24 uU/ml). A Growth hormone (GH) assay was done following IV administration of 0.1 IU/kg of Plain Insulin, on samples collected at 30 and 60 minutes following the dose. Both samples had normal GH levels (< 10 mcg/L). Plasma Leptin assay and genetic analysis was not done due to resource limitation. The child was diagnosed as a case of congenital generalized lipodystrophy Type 1 and started on Insulin therapy with Human Insulin at 2 Units/kg SC in 2 divided doses and oral Atorvastatin 10 mg once daily. Dietary therapy with high fiber, low fat diet and small meals was advised. The proportions of easily digestible and simple carbohydrates were kept lesser. Topical retinoids (0.025% Isotretinoin) were prescribed for the acanthosis nigricans. The child is on regular follow-up and continues to show accelerated growth, precocity and severe insulin resistance. On therapy his blood sugar and lipid profile are within acceptable limits for age and close tracking of blood pressure for hypertension is being done.

Discussion

Berardinelli-Seip syndrome was reported independently by Waldemer Berardinelli in 1954 [2] and Martin Fredrik Seip in 1959 [3]. It is characterized by generalized lipodystrophy, acanthosis nigricans, elevated BMR, hyperlipidemia, hepatomegaly and non-ketotic insulin resistant diabetes mellitus. Studies of pituitary and adrenal function, including GH assay have been normal. Consanguinity has been reported from families with more than one affected sibling

[4]. Other clinical characteristics of this syndrome are prominent superficial veins, muscle hypertrophy, hirsutism, abundant curly scalp hair, voracious appetite, accelerated skeletal growth with tall stature and precocious development of genitals. Hyperlipidemia, hyperinsulinemia, and insulin resistant non-ketotic diabetes mellitus develop gradually leading to an anabolic syndrome worsened by a voracious appetite and is reflected by increasing hepatomegaly caused by fatty infiltration which progresses to cirrhosis and portal hypertension [5,6]. Growth velocity is increased in preschool age children, which tapers off later in childhood. Hypothalamic releasing factors that are not normally found in plasma have been identified in affected patients and suggest a lack of hypothalamic regulation. Mabry et al gave evidence for abnormal pituitary function with secretion of an abnormal hormone with melanotropic and growth hormone properties [7]. Others have reported the presence of insulin-antagonizing and fat mobilizing substance in the urine [8]. Berardinelli-Seip syndrome is inherited as an autosomal recessive disorder. It is caused by mutations in the gene encoding for 1-acylglycerol-3-phosphate O-acyltransferase-2 (AGPAT-2) on chromosome 9q34 (Type 1) or on a gene encoding Seipin on chromosome 11q13 called as Berardinelli-Seip congenital lipodystrophy-2 (BSCL-2) (Type 2). The gene encoding AGPAT-2 catalyses an essential reaction in the biosynthetic pathway of glycerophospholipids and triglycerides. These mutations affect triacylglycerol synthesis in adipose tissue, resulting in triglyceride-depleted adipocytes. The BSCL-2 critical region harbors a plausible candidate gene RXRA that plays a central role in adipocyte differentiation [9,10]. Pluripotent mesenchymal stem cells give rise to preadipocytes, which under the influence of insulin, steroids, leptin and adipogenic transcription factors like seipin get differentiated to adipocytes. Triglyceride synthesis in adipose tissue via the classical pathway requires glycerol-3-phosphate as the initial substrate, while in the small intestine synthesis of triglycerides occurs via the alternative pathway using monoacylglycerol. Activation of adipocytes under various transcription factors results in expression of AGPAT-2 with synthesis of triglyceride (Figure 2). In the classical pathway acylation of glycerol-3-phosphate by AGPAT-2 is required for triglyceride synthesis. Intracellularly triglycerides are stored

Cell stage	Development		Differentiation		Death/ Apoptosis
Progression					
Cell type	Mesenchymal cell	Preadipocyte	Adipocyte	Mature adipocyte	Cell death
Cell function	Differentiation	Development	Lipogenesis		Apoptosis
Influencing factors	Transcription factors	Insulin, Cortisol, Seipin, AKT-2	AGPAT		LMNA, ZMPSTE24
Cell size			Fasting (smaller)	Feeding (larger)	

Figure 2: The various stages of adipocyte development and differentiation with their function and influencing factors.

Abbreviations: AKT-2: AKT murine thymoma oncogene homolog 2; AGPAT: Acylglycerol-Phosphate-Acyltransferase; LMNA: Lamin A/C; ZMPSTE24: Zinc Metalloproteinase.

as lipid droplets which emerge as vesicles from the endoplasmic reticulum. These vesicles fuse together under the influence of several proteins including seipin located on the vesicle wall to form large lipid droplets. These large lipid droplets then merge with caveolin vesicles containing fatty acids with resultant translocation of fatty acids to lipid droplets. Depending on the availability of substrate the lipid droplets shrink and expand [11]. Agrawal et al pointed out that individuals with congenital generalized lipodystrophy who carry mutations in the BSCL-2 gene, seem to have mild mental retardation and cardiomyopathy, features not seen in families they studied with AGPAT-2 mutations. Based on the high expression of BSCL-2 in brain and weak expression in adipocytes, a primary defect in hypothalamic pituitary axis has been suggested [9]. Berardinelli-Seip syndrome is the most important of the inherited generalized lipodystrophies. Inherited forms of partial lipodystrophies include the Dunnigan variety of familial partial lipodystrophy, lipodystrophy associated with Mandibuloacral dysplasia, and lipodystrophy in association with SHORT syndrome i.e short stature, hyperextensible joints, ocular depression, Reiger's anomaly and teething delay. Of the acquired lipodystrophies, Protease inhibitor therapy in patients with HIV infection, acquired generalized lipodystrophy of autoimmune origin or in association with autoimmune diseases, and the Barraquer-Simons syndrome are noteworthy [12]. Control of the diabetes with insulin is difficult to achieve, and does not affect the course of the lipodystrophy. Patients should have four regular meals and avoid large meals because they have limited ability to store energy as fat, lacking the buffer capacity of normal adipose tissue. Easily digestible carbohydrates should be restricted and dietary fiber is important [7]. Low fat diet with medium chain triglycerides, polyunsaturated fats and statins may help to regulate the triglyceride levels. Dietary fat regulation of energy consumption is the most important and efficacious intervention. Selective dopamine blocker Pimozide and serotonergic antagonist Fenfluramine have been used in cases of acquired generalized lipodystrophy, but are ineffective in this condition. Newer modalities including Leptin therapy is being evaluated in these patients [13]. Recombinant methionyl human leptin (Metreleptin) administered as a once or twice daily subcutaneous injection mimics the natural leptin circadian cycle. The recommended starting dose is dependent on the body weight of the subject, where for a body weight ≥ 40 kg, the maximum daily dose is 0.13 mg/kg; in people with a body weight < 40 kg, the maximum daily dose is 10 mg/day [14].

Conclusion

In conclusion, we present a rare multisystem metabolic disorder with severe insulin resistance and early appearance of diabetes mellitus managed with Insulin therapy, oral statin and dietary management. Since the child had intact intellectual functions and

no cardiomyopathy, he was diagnosed to have Type 1 congenital generalized lipodystrophy.

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